PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE:

Diamet XR 500

Diamet XR 750

Diamet XR 1000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Active substance: Metformin Hydrochloride

Each Diamet XR 500 extended release tablet contains 500 mg metformin hydrochloride.

Each Diamet XR 750 extended release tablet contains 750 mg metformin hydrochloride.

Each Diamet XR 1000 extended release tablet contains 1000 mg metformin hydrochloride.

Sugar free

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

3. PHARMACEUTICAL FORM:

Diamet 500mg Extended Release Tablets:

White to off-white, capsule shaped tablet debossed with 'SR 500' on one side and plain on other side.

Diamet 750mg Extended Release Tablets:

White to off-white, capsule shaped tablet debossed with 'SR 750' on one side and plain on other side.

Diamet 1000mg Extended Release Tablets:

White to off-white, oval tablet debossed with 'SR 1000' on one side and plain on other side

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. Diamet XR can be given alone as initial therapy or can be administered in combination with other oral antidiabetic medicines or with insulin.

4.2 Posology and method of administration

Diamet XR 500 mg:

The usual starting dose is one tablet daily given with the evening meal.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dosage is 4 tablets daily.

Dosage increases should be made in increments of 500 mg every 10 to 15 days, up to a maximum of 2000 mg once daily with an evening meal. If glycaemic control is not achieved with Diamet XR 500 mg 4 tablets once daily, Diamet XR 500 mg 2 tablets twice daily should be considered, with both doses given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Diamet XR 750 mg

The usual starting dose is one tablet daily given with the evening meal.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The recommended dosage is 2 tablets once daily, with the evening meal.

If glycaemic control is not achieved with Diamet XR 750 mg 2 tablets once daily Diamet XR 750 mg may be increased to a maximum dose of 3 tablets once daily with the evening meal.

If glycaemic control is not achieved on Diamet XR 750 mg 3 tablets once daily, one tablet of Diamet XR 750 mg in the morning and two tablets of Diamet XR 750 mg in the evening should be considered, with both doses being given with food.

If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Diamet XR 1000 mg

Diamet XR 1000 mg is intended as maintenance therapy for patients already treated with either 1000 mg (2 tablets of Diamet XR 500) or 2000 mg (4 tablets of Diamet XR 500) of sustained release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3000 mg daily.

Switching patients already treated with metformin tablets

In patients already treated with metformin tablets, the starting dose of Diamet XR prolonged release tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Diamet XR prolonged release tablets is not recommended.

Switching patients from other oral antidiabetic medicines

If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate Diamet XR prolonged release tablets at the doses indicated above.

Combination therapy with insulin

Diamet XR prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is Diamet XR 500 mg once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose

measurements. After titration, switch to Diamet XR 1000 mg may be considered.

Other combination therapy

See (section 4.4).

Special populations

Elderly

Due to the potential for decreased renal function in elderly subjects, the dosage for the Diamet XR range should be adjusted based on renal function. Regular assessment of renal function is necessary. (See section 4.4.)

Paediatric population

In the absence of available data, the Diamet XR range should not be used in children.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to metformin 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

- Renal failure or renal dysfunction (Creatinine clearance < 60mL/min).
- Acute conditions with the potential to alter renal function such as:
  - dehydration
  - severe infection,
  - shock
  - intravascular administration of iodinated contrast media
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
  - decompensated heart failure
  - respiratory failure,
  - recent myocardial infarction,
  - shock
  - pancreatitis
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (acute or chronic)
- The use of DIAMET XR during pregnancy is not advised.

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is associated with the use of Diamet XR range.

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to Diamet XR administration.

In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and Diamet XR range therapy should be stopped.

Lactic acidosis is a medical emergency, which must be treated in hospital.

Diamet XR range is excreted by the kidney and regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus.

The incidence of lactic acidosis may be reduced by assessing also other associated risk factors such as poorly controlled diabetes mellitus, type 2: 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 a coma. Diagnostic laboratory findings include a decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, Diamet XR should be discontinued and the patient should be hospitalised immediately.

Renal function

As Diamet XR 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.

Diamet XR range therapy should be stopped 2-3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained.

The use of Diamet XR formulations 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 Diamet XR formulations should have an annual estimation of vitamin B12 levels, since Diamet XR range may cause mal-absorption of vitamin B12, which may result in megaloblastic anaemia.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Diamet XR may be used with a regular monitoring of cardiac and renal function.

