Approved 14/08/2020

SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):
METFORMIN 500 STRIDES (Tablets)
METFORMIN 850 STRIDES (Tablets)
METFORMIN 1000 STRIDES (Tablets)

COMPOSITION:
METFORMIN 500 STRIDES: Each film-coated tablet contains metformin hydrochloride 500 mg.
METFORMIN 850 STRIDES: Each film-coated tablet contains metformin hydrochloride 850 mg.
METFORMIN 1000 STRIDES: Each film-coated tablet contains metformin hydrochloride 1000 mg.

PHARMACOLOGICAL CLASSIFICATION:
A 21.2 Oral hypoglycaemic agents.

PHARMACOLOGICAL ACTION:
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin has no significant effects on the secretion of glucagons, cortisol, growth hormone, or somatostatin.

Metformin may act via 3 mechanisms:
1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of intestinal glucose absorption.

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 is 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 µ/ml. Maximum metformin plasma levels (C_{max}) do not exceed 4 µ/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, 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 ranges 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.

Paediatrics:
After single doses of metformin 500 mg paediatric patients show similar pharmacokinetic profiles to that observed in healthy adults.

INDICATIONS:
METFORMIN STRIDES is indicated for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.
- In adults, **METFORMIN STRIDES** film-coated tablets may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.
- In children over 12 years of age and adolescents with type 2 diabetes, **METFORMIN STRIDES** film-coated tablets may be used as monotherapy or in combination with insulin.

CONTRA-INDICATIONS:
METFORMIN STRIDES is contra-indicated in the following:
- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis and diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females).
- Acute conditions with the potential to alter renal function, such as:
- Dehydration.
- Severe infection.
- Shock.
- Intravascular administration of iodinated contrast agents (see **"WARNINGS"** and **"Special Precautions"**).
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and lactation.

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 **METFORMIN STRIDES** accumulation. Reported cases of lactic acidosis in patients on **METFORMIN STRIDES** have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Diagnosis:
Lactic acidosis is characterised 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 STRIDES** should be discontinued and the patient should be hospitalised immediately.

Renal function:
As **METFORMIN STRIDES** is excreted by the 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.

Administration of iodinated contrast agents:
As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, **METFORMIN STRIDES** 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:
METFORMIN STRIDES should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents:
The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with **METFORMIN STRIDES** is initiated.

No effect of **METFORMIN STRIDES** on growth and puberty has been detected during controlled clinical studies of one-year duration, but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of **METFORMIN STRIDES** on these parameters in **METFORMIN STRIDES**-treated children, especially in prepubescent children, is recommended.

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 STRIDES** alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

INTERACTIONS:
Use of **METFORMIN STRIDES** with other medicines that lower blood glucose concentrations increases the risk of hypoglycaemia, while medicines that increase blood glucose may reduce the effect of **METFORMIN STRIDES** therapy.

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 **METFORMIN STRIDES** accumulation and a risk of lactic acidosis.
METFORMIN STRIDES 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.

Combinations requiring precautions for use:
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 medicine during therapy with the other medicine and upon its discontinuation.

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

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

An interaction between **METFORMIN STRIDES** and anticoagulants is a possibility and dosage of the latter may need adjustment.

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has net been established in humans, However, animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.
When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with **METFORMIN STRIDES**, but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

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

Adults:
Initially, one 500 mg tablet three times a day, or one 850 mg or 1000 mg tablet twice a day, with or after food. After 10 to 15 days the dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastrointestinal tolerability. Good diabetic control may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks. If control is incomplete a cautious increase in dosage to a maximum of 2550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of **METFORMIN STRIDES**.

Children and adolescents:
METFORMIN STRIDES can be used in children from 12 years of age and adolescents.
The usual starting dose is 500 mg or 850 mg once daily, given during meals or after meals. 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 of **METFORMIN STRIDES** is 2000 mg daily, taken in 2 or 3 divided doses.

Elderly:
METFORMIN STRIDES dose in the elderly should be adjusted based on renal function.

Combination therapy:
See **"Special Precautions"**.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects:
The following side-effects may occur while using **METFORMIN STRIDES**:

Blood and lymphatic system disorders:
Less Frequent: Megaloblastic anaemia.

Metabolic and nutrition disorders:
Less Frequent: Hypoglycaemia and lactic acidosis (see **"Special Precautions"**).

*The following side-effects have been reported and frequencies are unknown:*Decrease of vitamin B12 and folic acid absorption with decreased serum levels during long-term use of **METFORMIN STRIDES**. This change is generally without clinical significance.

Neuropsychiatric system disorders:
Frequent: Headache.

Gastrointestinal system disorders:
Frequent: Nausea, vomiting, diarrhoea, loss of appetite, flatulence, dyspepsia and metallic taste.
The following side-effects have been reported and frequencies are unknown: Abdominal pain.

These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that **METFORMIN STRIDES** be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders:
The following side-effects have been reported and frequencies are unknown:
Mild erythema in some hypersensitive individuals.

General disorders:
Frequent: Weight loss.

Special Precautions:
Lactic acidosis has occurred to a greater extent in patients with contra-indications to therapy. In patients with a metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia) lactic acidosis should be suspected and **METFORMIN STRIDES** therapy stopped. Lactic acidosis is a medical emergency which must be treated in hospital.

METFORMIN STRIDES is excreted by the kidney and regular monitoring of renal function is advised in all diabetics.

METFORMIN STRIDES therapy should be stopped 2-3 days before surgery and clinical investigations, such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained.
The use of **METFORMIN STRIDES** is not advised in conditions which may cause dehydration or in patients suffering from serious infections, trauma or on low calorie intake.

Patients receiving continuous **METFORMIN STRIDES** therapy should have an annual estimation of vitamin B12 levels because of reports of decreased vitamin B12 and folic acid absorption.

During concomitant therapy with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with **METFORMIN STRIDES** and insulin may be necessary to be carried out in hospital, because of the possibility of hypoglycaemia, until the correct ratio of the two medicines has been obtained.

Contra-indications should be carefully observed.

KNOWN SYMPTONS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Hypoglycaemia can occur when **METFORMIN STRIDES** 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. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and **METFORMIN STRIDES** is haemodialysis. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

IDENTIFICATION:
METFORMIN 500 STRIDES: White coloured, film-coated, round, biconvex tablets scored on one side and '500' embossed on the other side.
METFORMIN 850 STRIDES: White coloured, film-coated, round, biconvex tablets scored on one side and '850' embossed on the other side.
METFORMIN 1000 STRIDES: White capsule-shaped, biconvex, film-coated tablets having central breakline on one side and plain on the other side.

PRESENTATION:
METFORMIN 500 STRIDES: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 9 blisters (90 tablets).
METFORMIN 850 STRIDES: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 6 blisters (60 tablets).
METFORMIN 1000 STRIDES: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 6 blisters (60 tablets).

STORAGE INSTRUCTIONS:
Store at or below 25 °C.
Protect from light and moisture.
The blister should not be removed from the carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
METFORMIN 500 STRIDES: 44/21.2/0774
METFORMIN 850 STRIDES: 44/21.2/0775
METFORMIN 1000 STRIDES: 44/21.2/0776

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:
Strides Pharma SA (Pty) Ltd.
106 16th Road,
Building 2,
Midrand
1686

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
02 October 2017

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500 mm

200 mm

Front Side

Open Size: 200 x 500 mm
Folding Size:
Layout No.:
No. of folds: