Approved Professional Information for Medicines for Human Use:

METFORMIN ASCENDIS 500/850

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

METFORMIN ASCENDIS 500 mg film-coated tablets

METFORMIN ASCENDIS 850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METFORMIN ASCENDIS 500 Film-coated Tablet

Each film-coated tablet contains metformin hydrochloride 500 mg.

Contains sugar: lactose monohydrate 66,60 mg

METFORMIN ASCENDIS 850 Film-coated Tablet

Each film-coated tablet contains metformin hydrochloride 850 mg.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

METFORMIN ASCENDIS 500 film-coated tablets

Biconvex, white, film-coated tablets with a slight distinctive odour.

METFORMIN ASCENDIS 850 film-coated tablets

Biconvex, white, film-coated, round tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 ASCENDIS film-coated tablets may be used as monotherapy, or in combination with other oral anti-diabetic medicines or insulin.
- In children over 12 years of age and adolescents with type 2 diabetes, METFORMIN ASCENDIS film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin hydrochloride immediate-release as first-line therapy after diet failure.

4.2 Posology and method of administration

Posology

Monotherapy or combination with other oral antidiabetic medicines

Adults:

- Initially, one 500 mg tablet three times a day, or one 850 mg or 1 000 mg tablet twice a day, with or after meals.
- 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 2 550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of METFORMIN ASCENDIS.
- In patients receiving a high metformin dose (2000 to 3000 mg per day), it is possible to replace two METFORMIN ASCENDIS film-coated tablets with one METFROMIN ASCENDIS 1000 mg film-coated tablet.
- The maximum recommended dose of METFORMIN ASCENDIS is 3000 mg daily, taken as 3 divided doses.
- If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate metformin at the dose indicated above.

Combination with insulin

METFORMIN ASCENDIS and insulin may be used in combination therapy to achieve better blood glucose control. METFORMIN ASCENDIS is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Special populations

Elderly population

Due to the potential for decreased renal function in elderly subjects, it is recommended that the METFORMIN ASCENDIS dose be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older (see section 5.1) METFORMIN ASCENDIS initiation is therefore not recommended in these patients (see section 4.4).

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

METFORMIN ASCENDIS may be used in patients with moderate renal impairment stage 3 (creatinine clearance [CrCl] between 30 and 59 mL/min or estimated glomerular filtration rate [eGFR] between 30-59 ml/min/1,73 m^2) only in the absence of other conditions that may increase the risk of lactic acidosis (see section 4.4) and with the following dose adjustments: The starting dose is 500 mg or 850 mg METFORMIN ASCENDIS. The maximum daily dose is 1000 mg.

The renal function should be closely monitored:

- Every 3-6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1,73 m^2.
- Every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1,73 m^2.

If CrCl or eGFR fall below 30 mL/min or 30 mL/min/1,73 m^2 respectively, METFORMIN ASCENDIS must be discontinued immediately.

GFR (mL/min)	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be consideration in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated

Paediatric population

METFORMIN ASCENDIS can be used in children from 12 years of age and adolescents as monotherapy or in combination with insulin.

- 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 ASCENDIS is 2 000 mg daily, taken as 2 or 3 divided doses.

Method of administration

METFORMIN ASCENDIS is for oral administration.

It is important that METFORMIN ASCENDIS tablets be taken in divided doses with meals.

4.3 Contraindications

- Hypersensitivity to the metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Disease (especially acute disease or worsening of chronic disease) which may cause tissue hypoxia, such as unstable congestive heart failure, respiratory failure, recent myocardial infarction or shock.
- Severe renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1,73 m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection or shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

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 cardiorespiratory 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 ASCENDIS 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 ASCENDIS -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 section 4.3 and 4.5).

Patients and care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking METFORMIN ASCENDIS 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 ratios.

Renal function

GFR should be assessed before METFORMIN ASCENDIS initiation 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.

METFORMIN ASCENDIS 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 ASCENDIS may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, METFORMIN ASCENDIS is contraindicated (see section 4.3).

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in METFORMIN ASCENDIS accumulation and an increased risk of lactic acidosis. METFORMIN ASCENDIS 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 re-evaluated and found to be stable (see sections 4.2 and 4.5.)

Surgery

METFORMIN ASCENDIS 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.

Paediatric population

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with METFORMIN ASCENDIS is initiated.

No effect of METFORMIN ASCENDIS 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 ASCENDIS on these parameters in METFORMIN ASCENDIS treated children, especially prepubescent children is recommended.

Children aged between 10 and 12 years

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of METFORMIN ASCENDIS in these children did not differ from efficacy and safety in older children and adolescents, particular cautions is recommended when prescribing to children aged between 10 and 12 years.

