Professional Information for BIGSENS XR range

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BIGSENS XR extended release tablets

BIGSENS XR 750 extended release tablets

BIGSENS XR 1 000 extended release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended release **BIGSENS XR** tablet contains 500 mg metformin hydrochloride.

Each extended release **BIGSENS XR 750** tablet contains 750 mg metformin hydrochloride.

Each extended release **BIGSENS XR 1 000** 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.

BIGSENS XR: White to off-white, capsule shaped, uncoated tablets, debossed with ‘63’ on one side and ‘Z’ on the other side.

BIGSENS XR 750: White to off-white, capsule shaped, biconvex tablets, plain on both sides.

BIGSENS XR 1 000: White to off-white, capsule shaped, bevelled biconvex tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIGSENS XR 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. **BIGSENS XR** 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

BIGSENS XR:

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 **BIGSENS XR** given once daily, 1 000 mg (2 tablets) of **BIGSENS XR** 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.

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

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

If glycaemic control is not achieved on **BIGSENS XR 750** 3 tablets once daily, one tablet of **BIGSENS XR 750** in the morning and two tablets of **BIGSENS XR 750** 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.

BIGSENS XR 1 000:

BIGSENS XR 1 000 is intended as maintenance therapy for patients already treated with either 1 000 mg (2 tablets of 500 mg **BIGSENS XR**) or 2 000 mg (4 tablets of 500 mg **BIGSENS XR**) 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 immediate release tablets, the starting dose of **BIGSENS XR** 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 **BIGSENS XR** 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 **BIGSENS XR** at the doses indicated above.

Combination therapy with insulin:

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

Other combination therapy:

See section 4.4.

Special populations

Elderly:

Due to the potential for decreased renal function in elderly patients, the dosage for **BIGSENS XR** 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, **BIGSENS XR** 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 **BIGSENS XR** (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). **BIGSENS XR** 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

BIGSENS XR 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 **BIGSENS XR**. 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), **BIGSENS XR** 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 **BIGSENS XR** should be stopped immediately and the patient hospitalised if metabolic acidosis is suspected.

Renal function

Serum creatinine levels should be determined before treatment with **BIGSENS XR** is started and regularly thereafter, since

BIGSENS XR 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.

BIGSENS XR 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 **BIGSENS XR** 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 **BIGSENS XR** formulations should have an annual estimation

of vitamin B_{12} levels, since **BIGSENS XR** range may cause mal-absorption 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, **BIGSENS XR** may be used with regular monitoring of cardiac and renal function. **BIGSENS XR** 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 for **BIGSENS XR** 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, **BIGSENS XR** 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:

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

BIGSENS XR 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:

BIGSENS XR 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 **BIGSENS 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. 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 **BIGSENS XR** 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 **BIGSENS XR** accumulation and a risk of lactic acidosis. Treatment with **BIGSENS XR** 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 **BIGSENS XR**, close monitoring of renal function is necessary.

Glucocorticoids, beta2-agonists and diuretics:

Caution is advised when administering **BIGSENS XR** 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 **BIGSENS XR** 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 **BIGSENS XR**.
If necessary, the dosage of **BIGSENS XR** 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 **BIGSENS XR** with

- Inhibitors of OCT_1 (such as verapamil) may reduce efficacy of **BIGSENS XR**.
- Inducers of OCT_1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of **BIGSENS XR**.
- Inhibitors of OCT_2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of **BIGSENS XR** 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 **BIGSENS XR**.

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

Anticoagulants:

BIGSENS XR 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 **BIGSENS XR** is co-administered with sulphonylureas, as this combined therapy may cause hypoglycaemia.

Vitamins:

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

Paediatric population:

No data available.

4.6 Fertility, pregnancy and lactation

The use of **BIGSENS XR** 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 **BIGSENS XR** 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 **BIGSENS XR** 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

BIGSENS XR 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 **BIGSENS XR**.

4.7 Effects on ability to drive and use machines

BIGSENS XR 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 **BIGSENS XR** 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 **BIGSENS XR** discontinuation.

Skin and subcutaneous tissue disorders:

Less frequent: Erythema, pruritus and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **BIGSENS XR** is important. It allows continued monitoring of the benefit/risk balance of **BIGSENS XR**. 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 **BIGSENS XR** 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 **BIGSENS XR** 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 1500 mg of metformin extended release tablets 750 mg, a mean plasma concentration of 1193 ng/mL is achieved after a median value of 5 hours (range of 4 to 12hours). At steady-state, both C_{max} 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 C_{max} 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 **BIGSENS XR**, 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 – 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

BIGSENS XR: 48 months.

BIGSENS XR 750: 24 months.

BIGSENS XR 1 000: 24 months.

6.4 Special precautions for storage

Store at or below 25 °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.

BIGSENS XR: Pack sizes: 90, 120 or 360 tablets.

BIGSENS XR 750: Pack sizes: 60 or 90 tablets.

BIGSENS XR 1 000: 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

BIGSENS XR: 51/21.2/0683

BIGSENS XR 750: 55/21.2/0672

BIGSENS XR 1 000: 55/21.2/0673.

9. DATE OF FIRST AUTHORISATION

BIGSENS XR: 1 August 2019

BIGSENS XR 750: 18 July 2023

BIGSENS XR 1 000: 18 July 2023.

10. DATE OF REVISION OF THE TEXT