PACKAGE INSERT FOR BIGSENS 500; 850 & 1000

SCHEDULING STATUS
S3

PROPRIETARY NAME (AND DOSAGE FORM)
BIGSENS 500 (film coated tablets)
BIGSENS 850 (film coated tablets)
BIGSENS 1000 (film coated tablets)

COMPOSITION
Per film coated tablet:
BIGSENS 500: Metformin hydrochloride 500 mg
BIGSENS 850: Metformin hydrochloride 850 mg
BIGSENS 1000: Metformin hydrochloride 1000 mg

PHARMACOLOGICAL CLASSIFICATION
A.21.2 Oral Hypoglycaemic

PHARMACOLOGICAL ACTION
Metformin is a biguanide oral anti-hyperglycaemic agent. Its mode of action is thought to be increased peripheral glucose utilization mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

Absorption:
After an oral dose of metformin, T_{max} is reached in 2,5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin; following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution:
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Volume of Distribution ranged between 63-276 L.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

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.

INDICATIONS

BIGSENS is indicated for:
Type II diabetes mellitus when diet has failed and especially if the patient is overweight. **BIGSENS** can be given alone as initial therapy, or can be administered in combination with a sulphonylurea or insulin.

CONTRA-INDICATIONS

- Hypersensitivity to metformin hydrochloride or any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma, or the history thereof.
- Impaired renal function.
- Pancreatitis.
- Chronic liver disease.
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.
- Cardiac failure and recent myocardial infarction.
- Conditions associated with hypoxia.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Safety in pregnancy and lactation has not been established.
- Children - safety and efficacy have not been established.

WARNINGS

Lactic acidosis:
Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to **BIGSENS** accumulation. Reported cases of lactic acidosis in patients on **BIGSENS** have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetics, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:
Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain and hypothermia followed by 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 hospitalized immediately.

Renal function:
As **BIGSENS** is excreted by kidney, 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.

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.

The administration of **BIGSENS** may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Administration of iodinated contrast agent:
As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, **BIGSENS** 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.

Surgery:
BIGSENS should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

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.
- Although **BIGSENS** alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulphonylureas.

INTERACTIONS
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 agents:
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in **BIGSENS** accumulation and a risk of lactic acidosis.

BIGSENS 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.

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Cimetidine: Reduced renal clearance of **BIGSENS** has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: BIGSENS has been reported to diminish the activity of warfin, and so dose adjustments of **BIGSENS** should be considered.

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

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

PREGNANCY AND LACTATION
The use of **BIGSENS** during pregnancy is not advised. There is no information available concerning the safety of **BIGSENS** during lactation.

DOSAGE AND DIRECTIONS FOR USE
It is important that **BIGSENS** tablets be taken in divided doses with meals.

Adults: Initially, one 500 mg tablet three times a day, with or after food.
After 10 to 15 days the dose should be adjusted, or increased to 850 mg or 1000 mg twice daily. A slow increase in dose may improve gastro-intestinal tolerability. If control is incomplete a cautious increase in dosage to a maximum of 3 g daily is justified. Once control has been obtained it may be possible to reduce the dosage of **BIGSENS**.

Children: BIGSENS is not recommended for use in type 1 diabetes mellitus.

Elderly: BIGSENS is indicated in the elderly, but not when renal function is impaired (see **"SPECIAL PRECAUTIONS"**).

Combination therapy: see **"SPECIAL PRECAUTIONS"**.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
SIDE EFFECTS:
Blood and the lymphatic system disorders:

Less frequent: Megaloblastic anaemia.

Nervous system disorders:
Frequent: Metallic taste.

Gastro-intestinal disorders:
Frequent: Anorexia, nausea, vomiting, constipation, and diarrhoea.

Renal and urinary disorders:
Less frequent: Ketoacidosis and ketonuria.

Hepato-biliary disorders:
Less frequent: Severe cholestatic hepatitis.

General disorders:
Less frequent: Hypersensitivity, hypoglycaemia.

SPECIAL PRECAUTIONS:
LACTIC ACIDOSIS ASSOCIATED WITH THE USE OF BIGSENS. IN PATIENTS WITH A METABOLIC ACIDOSIS AND NOT HAVING EVIDENCE OF KETOACIDOSIS (KETONURIA AND KETONAEMIA), LACTIC ACIDOSIS SHOULD BE SUSPECTED AND BIGSENS THERAPY STOPPED. LACTIC ACIDOSIS IS A MEDICAL EMERGENCY, WHICH MUST BE TREATED IN HOSPITAL.
BIGSENS IS EXCRETED BY THE KIDNEY AND REGULAR MONITORING OF RENAL FUNCTION IS ADVISED IN ALL DIABETICS. BIGSENS 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 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 SHOULD HAVE AN ANNUAL ESTIMATION OF VITAMIN B12 LEVELS, SINCE BIGSENS MAY CAUSE MALABSORPTION OF VITAMIN B12, WHICH MAY RESULT IN MEGALOBLASTIC ANAEMIA. DURING CONCOMITANT TREATMENT WITH A SULPHONYLUREA, BLOOD GLUCOSE SHOULD BE MONITORED BECAUSE COMBINED THERAPY MAY CAUSE HYPOGLYCAEMIA. STABILISATION OF DIABETIC PATIENTS WITH BIGSENS AND INSULIN SHOULD BE CARRIED OUT IN HOSPITAL BECAUSE OF THE POSSIBILITY OF HYPOGLYCAEMIA UNTIL THE RATIO OF THE TWO DRUGS HAS BEEN OBTAINED. CONTRAINDICATIONS SHOULD BE CAREFULLY OBSERVED.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Hypoglycaemia can occur when **BIGSENS** 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.

Treatment of overdosage:
There is no specific antidote for overdose with **BIGSENS**. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

IDENTIFICATION
BIGSENS 500 film coated tablet is a white to off-white round shaped film-coated tablet debossed with the logo of '70' on one side and 'Z' on the other side.
BIGSENS 850 film coated tablet is a white to off-white oval shaped film-coated tablet debossed with the logo of '69' on one side and 'Z' on the other side.
BIGSENS 1000 film coated tablet is a white to off-white, oval shaped, biconvex, film-coated tablet with bisect on both sides; one side of the bisect is debossed with 'Z' and other side of the bisect is debossed with '71'.

PRESENTATION
BIGSENS 500 film coated tablets are packed as 56, 84, 100 and 500 tablets in white HDPE containers with white PP child resistant caps.
BIGSENS 850 film coated tablets are packed as 56, 60 and 300 tablets in white HDPE containers with white PP child resistant caps.
BIGSENS 1000 film coated tablets are packed as 60, 100, 500 and 1000 tablets in white HDPE containers with white PP child resistant caps.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
Store in the original package to protect from light and moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
BIGSENS 500 film coated tablets: 39/21.2/0638
BIGSENS 850 film coated tablets: 39/21.2/0639
BIGSENS 1000 film coated tablets: 41/21.2/0193

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