1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

METRYXA 500 mg XR (film-coated tablet)

METRYXA 750 mg XR (film-coated tablet)

METRYXA 1000 mg XR (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METRYXA 500 mg XR:

Each extended - release tablet contains metformin hydrochloride 500 mg.

METRYXA 750 mg XR:

Each extended - release tablet contains metformin hydrochloride 750 mg.

METRYXA 1000 mg XR:

Each extended - release tablet contains metformin hydrochloride 1000 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

METRYXA 500 mg XR:

White, Oval shaped, film coated tablets, debossed “MT” on one side and “500” on other side.

METRYXA 750 mg XR:

White, Oval shaped, film coated tablets, debossed “MT” on one side and “750” on other side.

METRYXA 1000 mg XR:

White, Oval shaped, film coated tablets, debossed “MT” on one side and “1000” 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 does not result in adequate glycaemic control. **METRYXA 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

METRYXA 500 mg XR:

The usual starting dose is one tablet daily given with the evening meal. After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended. This should be done gradually to 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 **METRYXA 500 mg XR** 4 tablets once daily, **METRYXA 500 mg XR** 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.

METRYXA 750 mg XR:

The usual starting dose is one tablet daily. After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended. This should be done gradually to improve

gastro-intestinal tolerability. The recommended dosage is 2 tablets once daily, with an evening meal. If glycaemic control is not achieved with **METRYXA 750 mg XR** 2 tablets once daily, **METRYXA 750 mg XR** may be increased to a maximum dose of 3 tablets once daily with the evening meal. If glycaemic control is not achieved with **METRYXA 750 mg XR** 3 tablets once daily, one tablet of **METRYXA 750 mg XR** in the morning and two tablets of **METRYXA 750 mg XR** 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.

METRYXA 1000 mg XR:

METRYXA 1000 mg XR is intended as maintenance therapy for patients already treated with either 1 000 mg (2 tablets of METRYXA 500 mg XR) or 2 000 mg (4 tablets of METRYXA 500 mg XR). 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 **METRYXA 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 daily, switching to **METRYXA XR** tablets 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 **METRYXA XR** prolonged release tablets at the doses indicated above.

Combination therapy with insulin:

METRYXA XR prolonged release tablets and insulin may be used in combination therapy to

achieve better blood glucose control. The usual starting dose is **METRYXA 500 mg XR** once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switching to **METRYXA 1000 mg XR** may be considered.

Other combination therapy: See section 4.4

It is recommended to regularly monitor (every 3-6 months) the glycaemic status as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.

Special Populations

Elderly population

Due to the potential for decreased renal function in elderly subjects, the dosage for **METRYXA XR** should be adjusted based on renal function. Regular assessment of renal function is necessary.

Paediatric population

In the absence of available data, **METRYXA XR** should not be used in children.

Method of administration

For oral use:

METRYXA XR should be taken with food.

4.3. Contraindications

- Hypersensitivity to metformin hydrochloride or any of the other ingredients as listed in section 6.1.
- 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 **METRYXA XR** during pregnancy is not advised.

4.4. Special warnings and precautions for use

- All patients should implement improvements to diet and/or exercise, with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- Patients should be regularly monitored in order to adjust and calibrate treatment and dosages accordingly.

Lactic acidosis

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to **METRYXA XR** administration. In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and **METRYXA XR** range therapy should be stopped. Lactic acidosis is a medical emergency, which must be treated in hospital.

METRYXA 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 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

METRYXA XR, obtain an estimated glomerular filtration rate (eGFR).

- **METRYXA XR** is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.
- Initiation of **METRYXA 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 **METRYXA 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 **METRYXA XR** whose eGFR falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.
- Interactions — Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in **METRYXA XR**-treated 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 **METRYXA 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 **METRYXA 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 **METRYXA XR**.

Diagnosis: Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Metformin Teva ER and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

METRYXA XR is excreted by the kidney and must not be used in patients with renal failure or renal dysfunction (creatinine clearance < 60 mL/min) (see section 4.3).
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.

Due to the potential for decreased renal function in elderly subjects, the dosage for **METRYXA XR** should be adjusted based on renal function. 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 **METRYXA 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 **METRYXA XR** formulations should have an annual estimation of vitamin B12 levels, since **METRYXA XR** range may cause mal-absorption of vitamin B12, which may result in megaloblastic anaemia.

Surgery

METRYXA XR should be discontinued 48 hours before elective surgery with general anaesthesia, and reinstated only after control of renal function has been regained.

Administration of iodinated contrast medicines:

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. **METRYXA XR** should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Concomitant medicines

In order to avoid hypoglycaemia, caution is advised when Metformin Teva ER is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides). Blood glucose should be monitored. Stabilisation of diabetic patients with **METRYXA 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 **METRYXA XR** accumulation and a risk of lactic acidosis. **METRYXA 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 **METRYXA XR** has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: **METRYXA 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 **METRYXA XR** with sulphonylurea may cause hypoglycaemia (see section 4.4).

Vitamins: Long-term treatment with **METRYXA XR** may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of **METRYXA 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 **METRYXA XR** may increase the risk for lactic acidosis.

Medicines that reduce METRYXA 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.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of **METRYXA XR** with

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

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

Breast-feeding

Metformin is excreted into human breast milk. Breastfeeding is not recommended during metformin treatment.

Fertility

Fertility of male or female rats was unaffected by metformin when administered 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

METRYXA XR range therapy on its own has no effect on the ability to drive or to use machines. Care should however be taken when **METRYXA 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

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 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 **METRYXA 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 **METRYXA XR** 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Hypoglycaemia can occur when **METRYXA 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.

High overdose or concomitant risks of **METRYXA XR** may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Treatment of overdosage

There is no specific antidote for overdose with **METRYXA 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

Pharmacological classification*:* A 21.2 Oral hypoglycaemics

ATC code: A10BA02 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.

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

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2,5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2 000 mg of metformin prolonged release tablets is similar to that observed after administration of 1 000 mg of metformin immediate release tablets twice daily.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30 % (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2 000 mg of metformin as prolonged release tablets.

Following a single oral dose of **METRYXA 500 mg XR** peak plasma levels (Cmax) are achieved with a median value of 7 hours.

Following a single oral dose of 1 500 mg of **METRYXA 750 mg XR**, a mean peak plasma concentration of 1 193 ng/mL is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Following a single oral dose in the fed state of one tablet of **METRYXA 1000 mg XR**, a mean peak plasma concentration of 1 214 ng/mL is achieved with a median time of 5 hours (range of 4 to 10 hours).

When the 1 000 mg 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 1 hour).

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

hypromellose K-100 M, povidone K-30, purified water, colloidal anhydrous silica, hypromellose K-15 M, magnesium stearate, opadry OY-7300

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 OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

BLISTER: Multiple blisters may be packed in a varnished, printed cardboard carton.

METRYXA XR (all strengths) are presented in clear, transparent PVC/PVDC and Aluminium foil blister packs.

Keep the blisters in the carton until required for use.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

Unimed Healthcare (Pty) Ltd

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8 REGISTRATION NUMBERS

METRYXA 500 mg XR: 58/21.2/0193.190

METRYXA 750 mg XR: 58/21.2/0194.191

METRYXA 1000 mg XR: 58/21.2/0195.192

9 DATE OF FIRST AUTHORISATION

22 May 2026

10 DATE OF REVISION OF TEXT