APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CARBUCE 500 (Film-coated tablets)

CARBUCE 850 (Film-coated tablets)

CARBUCE 1000 (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CARBUCE 500: Each film-coated tablet contains metformin hydrochloride 500 mg.

CARBUCE 850: Each film-coated tablet contains metformin hydrochloride 850 mg.

CARBUCE 1000: Each film-coated tablet contains metformin hydrochloride 1 000 mg.

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

CARBUCE 500: White coloured, intact film-coated, round, biconvex tablets scored on one side and ‘500’ debossed on the other side.

CARBUCE 850: White coloured, intact film-coated, round, biconvex tablets plain on one side and ‘850’ debossed on the other side.

CARBUCE 1000: White capsule-shaped, biconvex, intact film-coated tablets having central breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARBUCE 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, **CARBUCE** 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, **CARBUCE** film-coated tablets may be used as monotherapy or in combination with insulin.

4.2 Posology and method of administration

Posology

It is important that **CARBUCE** tablets be taken in divided doses with meals.

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 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 2 550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of **CARBUCE**.

Special Dosage Instructions:

Children and adolescents:

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with **CARBUCE** is initiated.

CARBUCE 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 **CARBUCE** is 2 000 mg daily, taken in 2 or 3 divided doses.

Elderly:

CARBUCE dose in the elderly should be adjusted based on renal function.

Patients with renal impairment:

As **CARBUCE** 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.

4.3 Contraindications

CARBUCE 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 section 4.4**).

- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to **CARBUCE** accumulation. Reported cases of lactic acidosis in patients on **CARBUCE** 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, **CARBUCE** should be discontinued and the patient should be hospitalised immediately.

Renal impairment:

As **CARBUCE** is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

Administration of iodinated contrast agents:

As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, **CARBUCE** 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:

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

No effect of **CARBUCE** 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 **CARBUCE** on these parameters in **CARBUCE**-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.
- **CARBUCE** alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

4.5 Interaction with other medicines and other forms of interaction

Use of **CARBUCE** with other medicines that lower blood glucose concentrations increases the risk of hypoglycaemia, while medicines that increase blood glucose may reduce the effect of **CARBUCE** 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 **CARBUCE** accumulation and a risk of lactic acidosis.

CARBUCE 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 **CARBUCE** has been reported during cimetidine therapy, so a dose reduction should be considered.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

CARBUCE is contra-indicated in pregnancy (**see section 4.3**).

Breastfeeding

CARBUCE is contra-indicated in breastfeeding (**see section 4.3**).

Fertility

No data on fertility is available.

4.7 Effects on ability to drive and use machines

CARBUCE has no influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less Frequent	Megaloblastic anaemia.
Metabolism and nutrition disorders	Less Frequent	Hypoglycaemia and lactic acidosis
	Unknown	Decrease of vitamin B12 and folic

MedDRA system organ class	**Frequency**	**Adverse reactions**
		acid absorption with decreased serum levels
Nervous system disorders	Frequent	Headache
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, loss of appetite, flatulence, dyspepsia and metallic taste.
	Unknown	Abdominal pain
Skin and subcutaneous tissue disorders	Unknown	Mild erythema in some hypersensitive individuals
General disorders and administration site conditions	Frequent	Weight loss

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

The applicant can be reached at the following contact number: 010 045 2500.

4.9 Overdose

Hypoglycaemia can occur when **CARBUCE** 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 **CARBUCE** is haemodialysis. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.2 Oral hypoglycaemics.

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins. 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 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.

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 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.

Biotransformation:

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.

5.2 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal Silica

Hypromellose

Macrogol 6000

Magnesium stearate

Maize starch

Povidone PVP K-30

Propylene glycol

Purified Talc

Sodium starch Glycolate

Titanium dioxide (CI no. 77891)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from light and moisture.

The blister should not be removed from the carton until required for use.

6.5 Nature and contents of container

CARBUCE 500: Tablets are packed in transparent/colourless PVC/PE/PVDC/aluminium blisters containing 56, 84, 90 or 112 film-coated tablets. The blister strips are packed in a printed carton.

CARBUCE 850: Tablets are packed in transparent/colourless PVC/PE/PVDC/aluminium blisters containing 28, 56, 60 or 84 film-coated tablets. The blister strips are packed in a printed carton.

CARBUCE 1000: Tablets are packed in transparent/colourless PVC/PE/PVDC/aluminium blisters containing 60 film-coated tablets. The blister strips are packed in a printed carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd.

106 16th Road,

Building 2, Midrand

1685

8. REGISTRATION NUMBER(S)

CARBUCE 500: 44/21.2/0774

CARBUCE 850: 44/21.2/0775

CARBUCE 1000: 44/21.2/0776

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

18 November 2022