**SCHEDULING STATUS**

S3

**1. NAME OF THE MEDICINE**

**METFORMIN 500 XR ADCO,** 500 mg, prolonged release tablets
**METFORMIN 1000 XR ADCO,** 1 000 mg**,** prolonged release tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

METFORMIN 500 XR ADCO:
Each prolonged release tablet contains 500 mg metformin hydrochloride.
Sugar free.
For full list of excipients, see section 6.1.

METFORMIN 1000 XR ADCO:
Each prolonged release tablet contains 1 000 mg metformin hydrochloride.
Sugar free.
For full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

METFORMIN 500 XR ADCO:
Prolonged release tablets.
White to off white capsule shaped, biconvex, bevelled edge tablet, with occasionally mottled appearance, debossed with "TL001" on one side and plain on other side.

METFORMIN 1000 XR ADCO:
Prolonged release tablets.
White to off white oval, biconvex, bevelled edge, uncoated tablet with occasionally mottled appearance, debossed 'TL089' on one side and plain on 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 do not result in adequate glycaemic control. METFORMIN XR ADCO 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**

METFORMIN 500 XR ADCO:
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 gastro-intestinal tolerability. The maximum recommended dosage is four 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 METFORMIN 500 XR ADCO four tablets once daily, METFORMIN 500 XR ADCO two 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.

METFORMIN 1000 XR ADCO:
METFORMIN 1000 XR ADCO is intended as maintenance therapy for patients already treated with either 1 000 mg (two tablets of METFORMIN 500 XR ADCO) or 2 000 mg (four tablets of METFORMIN 500 XR ADCO) of sustained release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3 000 mg daily.

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

**Switching patients from other oral antidiabetic agents**
If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate METFORMIN XR ADCO prolonged release tablets at the doses indicated above.

**Combination therapy with insulin**
METFORMIN XR ADCO prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is METFORMIN 500 XR ADCO once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switch to METFORMIN 1000 XR ADCO may be considered.

**Other combination therapy**
Refer to section 4.4.

**Special populations**
***Elderly***
Due to the potential for decreased renal function in elderly subjects, the dosage for the METFORMIN XR ADCO should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

**Paediatric population**

***Children***

In the absence of available data, the METFORMIN XR ADCO range should not be used in children.

**Method of administration**

For oral administration.

**4.3 Contraindications**

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis or diabetic pre-coma).
- Renal failure, renal dysfunction (creatinine clearance < 60 mL/min) or severe renal failure (GFR < 30 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 (especially acute disease or worsening of chronic disease) such as decompensated cardiac or respiratory failure, pancreatitis, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- The use of METFORMIN XR ADCO during pregnancy is not advised.

**4.4 Special warnings and precautions for use**

**Lactic acidosis**

Lactic acidosis is associated with the use of METFORMIN XR ADCO.
Lactic acidosis is a less frequent, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to METFORMIN XR ADCO administration. Most often, lactic acidosis 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 provider is recommended.

In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonemia), lactic acidosis should be suspected and METFORMIN XR ADCO therapy should be stopped.
Lactic acidosis is a medical emergency, which must be treated in hospital.

Medicines 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 medicines that may cause lactic acidosis (see sections 4.3 and 4.5). Patients and /or caregivers should be informed of the risk of lactic acidosis.

*Diagnosis of lactic acidosis*
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings include a decreased blood pH (< 7,35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, METFORMIN XR ADCO should be discontinued and the patient should be hospitalised immediately.

**Renal function**
As METFORMIN XR ADCO 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,
- two to four times a year in patients with serum creatinine levels at the upper limit of normal and 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 a NSAID.
METFORMIN XR ADCO therapy should be stopped 2-3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography are reinstated only after control of renal function has been regained.

The use of METFORMIN XR ADCO 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 XR ADCO formulations should have an annual estimation of vitamin $B_{12}$ levels, since METFORMIN XR ADCO range may cause malabsorption of vitamin $B_{12}$, which may result in megaloblastic anaemia.

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).

**Elderly**
Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

**Administration of iodinated contrast agent**
Intravascular administration of iodinated contrast agents in radiological studies (such as intravenous urography and intravenous angiography) can lead to renal failure or contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis.
METFORMIN XR ADCO should be discontinued prior to, or at the time of the imaging procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable (see sections 4.2 & 4.5).

**Surgery**
METFORMIN XR ADCO should be discontinued 48 hours before elective surgery under general, spinal or epidural anaesthesia. Therapy should not be resumed earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

**Other precautions**
METFORMIN XR ADCO alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g., sulphonylureas or meglitinides).

Stabilisation of diabetic patients with METFORMIN XR ADCO and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained (see section 4.3).

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.

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

METFORMIN 500 XR ADCO:
This medicine contains 23 mg sodium per 500 mg tablet, equivalent to 1,12 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

METFORMIN 1000 XR ADCO:
This medicine contains 25 mg sodium per 1 000 mg tablet, equivalent to 1,24 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

**4.5 Interactions with other medicines and other forms of interaction**
**INADVISABLE COMBINATIONS:**
***Alcohol***
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.
Avoid consumption of alcohol and alcohol-containing medications.

***Iodinated contrast agents***
Intravascular administration of iodinated contrast agents may lead to METFORMIN XR ADCO accumulation and a risk of lactic acidosis.
METFORMIN XR ADCO should be discontinued prior to, or at the time of the imaging procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable (see sections 4.2 & 4.4).

**COMBINATIONS REQUIRING PRECAUTIONS FOR USE:**
***Some medicines 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 medicines in combination with METFORMIN XR ADCO, close monitoring of renal function is necessary.

