PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL-METFORMIN 500 mg TABLETS

AUSTELL-METFORMIN 850 mg TABLETS

COMPOSITION

AUSTELL-METFORMIN 500 mg:

Each film coated tablet contains metformin hydrochloride 500 mg.

AUSTELL-METFORMIN 850 mg:

Each film coated tablet contains metformin hydrochloride 850 mg.

Excipients:

Tablet core:

coloidal anhydrous silica, magnesium stearate, povidone (PVPk - 30), sodium starch glycolate, starch maize

Tablet Coating:

hypromellose, macrogol 6000, propylene glycol, purified talc, titanium dioxide (E171).

CATEGORY AND CLASS

A 21.2 Oral Hypoglycaemics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

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.

Pharmacokinetic properties:

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 (Cmax) 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 in 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

AUSTELL-METFORMIN is indicated for:

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

CONTRAINDICATIONS

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic keto-acidosis, diabetic pre-coma, or the history thereof.
- Impaired renal failure 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.
- Safety and efficacy has not been established in children.

WARNINGS AND SPECIAL PRECAUTIONS

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 **AUSTELL-METFORMIN** accumulation. Reported cases of lactic acidosis in patients on **AUSTELL-METFORMIN** 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 diabetes, 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 metabolicacidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.

SPECIAL PRECAUTIONS:

Lactic acidosis associated with the use of AUSTELL-METFORMIN. In patients with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and AUSTELL-METFORMIN therapy stopped. Lactic acidosis is a medical emergency, which must be treated in hospital. AUSTELL-METFORMIN is excreted by the kidney and regular monitoring of renal function is advised in all diabetics.

AUSTELL-METFORMIN therapy should be stopped 2-3 days before surgery and before clinical investigations such as intravenousurography and intravenous angiography, and reinstatedonly after control of renal function has been regained.

The use of AUSTELL-METFORMIN 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 AUSTELL-METFORMIN should have an annual estimation of vitamin B_{12} levels, since AUSTELL-METFORMIN may cause malabsorption of vitamin B_{12} and folic acid, 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 AUSTELL-METFORMIN 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.

Renal function:

As **AUSTELL-METFORMIN** 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.

The administration of **AUSTELL-METFORMIN** 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, **AUSTELL-METFORMIN** should be discontinued prior to, or at the time of the test and not reinstituted until after 48 hours, and only after renal function has been re-evaluated and found to be normal.

Surgery:

AUSTELL-METFORMIN 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 **AUSTELL-METFORMIN** alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulfonylureas.

Effects on ability to drive and use machines

AUSTELL-METFORMIN 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 **AUSTELL-METFORMIN** is used in combination with other antidiabetic medicines (e.g. sulfonylureas, insulin or meglitinides).

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 **AUSTELL-METFORMIN** accumulation and a risk of lactic acidosis.

AUSTELL-METFORMIN should be discontinued prior to, or at the time of the test and not reinstituted until after 48 hours, and only after renal function has been re-evaluated and found to be normal.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with **AUSTELL-METFORMIN**, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the **AUSTELL-METFORMIN** dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT):

AUSTELL-METFORMIN is a substrate of both transporters OCT1 and OCT2.

Co-administration of **AUSTELL-METFORMIN** with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of **AUSTELL-METFORMIN**.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of **AUSTELL-METFORMIN**.

- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of **AUSTELL-METFORMIN** and thus lead to an increase in **AUSTELL-METFORMIN** plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of **AUSTELL-METFORMIN**.

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

Anticoagulants: AUSTELL-METFORMIN has been reported to diminish the activity of warfarin, therefore dose adjustments of **AUSTELL-METFORMIN** should be considered.

Sulphonylurea: Concomitant therapy of **AUSTELL-METFORMIN** with sulphonylurea may cause hypoglycaemia.

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

HUMAN REPRODUCTION

The use of **AUSTELL-METFORMIN** during pregnancy is not advised.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with **AUSTELL-METFORMIN** 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.

There is no information available concerning the safety of **AUSTELL-METFORMIN** during lactation.

DOSAGE AND DIRECTIONS FOR USE

It is important that **AUSTELL-METFORMIN** 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 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 **AUSTELL-METFORMIN.**

Children: AUSTELL-METFORMIN is not recommended for use in type 1 diabetes mellitus.

Elderly: AUSTELL-METFORMIN is indicated in the elderly, but not when renal function is impaired. (See WARNINGS AND SPECIAL PRECAUTIONS).

Combination therapy: see " WARNINGS AND SPECIAL PRECAUTIONS "

SIDE EFFECTS

The following side effects may occur under treatment with **AUSTELL-METFORMIN**:

Metabolism and nutrition disorders

Less Frequent: Lactic acidosis (See WARNINGS AND SPECIAL PRECAUTIONS), Decrease of vitamin B_{12} and folic acid absorption with decrease of serum levels during long-term use of **AUSTELL-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. These side effects may occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Less Frequent: Liver function tests abnormalities or hepatitis resolving upon **AUSTELL-METFORMIN** discontinuation.

Skin and subcutaneous tissue disorders

Less Frequent: Skin reactions such as erythema, pruritus, urticaria

Paediatric population

Paediatric population aged 10-16 years may experience side effects similar in nature and severity to that in adults.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Hypoglycaemia can occur when **AUSTELL-METFORMIN** 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 **AUSTELL-METFORMIN** is haemodialysis.

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 **AUSTELL-METFORMIN.** Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

IDENTIFICATION

AUSTELL-METFORMIN 500 mg:

White coloured, film coated, round, biconvex tablets with ‘500’ embossing.

AUSTELL-METFORMIN 850 mg:

White coloured, film coated, round, biconvex tablets with ‘850’ embossing.

PRESENTATION

AUSTELL-METFORMIN 500 mg:

Blister pack (Clear PVDC coated PVC film and Aluminium foil) of 10 x 10, 4 x 14 and 6 x 14 tablets.

Bulk pack (HDPE containers) of 500 tablets.

AUSTELL-METFORMIN 850 mg:

Blister pack (Clear PVDC coated PVC film and Aluminium foil) of 2 x 14, 6 x 10, 4 x 14 and 6 x 14 tablets.

Bulk pack (HDPE containers) of 300 tablets.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 ºC. Protect from light.

Keep the blisters in the carton until required for use.

Keep the container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AUSTELL-METFORMIN 500 mg: A38/21.2/0504

AUSTELL-METFORMIN 850 mg: A38/21.2/0505

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

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