1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

FORTESE XR 500 Extended release tablet

FORTESE XR 750 Extended release tablet

Metformin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FORTESE XR 500: Each extended release tablet contains 500 mg of metformin hydrochloride.

FORTESE XR 750: Each extended release tablet contains 750 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

Sugar-free.

3. PHARMACEUTICAL FORM

Extended release tablet.

FORTESE XR 500: White to off white, oval shaped, biconvex, tablets with 'MX500' debossed on one side and plain on other.

FORTESE XR 750: White to off white, capsule shaped tablets with 'MX750' debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

Therapeutic indications

FORTESE XR is indicated for the treatment of type 2 diabetes mellitus, particularly in overweight patient, when diet and exercise alone do not result is adequate glycaemic control. **FORTESE 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:

FORTESE XR 500: 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 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 4 tablets of **FORTESE XR 500** taken once daily, the 2 tablets of **FORTESE XR 500** taken 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.

FORTESE XR 750: 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 of the recommended dosage is 2 tablets once daily, with the evening meal. If glycaemic control is not achieved with two tablets of **FORTESE XR 750** once a day, then the daily dose **FORTESE XR 750** may be increased to a maximum dose of 3 tablets per day. If glycaemic control is not achieved with 3 tablets once daily, then dose of one tablet in the morning and two tablets in the evening should be considered, both

doses should be given with a meal. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3 000 mg daily.

Switching patients already treated with metformin tablets: In patients already treated with metformin tablets, the starting dose of **FORTESE 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 **FORTESE XR** prolonged release 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 **FORTESE XR** at the dosage indicated above.

Combination therapy with insulin: **FORTESE XR** and insulin may be: used in combination therapy to achieve better blood glucose control. The usual starting dose is **FORTESE XR 500** once daily in the evening with food, while insulin dosage is adjusted on the basis of blood glucose measurements.

Other combination therapy: See section 4.4.

Special populations:

Elderly: Due to the potential for decreased renal function in elderly subjects, the dosage for the **FORTESE XR** range should be adjusted based on renal function. Regular assessment of renal function is necessary (See section 4.4).

Paediatric population:

Children: **FORTESE XR** range should not be used in children.

Method of administration: Oral and always with food.

4.3 Contraindications

FORTESE XR is contraindicated in:

- Hypersensitivity to metformin or to any of the excipients of **FORTESE XR** listed in section 6.1.
- Children under the age of 12 years.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis and diabetic pre-coma).
- Renal failure or renal dysfunction (creatinine clearance < 60 ml/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock and intravascular administration of iodated contrast media.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, pancreatitis, recent myocardial infarction and shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardio-respiratory 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 professional is recommended. 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 care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidosis dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin 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:

GFR should be assessed before treatment initiation and regularly thereafter, see *section 4.2*. 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 medicines:

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin 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 revaluated and found to be stable, see *sections 4.2 and 4.5*.

Surgery:

Metformin must be discontinued at the time of surgery under general,

spinal or epidural anaesthesia. Therapy may be restarted no 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:

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 anti-diabetics (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:

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 medicines.

Iodinated contrast medicines:

Metformin must 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 4.4.

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 cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicines with intrinsic hyperglycaemic activity (e.g., glucocorticoids (and sympathomimetics):

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 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 **FORTESE XR** has been reported during cimetidine therapy, so dose reduction should be considered.

Anticoagulants: **FORTESE XR** has been reported to reduce the activity of warfarin, and so dose adjustments and increased frequencies of INR determinations should be considered.

Sulphonylurea: Concomitant therapy of **FORTESE XR** with sulphonylurea may cause hypoglycaemia.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety and efficacy of **FORTESE XR** has not been established. As a precaution **FORTESE XR** should not be used in pregnancy (see section 4.3).

Breast-feeding:

There is no information available concerning the safety of **FORTESE XR** during lactation, therefore breastfeeding is not recommended during metformin treatment (see section 4.3).

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

FORTESE 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 medicines (e.g., sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

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.

Adverse reactions are ranked below using the following convention: *Frequent; less frequent and frequency unknown*

Metabolism and nutrition disorders:

Less frequent: Lactic acidosis (see section 4.4). Decrease of vitamin B_{12} 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: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. A slow increase of the dose may also improve gastrointestinal tolerability.

Frequency unknown: Constipation

Renal and urinary disorders:

Frequency unknown: Ketoacidosis and ketonuria

Hepato-biliary disorders:

Less frequent: Isolated reports of liver function tests abnormalities or severe cholestatic hepatitis resolving upon metformin discontinuation.

Frequency unknown: Pancreatitis

Skin and subcutaneous tissue disorders:

Less frequent: Skin reactions such as erythema, pruritis, urticaria

Endocrine disorders:

Less frequent: hypoglycaemia

Immune system disorders:

Frequency unknown: hypersensitivity (vasculitis, pneumonitis)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals 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 Alternatively all adverse events can be reported to Alkem Laboratories via the e-mail: pharmacist.rsa@Alkem.com.

4.9 Overdose

Hypoglycaemia can occur when PN is given with a sulphonylurea, insulin or alcohol, High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. There is no specific antidote for overdose with **FORTESE XR** range. Treatment is supportive and symptomatic, and should be directed at correcting fluid loss and metabolic disturbances. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral anti-diabetics.

ATC Code: A10BA02: Gastrointestinal tract and metabolism

Pharmacological classification: A.21.2 Oral Hypoglycaemic

Metformin is a biguanide oral anti-hyperglycaemic medicine, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Its mode of action is thought to be increased peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing 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:

After an oral dose of the extended release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

Following a single oral administration of 1500 mg of metformin extended release, as 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak concentration is lower than the plasma peak concentration and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution range between 63 – 276 l/kg.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. There is no biliary excretion.

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethyl cellulose sodium

Copovidone

Hydroxy propyl methyl cellulose

Microcrystalline cellulose

Magnesium stearate

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove strip from carton until required for use. Keep bottle tightly closed. Store in the original package in order to protect from moisture.

Store all medicine out of reach of children.

6.5 Nature and contents of container

FORTESE XR 500 are packed PVC/PVDC/ aluminium blister packs of 10 tablets (inserted in a printed cardboard carton) and in HDPE bottles of 100, 500 and 1000 Tablets.

FORTESE XR 750 is packed in PVC/PVDC/ aluminium blister packs of 10 tablets (inserted in a printed cardboard carton) and in HDPE bottles of 100 and 500 Tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Alkem Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive

Block A, Office 202

Irene Ext.30, Centurion

0157

8. MARKETING AUTHORISATION NUMBER(S)

To be allocated by authority.

9. DATE OF REVISION OF THE TEXT

To be allocated by authority.