***Glucocorticoids (systemic and local routes), beta-2-agonists (sympathomimetics), 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.

***Anticoagulants:*** Metformin as in METFORMIN XR ADCO 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 METFORMIN XR ADCO with sulphonylurea may cause hypoglycaemia.

***Vitamins*****:** Long-term treatment with METFORMIN XR ADCO may cause vitamin $B_{12}$ mal-absorption in the gastro-intestinal tract, thus a dose reduction of METFORMIN XR ADCO should be considered.

***Organic cation transporters (OCT)***
METFORMIN XR ADCO is a substrate of both transporters OCT1 and OCT2.
Co-administration of METFORMIN XR ADCO with

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

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

**4.6 Fertility, pregnancy and lactation**
***Pregnancy***
The use of METFORMIN XR ADCO during pregnancy is not advised.

***Breastfeeding***
There is no information available concerning the safety of METFORMIN XR ADCO during lactation.

***Fertility***
No information available.

**4.7 Effects on ability to drive and use machines**
METFORMIN XR ADCO 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 XR ADCO is used in combination with other antidiabetic medicines such as (sulphonylureas, insulin and meglinitides e.g., repaglinide).

**4.8 Undesirable effects**
***a. Summary of the safety profile***
During treatment initiation, the most frequent adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

***b. Tabulated summary of adverse reactions***

| SYSTEM ORGAN CLASS | FREQUENCY | ADVERSE REACTIONS |
|---|---|---|
| **Metabolism and nutrition disorders** | Less frequent | Decrease of vitamin $B_{12}$ absorption with decrease of serum levels during long-term use of the METFORMIN XR ADCO range. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.<br>Lactic acidosis (see section 4.4). |
| **Nervous system disorders** | Frequent | Taste disturbance. |
| **Gastrointestinal disorders** | Frequent | Nausea, vomiting, diarrhoea, abdominal pain and loss of [1]appetite. |
| **Hepato-biliary disorders** | Less frequent | Isolated reports of liver function tests abnormalities or hepatitis resolving on METFORMIN XR ADCO discontinuation. |
| **Skin and subcutaneous tissue disorders** | Less frequent | Skin reactions such as erythema, pruritus and urticaria. |

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

[1]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.

*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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

Hypoglycaemia can occur when METFORMIN XR ADCO 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.

Treatment of overdosage
Lactic acidosis is a medical emergency and must be treated in hospital.
There is no specific antidote for overdose with METFORMIN XR ADCO. Intense symptomatic and supportive treatment is recommended and should be directed at correcting fluid loss and blood glucose levels. Haemodialysis is the most effective way to remove lactate and metformin.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglycaemics.
ATC Code: A10/BA02: Gastrointestinal tract and metabolism

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.

***Mechanism of action***

Metformin may act via three mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,
- in muscle, by increasing glucose/ insulin 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 (GLUT).

### 5.2 Pharmacokinetic properties

***Absorption***

Following a single oral dose of METFORMIN 500 XR ADCO peak plasma levels ($C_{max}$) are achieved with a median value of seven hours.

Following a single oral administration in the fed state of one tablet of METFORMIN 1000 XR ADCO, a mean peak plasma concentration of 1 214 ng/mL is achieved after a median time of five hours (range of four to ten hours). METFORMIN 1000 XR ADCO was shown to be bioequivalent to METFORMIN 500 XR ADCO, at a dose of 1 000 mg, with respect to $C_{max}$ and AUC in healthy fed and fasted subjects.
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.
No accumulation is observed after repeated administration of up to 2 000 mg of metformin as prolonged release tablets.

When the 1 000 mg metformin prolonged release tablet is administered in fed conditions the AUC is increased by 77 % ($C_{max}$ is increased by 26 % and $T_{max}$ is slightly prolonged by about one hour) relative to intake in the fasting state. Although there is no information on the exposure after the 500 mg prolonged release tablets. It is presumed that similar increased exposure occurs with these formulations when given in the fed-state.

***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 red blood cells most likely represent a secondary compartment of distribution.
The mean volume of distribution (Vd) ranged between 63 – 276 L.

***Biotransformation***
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.

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.

*Other special populations*
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).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

METFORMIN 500 XR ADCO:
Carboxymethylcellulose (Sodium CMC) 9M31F PH
Hypromellose K 100M
Magnesium stearate

METFORMIN 1000 XR ADCO:
Carmellose sodium
Hypromellose K 100M
Magnesium stearate

Povidone K 90

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
METFORMIN 500 XR ADCO: 36 months.
METFORMIN 1000 XR ADCO: 36 months.

**6.4 Special precautions for storage**
Store at or below 25 °C.

**6.5 Nature and contents of container**
METFORMIN 500 XR ADCO:

- 10 X 10 prolonged release tablets are packed in clear, transparent, non-toxic PVC/PVDC film on a printed aluminium foil blister pack with a heat seal lacquer.

The blisters are further packed into a carton with a leaflet.

METFORMIN 1000 XR ADCO:

- 6 x 10 prolonged release tablets are packed in blister strips composed of plain aluminium foil and clear, transparent, non-toxic PVC/PVDC film with text matter printed on dull surface of aluminium (with NC coating) and heat seal lacquer coating on other side (silver coloured).

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand
1685
Customer Care: 0860 ADCOCK/232625

**8. REGISTRATION NUMBER(S)**
METFORMIN 500 XR ADCO: 56/21.2/0728
METFORMIN 1000 XR ADCO: 56/21.2/0473

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 February 2024

## 10. DATE OF REVISION OF THE TEXT

Not applicable

adcock ingram

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