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 ASSENDIS may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing METFORMIN ASCENDIS dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should

be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency.

METFORMIN ASCENDIS therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

METFORMIN ASCENDIS alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

Excipient lactose

This medicine contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 or malnutrition or hepatic impairment.

Iodinated contrast agents

METFORMIN ASCENDIS must be discontinued prior to, or at the time of the imaging procedure and not restarted until 48 hours after provided that renal function has been re-evaluated and found to be stable~~,~~ (see section 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 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 METFORMIN ASCENDIS, close monitoring of renal function is necessary.

Medicines 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 METFORMIN ASCENDIS dosage during therapy with the respective medicines and upon its discontinuation.

Organic cation transporters (OCT)

METFORMIN ASCENDIS is a substrate of both transporters OCT1 and OCT2.

Co-administration of METFORMIN ASCENDIS with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased congenital abnormalities and perinatal mortality.

A limited amount of data from the use of METFORMIN ASCENDIS in pregnant women does not indicate an increased risk of congenital abnormalities.

Safety in pregnancy has not 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 ASCENDIS 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.

Breastfeeding

METFORMIN ASCENDIS is excreted into milk in lactating rats.

METFORMIN ASCENDIS is excreted into human breast milk in very small amounts. No adverse effects were observed in breastfed newborns/infants.

However, as only limited data are available, breast-feeding is not recommended during METFORMIN ASCENDIS treatment.

A decision on whether to discontinue breast-feeding or to discontinue METFORMIN ASCENDIS needs to take into account the benefit of breast-feeding, the importance of the medicinal product to the mother, and the potential risk of adverse effects in the infant.

Fertility

Fertility of male or female rats was unaffected by METFORMIN ASCENDIS 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

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

4.8 Undesirable effects

a) Summary of the safety profile

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with metformin hydrochloride.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Metabolism and nutrition disorders	Vitamin B12 decrease/deficiency (see section 4.4)	--	Lactic acidosis (see section 4.4)
Nervous system disorders	Taste disturbance	--	--

Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that METFORMIN ASCENDIS 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	--	Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.	--

Skin and subcutaneous tissue disorders	--	Skin reaction such as erythema, pruritis, urticaria	--

c. Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

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 Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Signs and symptoms

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of METFORMIN ASCENDIS or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and METFORMIN ASCENDIS is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 21.2 Oral Hypoglycaemic

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides

ATC Code: A10BA02

Mechanism of 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 may act via 3 mechanism:

(1) Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
(2) In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
(3) 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 (GLUTs) known to date.

5.2 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 ASCENDIS 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 ASCENDIS 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 5 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 litres.

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.

Paediatric population

Single dose study: After single doses of METFORMIN ASCENDIS 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

METFORMIN ASCENDIS 500:

Core tablet

colloidal silicon dioxide,

gelatine,

lactose monohydrate,

magnesium stearate,

sodium starch glycolate

Film-coating

isopropyl alcohol

Opadry white consisting of:

hypromellose

titanium dioxide

ethyl cellulose

diethyl phthalate

METFORMIN ASCENDIS 850:

Core tablet

colloidal silicon dioxide,

magnesium stearate,

maize starch,

povidone K-30

sodium starch glycolate

Film-coating

Opadry white consisting of:

hypromellose

purified Talc

titanium dioxide

propylene glycol

polyethylene glycol/macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package to protect from light and moisture.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

METFORMIN ASCENDIS 500**:**

10 Tablets are packed in aluminium and clear PVC blister strips. Ten blister strips are packed in an outer carton.

Alternatively, 14 tablets are packed in aluminium and clear PVC blister strips. Two/four/six/eight blister strips are packed in an outer carton or 28, 56 or 84 tablets are packed in Patient Ready Pack Pouches (for state tender purposes only).

500 tablets are packed in white HDPE containers with white PP child resistant caps or white HDPE screw-on caps.

METFORMIN ASCENDIS 850**:**

10 Tablets are packed in aluminium and clear PVC blister strips. Six blister strips are packed in an outer carton.

Alternatively, 14 tablets are packed in aluminium and clear PVC blister strips. Two/four/six blister strips are packed in an outer carton or 28, 56 or 84 tablets are packed in Patient Ready Pack Pouches (for state tender purposes only).

300 tablets are packed in white HDPE containers with white PP child resistant caps or white HDPE screw-on caps.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

METFORMIN ASCENDIS 500 film-coated tablets**:** 40/21.2/0466

METFORMIN ASCENDIS 850 film-coated tablets**:** 40/21.2/0467

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

METFORMIN ASCENDIS 500: 05 May 2016

METFORMIN ASCENDIS 850: 18 March 2016

10. DATE OF REVISION OF THE TEXT

25 July 2024