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

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, Diamet XR initiation is not recommended in these patients.

Administration of iodinated contrast medicines:

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Diamet XR 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:

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

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combination therapy may cause hypoglycaemia.

Stabilisation of diabetic patients with Diamet XR and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained (see Contra- Indications).

Contraindications should be carefully observed.

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

Thenusual laboratory tests for diabetes monitoring should be performed regularly.

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

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 alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

This medicine contains less than 1mmol sodium (23mg) per dosage unit, that is to say it is essentially 'sodium free'

4.5 Interaction with other medicines and other forms of interaction

<u>Concomitant use not recommended</u>

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment. Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast medicines

Intravascular administration of iodinated contrast agents may lead to Diamet XR accumulation and a risk of lactic acidosis. Diamet XR must 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 4.4.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Medical practitioners should inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, the dosage of the antidiabetic medicines should be adjusted during therapy with the other medicine and upon its discontinuation.

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

Cimetidine: Reduced renal clearance of Diamet XR has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: Diamet XR has been reported to diminish the activity of warfarin, and so dose adjustments and increased frequency of INR determinations should be considered.

Sulphonylurea: Concomitant therapy of Diamet XR with sulphonylurea may cause hypoglycaemia.

Vitamins: Long-term treatment with Diamet XR may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of Diamet XR should be considered.

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), diuretics and sympathomimetics).

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin 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. A dose reduction should be considered.

• 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, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Fertility, pregnancy, and lactation

The use of Diamet XR during pregnancy is contraindicated (see section 4.3).

Pregnancy

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

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development ~~(see section 5.3).~~

When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycaemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment.

Fertility

Fertility of male or female rats was unaffected by metformin 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 the 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.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic medicines (e.g. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin as in Diamet XR was similar in nature and severity to that reported in patients treated with metformin as in Diamet immediate release.

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

The following adverse reactions may occur with Diamet XR.

Metabolism and nutrition disorders

Less frequent: Lactic acidosis (see section 4.4.). Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an 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 undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most

cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Less frequent: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

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

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who- umc.org) found on SAHPRA website.

4.9 Overdose

Hypoglycaemia can occur when Diamet XR range 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. 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 Diamet XR range.

Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

Haemodialysis is the most effective way to remove lactate and metformin.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and Class: A 21.2 Oral hypoglycaemics

ATC Code: A10BA02:

Pharmacotherapeutic group: Biguanide, Blood glucose lowering medicines. 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.

Mechanism of action

Metformin may act via 3 mechanisms:

• reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis

• in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation

• and 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 (GLUT).

5.2 Pharmacokinetic properties

Absorption

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max}) for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of metformin 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin 750 mg was shown to be bioequivalent to Metformin 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin 1000 mg was shown to be bioequivalent to Metformin 500 mg at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak concentration 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 Vd ranged between 63-276 L.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. There is no biliary excretion.

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.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2)

6. Pharmaceutical particulars

6.1 List of excipients

Carmellose sodium, hypromellose, magnesium stearate, silica colloidal anhydrous.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C in original container to protect from moisture.

6.5 Nature and contents of container

DIAMET XR 500 mg Extended Release Tablets:

30's, 56's, 60's or 90's- DIAMET XR is packed in cartons containing 10 or 14 tablets packed in an aluminium foil blister 0.02 mm x 198 mm & a transparent PVC film 0.35 mm x 202 mm

DIAMET XR 750 mg Extended Release Tablets:

30's or 60's- DIAMET XR is packed in cartons containing 10 tablets packed in an aluminium foil blister 0.02 mm x 198 mm & a transparent PVC film 0.35 mm x 202 mm

DIAMET XR 1000 mg Extended Release Tablets:

30's, 56's, or 60's- DIAMET XR is packed in cartons containing 10 or 14 tablets packed in an aluminium foil blister 0.02 mm x 198 mm & a transparent PVC film 0.35 mm x 202 mm

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

DIAMET XR 500 : 57/21.2/0121

DIAMET XR 750: 57/21.2/0122

DIAMET XR 1000: 57/21.2/0123

9. Date of first authorization/Renewal of the authorization

03 June 2025

10. Date of revision of the text

TBI