

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

CADBOWER XR 500, 750 and 1 000 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg: One extended release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
750 mg: One extended release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
1000 mg: One extended release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.
These tablets are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended Release Tablet

500 mg: White to off-white, capsule-shaped, 16,50 mm x 8,20 mm uncoated tablet, debossed with "XR 500" on one side and plain on other side.
750 mg: White to off-white, capsule-shaped, 19,60 mm x 9,30 mm uncoated tablet, debossed with "XR 750" on one side and plain on other side.
1000 mg: White to off-white, capsule-shaped, 21,10 mm x 10,10 mm uncoated tablet, debossed with "XR 1 000" 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 exercise and dietary management alone does not result in adequate glycaemic control.

CADBOWER XR may be used as monotherapy as initial therapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration

Posology

CADBOWER XR 500 mg

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet of Metformin Hydrochloride 500 mg once daily.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. Gastrointestinal tolerability may improve with a slow increase of dose. The maximum recommended dose is 4 tablets of Metformin Hydrochloride 500 mg daily.
- 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 accomplished on 4 x CADBOWER XR 500 mg once daily, 2 X CADBOWER XR 500 mg twice daily should be considered. Both doses should be given with food. If glycaemic control is still not accomplished, patients may be converted to standard metformin tablets to a maximum dose of 3000 mg daily.

CADBOWER XR 750 mg

The usual starting dose is one tablet daily given with the evening meal.

After 10 to 15 days the dose should be modified based on blood glucose measurements. Gastrointestinal tolerability may improve with a slow increase of dose.

The recommended dosage is 2 tablets once daily, with the evening meal.

If glycaemic control is not achieved with CADBOWER XR 750 mg 2 tablets once daily then CADBOWER XR 750 mg may increase to a maximum dose of 3 tablets once daily with the evening meal.

If glycaemic control is not achieved on CADBOWER XR 750 mg 3 tablets once daily, then one tablet of CADBOWER XR 750 mg in the morning and two tablets of CADBOWER XR 750 mg in the evening should be considered. Both doses should be 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.

CADBOWER XR 1000 mg

CADBOWER XR 1000 mg is aimed as maintenance therapy for patients already treated with either 1000 mg (2 tablets of CADBOWER XR 500) or 2000 mg (4 tablets of CADBOWER XR 500) of extended release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3000 mg daily.

Switching patients already treated with metformin tablets

In patients already treated with immediate release metformin tablets, the starting dose of CADBOWER XR should be equivalent to the daily dose of metformin immediate release tablets.

In patients treated with metformin at a dose above 2000 mg daily, transferring to the extended release tablets is not recommended.

Switching patients from other oral antidiabetic agents

If switching from another oral antidiabetic medicine is intended: discontinue the other medicine and start CADBOWER XR at the dose indicated above.

Combination with insulin:

Metformin prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of CADBOWER XR is one 500 mg tablet once daily, with the evening meal, while insulin dosage is altered on the basis of blood glucose measurements. After titration, switch to CADBOWER XR 1000 mg may be considered.

Special populations

Elderly patients: due to the potential for decreased renal function in elderly subjects, the metformin dosage 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 sufficient available data, CADBOWER XR range should not be used in children.

Method of administration

CADBOWER XR should be administered with food and swallowed whole with a glass of water. CADBOWER XR should be given with the evening meal when administered once daily. The tablets should not be chewed, split or crushed.

4.3 Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
- Renal dysfunction or failure (creatinine clearance < 60 ml/min, GFR , 30 mL/min).
- Diabetic pre-coma.
- Hepatic insufficiency, alcoholism, acute alcohol intoxication
- Acute conditions with the potential to alter renal function such as: intravascular administration of iodinated contrast media, dehydration, shock and severe infection
- Acute or chronic disease which may cause tissue hypoxia such as: shock, pancreatitis, cardiac or respiratory failure, recent myocardial infarction.
- Any acute metabolic acidosis (diabetic ketoacidosis. Lactic acidosis)
- The use of CADBOWER XR during pregnancy is not advised.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a serious metabolic complication that has a high mortality in the absence of prompt treatment, that can occur due to metformin accumulation. Lactic acidosis is a medical emergency that must be treated in hospital. When patients present with a metabolic acidosis and do not have evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and CADBOWER XR range therapy should be stopped.

Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure.

As CADBOWER XR is excreted by the kidney; regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, prolonged fasting, excessive alcohol intake, ketosis, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma.

Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:

- at least two to four times annually in elderly subjects and in patients with creatinine clearance levels at the limit of normal.
- at least annually in patients with normal renal function.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special care should be employed in situations where renal function may become impaired, for example when initiating diuretic therapy or antihypertensive therapy and when starting therapy with an nonsteroidal anti-inflammatory drug (NSAID).

Therapy should be stopped 2-3 days before clinical investigations and surgery such as intravenous urography and intravenous angiography. Treatment can be reinstated only after control of renal function has been regained.

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

For Patients on long-term treatment with CADBOWER XR they should have an annual estimation of vitamin B12 levels, as CADBOWER XR may cause mal-absorption of vitamin B12. This could result in megaloblastic anaemia.

Elderly:

Due to the limited efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, CADBOWER XR introduction is not recommended in these patients.

Cardiac function:

Patients with heart failure are more at risk of renal insufficiency and hypoxia.

For patients with heart failure, CADBOWER XR is contraindicated. (See section 4.3).

Administration of iodinated contrast media:

The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may lead to metformin accumulation and risk of lactic acidosis. CADBOWER XR must be discontinued prior to, or at the time of the test and not started until 48 hours after, and renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery:

CADBOWER XR should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition provided normal renal function has been established.

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

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.

Metformin 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).

