PROFESSIONAL INFORMATION FOR

DIAPHAGE 500 / 850 / 1000

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIAPHAGE 500 (500 mg, film-coated tablet)

DIAPHAGE 850 (850 mg, film-coated tablet)

DIAPHAGE 1000 (1000 mg, film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIAPHAGE 500: each film-coated tablet contains metformin hydrochloride 500 mg.

Sugar free.

DIAPHAGE 850: each film-coated tablet contains metformin hydrochloride 850 mg.

Sugar free.

DIAPHAGE 1000: each film-coated tablet contains metformin hydrochloride 1000 mg.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

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

DIAPHAGE 850: white-coloured, intact film-coated, round, biconvex tablets scored on one side and ‘850’ embossed on the other side.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIAPHAGE 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, DIAPHAGE 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, DIAPHAGE 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 DIAPHAGE tablets be taken in divided doses with meals.

Adults

Initially, one 500 mg tablet two to 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 2250 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of DIAPHAGE.

Combination therapy

See **section 4.4**

Elderly

DIAPHAGE dose in the elderly should be adjusted based on renal function (see **section 4.4**).

Paediatric population

Children and adolescents

DIAPHAGE 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 DIAPHAGE is 2000 mg daily, taken in 2 or 3 divided doses.

Method of administration

To be taken orally.

Gastrointestinal disorders occur most frequently during initiation of therapy. To prevent them, it is recommended that DIAPHAGE be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve the gastrointestinal tolerability.

4.3 Contraindications

DIAPHAGE is contraindicated in the following:

- Hypersensitivity to metformin hydrochloride or to any of the excipients of DIAPHAGE (see **section 6.1**).

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Renal impairment (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females), severe renal failure (GFR < 30 mL/min)
- 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**).
- Acute or chronic disease which may cause tissue hypoxia, such as:
    - Cardiac or respiratory failure.
    - Recent myocardial infarction.
    - Shock.
    - Pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and lactation.
- Children with type 1 diabetes mellitus

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a rare but serious metabolic complication which most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. DIAPHAGE 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), DIAPHAGE should be temporarily discontinued and contact with a healthcare professional is recommended.

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in DIAPHAGE-treated patients.

Other risk factors for lactic acidosis are inadequately controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia, as well as concomitant use of medicines that may cause lactic acidosis (see **sections 4.3** and **4.5**).

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking DIAPHAGE and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Renal function

As DIAPHAGE is excreted by the kidneys, 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.

Regular monitoring of renal function is advised in all diabetics.

Decreased renal function in elderly subjects is frequent and asymptomatic.

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

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency.

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

Administration of iodinated contrast medicine

Intravascular administration of iodinated contrast materials may lead to contrast induced nephropathy, resulting in DIAPHAGE accumulation and an increased risk of lactic acidosis. DIAPHAGE should be discontinued prior to, or at the time of the imaging procedure and not re-instituted until at least 48 hours afterwards, provided that renal function has been re-evaluated and found to be stable, see **section 4.5**.

Surgery

DIAPHAGE should be discontinued 48 hours before elective surgery with 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.

DIAPHAGE therapy should be stopped 2 to 3 days before clinical investigations such as intravenous urography and intravenous angiography and reinstated only after control of renal function has been regained.

Children and adolescents

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

No effect of DIAPHAGE 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 DIAPHAGE on these parameters in DIAPHAGE treated children, especially pre-pubescent 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.

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

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with DIAPHAGE and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained. Contraindications should be carefully observed.

The use of DIAPHAGE is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake (see **section 4.3**).

Patients on long-term treatment with DIAPHAGE should have an annual estimation of Vitamin B12 levels, since DIAPHAGE may cause mal absorption of Vitamin B12, which may result in megaloblastic anaemia (see **section 4.8**).

4.5 Interaction with other medicines and other forms of interaction

Use of DIAPHAGE with other medicines that lower blood glucose concentrations increases the risk of hypoglycaemia, while medicines that increase blood glucose may reduce the effect of DIAPHAGE 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.

Iodated contrast agents

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

DIAPHAGE 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

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, 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 dosage of DIAPHAGE during therapy with the respective medicine and upon its discontinuation.

Organic Cation Transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of DIAPHAGE 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, trimethoprim, 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 DIAPHAGE, as metformin plasma concentration may increase. If needed, dose adjustment of DIAPHAGE may be considered as OCT inhibitors/inducers may alter the efficacy of DIAPHAGE.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with DIAPHAGE, 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.

Pregnancy

The use of DIAPHAGE in pregnancy is contraindicated. Safety in pregnancy has not been established in humans.

Breastfeeding

The use of DIAPHAGE in lactation is contraindicated. Safety and lactation has not been established in humans.

Metformin (DIAPHAGE) crosses the placenta and is distributed into breast milk in small amounts. Patients using DIAPHAGE should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

Patients should be alerted to the risk of hypoglycaemia when DIAPHAGE is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

a. Summary of the safety profile

During treatment initiation, the most frequent adverse reactions are nausea, vomiting, diarrhea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take DIAPHAGE in 2 or 3 daily doses and to increase the doses slowly.

b. Tabulated list of adverse reactions

MedDRA system organ class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Megaloblastic anaemia
Immune system disorders	Less frequent	Hypersensitivity
Metabolic and nutrition disorders	Frequent	Decrease of vitamin B12 and folic acid absorption (see **section 4.4**)
	Less frequent	Hypoglycaemia, lactic acidosis (see **section 4.4**).
Nervous system disorders	Frequent	Headache, taste disturbance
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation, diarrhoea, abdominal pain, loss of appetite (anorexia), flatulence, dyspepsia and metallic taste.
Hepato-biliary disorders	Frequency unknown	Liver function abnormalities, severe cholestatic hepatitis or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders	Less frequent	Skin reactions such as erythema, pruritus, urticaria.
General disorders	Frequent	Weight loss
Investigations	Less frequent	Hypoglycameia

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 "Adverse drug reactions and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ and to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Hypoglycaemia can occur when DIAPHAGE 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 DIAPHAGE 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 hypoglycaemic agents

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.

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.

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 tablet is approximately 50 to 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces is 20 to 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. Maximum metformin plasma levels (C_{max}) do 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, 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 concentration is lower than the plasma peak concentration 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 to 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.

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Colloidal anhydrous silica (Aerosil 200)

Magnesium stearate

Maize Starch

Povidone (PVP K-30)

Sodium starch glycollate (Primojel, Type A)

Film coating

Hypromellose

Polyethylene glycol (Macrogol 6000)

Propylene glycol

Purified talc

Titanium dioxide (CI no. 77891)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Store at or below 25 °C.
- 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

DIAPHAGE 500: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 9 blisters (90 tablets).

DIAPHAGE 850: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 6 blisters (60 tablets).

DIAPHAGE 1000: 10 tablets per transparent/colourless PVC/aluminium blister packed in a carton. Each carton contains 6 blisters (60 tablets).

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

DIAPHAGE 500: 44/21.2/0771

DIAPHAGE 850: 44/21.2/0772

DIAPHAGE 1000: 44/21.2/0773

DIAPHAGE 500:

Namibia: NS2 16/21.2/0183

Botswana: S2 BOT1702932

DIAPHAGE 850:

Namibia: NS2 16/21.2/0184

Botswana: S2 BOT1402550

DIAPHAGE 1000:

Namibia: NS2 16/21.2/0185

Botswana: S2 BOT1402551

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2013

10. DATE OF REVISION OF THE TEXT

22 March 2024