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

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not recommended

Alcohol

Acute alcohol intoxication is associated with an increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition
- hepatic insufficiency.

Avoid consumption of alcohol-containing medications and alcohol.

Iodinated contrast media

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. CADBOWER XR must be discontinued prior to, or at the time of the test and not restarted until 48 hours afterwards, and after renal function has been re-evaluated and found to be normal (see section 4.4).

Combinations requiring precautions for use

Medicines with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes), sympathomimetics (Beta-2-agonists) and diuretics). More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other medicines and upon its discontinuation.

Some medicines can negatively affect renal function which may increase the risk of lactic acidosis, e.g. including selective cyclo-oxygenase (COX) II inhibitors, NSAIDs, ACE inhibitors, diuretics (especially loop diuretics) and angiotensin II receptor antagonists. Close monitoring of renal function is necessary when initiating or using such products in combination with CADBOWER XR.

Cimetidine

Reduced renal clearance of CADBOWER XR has been reported during cimetidine therapy, a dose reduction can be considered.

Sulphonylurea

Concomitant therapy of CADBOWER XR with sulphonylurea may cause hypoglycaemia.

ACE-inhibitors

May decrease the blood glucose levels. The dosage of the antidiabetic medicine should be adjusted during therapy with the other medicine and upon its discontinuation, if necessary.

Anticoagulants

CADBOWER XR has been reported to decrease the activity of warfarin, and dose adjustments and increased frequency of INR determinations should be considered.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Combination therapy of CADBOWER XR 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 dolutegravir, trimethoprim, ranolazine, cimetidine, vandetanib, isavuconazole) may reduce the renal elimination of CADBOWER XR and lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may effect the efficacy and renal elimination of metformin.

Vigilance is therefore advised, specifically in patients with renal impairment, when these medicines are co-administered with CADBOWER XR, as metformin plasma concentration may increase. If required, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Vitamins

Long-term treatment with CADBOWER XR may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of CADBOWER XR should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of CADBOWER XR during pregnancy is not advised (See section 4.3).

Uncontrolled diabetes during pregnancy (permanent or gestational) is associated with increased risk of perinatal mortality and congenital abnormalities.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, fetal or embryonic development, postnatal or parturition development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breastfeeding

Metformin 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 CADBOWER XR treatment.

Fertility

Fertility female or male rats was unaffected by metformin when given 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

CADBOWER XR 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. sulphonylureas, insulin, or meglitinides).

4.8 Undesirable effects

a. Summary of the safety profile

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin Hydrochloride was similar in nature and severity to that reported in patients treated with Metformin Hydrochloride immediate release. During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Less frequent	Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Concern of such aetiology is recommended if a patient poses with megaloblastic anaemia. Lactic acidosis
Nervous system disorders	Frequent	Taste disturbance
Gastrointestinal disorders	Frequent	Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.
Hepato-biliary disorders	Less Frequent	Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders	Less Frequent	Skin reactions such as erythema, urticaria, pruritus

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

Concomitant use of CADBOWER XR range with a sulphonylurea, insulin or alcohol can cause hypoglycaemia. Lactic acidosis may develop in excessive dosage, and particularly if there is a possibility of accumulation. Intense supportive and symptomatic therapy is recommended. Therapy should be particularly directed at correcting blood glucose levels and correcting fluid loss.

Treatment of overdosage

There is no specific antidote for overdose with CADBOWER XR range. Treatment is symptomatic and supportive. It should be directed at correcting fluid loss and metabolic disturbances. Haemodialysis is the most effective way to remove metformin and lactate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A21.2 Oral hypoglycaemics

Metformin is a biguanide with antihyperglycaemic effects, lowering both postprandial glucose and basal plasma. 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 glycogenolysis and gluconeogenesis
- delay of intestinal glucose absorption
- and in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels (Cmax) are achieved with a median value of 7 hours, following a single oral dose of CADBOWER XR 500 mg. A mean plasma concentration of 1193 ng/ml is achieved after a median value of 5 hours (range of 4 to 12 hours), following a single oral dose of 1500 mg of CADBOWER XR 750 mg.

A mean peak plasma concentration of 1214 ng/ml is achieved after a median time of 5 hours (range of 4 to 10 hours), following a single oral administration in the fed state of one tablet of CADBOWER XR 1000 mg.

Both Cmax and AUC of metformin at steady-state, do not increase proportionally to the administered dose.

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

Relative to intake in the fasting state the AUC is increased by 77 %, Cmax is increased by 26 % and Tmax is slightly prolonged by about 1 hour when the 1000 mg metformin prolonged release tablet is administered in fed conditions. Although. It is presumed, as there is no information on the exposure after the 500 mg and 750 mg prolonged release tablets, that similar increased exposure occurs when given in the fed-state.

Distribution

Plasma protein binding is insignificant. Metformin partitions into erythrocytes. The plasma peak is higher than the blood peak and appears at approximately the same time. The red blood cells most likely correspond to a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation

Metformin is excreted unaffected in the urine. No metabolites have been recognised in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, signifying that metformin is eliminated by tubular secretion and glomerular filtration. After an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is reduced in proportion to that of creatinine. Therefore, there is an increased level of metformin in plasma as the elimination half-life is prolonged.

5.3 Preclinical safety data

Preclinical data reveal no special exposure for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, silica colloidal anhydrous, polyvinyl pyrrolidone - K30, hypromellose.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Tablets are supplied in transparent PVC/Aluminium blister packs containing 28 or 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road

Midrand

1686

8 REGISTRATION NUMBER(S)

CADBOWER XR 500: 49/21.2/0251

CADBOWER XR 750: 49/21.2/0252

CADBOWER XR 1000: 49/21.2/0253

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2021

10 DATE OF REVISION OF THE TEXT

N.A.

METXR/PI/A