SCHEDULING STATUS

S3

1. NAME OF THE MEDICINAL PRODUCT

METPLITIN 25 mg

METPLITIN 50 mg

METPLITIN 100 mg

Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METPLITIN 25 mg: Each tablet contains sitagliptin hydrochloride monohydrate, equivalent to 25 mg sitagliptin.

METPLITIN 50 mg: Each tablet contains sitagliptin hydrochloride monohydrate, equivalent to 50 mg sitagliptin.

METPLITIN 100 mg: Each tablet contains sitagliptin hydrochloride monohydrate, equivalent to 100 mg sitagliptin.

METPLITIN is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

METPLITIN 25 mg: White coloured, round shaped tablets (Diameter: approximately 6 mm) debossed with "411" on one side and plain on the other side.

METPLITIN 50 mg: Yellow coloured, round shaped tablets (Diameter: approximately 8 mm) debossed with "417" on one side and plain on the other side.

METPLITIN 100 mg: Brown coloured, round shaped tablets (Diameter: approximately 10 mm) debossed with "471" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy

METPLITIN is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Combination Therapy

METPLITIN is also indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a $PPAR_{\gamma}$ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single medicine do not provide adequate glycaemic control.

The combination of sitagliptin and sulphonylureas has not been adequately studied.

4.2 Posology and method of administration

Posology

General

The dose of METPLITIN in combination with metformin or a $PPAR_{\gamma}$ agonist is 100 mg once daily.

The dosage of metformin or $PPAR_{\gamma}$ agonist should be maintained, and METPLITIN administered concomitantly.

Special populations

Patients with renal insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 ml/min, approximately corresponding to serum creatinine levels of ≤ 150 µmol/litre in men and ≤ 133 µmol/litre in women), no dosage adjustment for METPLITIN is required.

For patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 ml/min, approximately corresponding to serum creatinine levels of > 150 µmol/litre to ≤ 265 µmol/litre in men and > 133 µmol/l to not ≤ 221 µmol/litre in women), the dose of METPLITIN is 50 mg once daily. This dose should be decreased if CrCl decreases to < 30ml/min.

For patients with severe renal insufficiency (CrCl < 30 ml/min, approximately corresponding to serum creatinine levels of > 265 µmol/litre in men and > 221 µmol/litre in women) or with endstage renal disease

requiring haemodialysis, the dose of METPLITIN is 25 mg once daily.

METPLITIN may be administered without regard to the timing of haemodialysis.

Patients with hepatic insufficiency

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency.

METPLITIN has not been studied in patients with severe hepatic insufficiency.

Elderly

No dosage adjustment is necessary for elderly patients.

Paediatric Population

There are no data available on the use of METPLITIN in patients younger than 18 years of age.

Therefore, use of METPLITIN in paediatric patients is not recommended.

Method of administration

METPLITIN is for oral use and can be taken with or without food.

If a dose of METPLITIN is missed, it should be taken as soon as the patient remembers.

A double dose of METPLITIN should not be taken on the same day.

4.3 Contraindications

- METPLITIN is contraindicated in patients with a known hypersensitivity to sitagliptin hydrochloride or any other component of METPLITIN (see section 6.1).
- A history of serious hypersensitivity reactions, such as anaphylaxis and angioedema to METPLITIN or other gliptins (DPP-4).
- METPLITIN has not been studied in patients with severe hepatic insufficiency (see Section 5.2).

4.4 Special warnings and precautions for use

General

METPLITIN should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Acute pancreatitis

In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent abdominal pain. Resolution of pancreatitis has been

observed after discontinuation of sitagliptin, as in METPLITIN. If pancreatitis is suspected, METPLITIN and other potentially suspect medicines should be discontinued immediately.

If acute pancreatitis is confirmed, METPLITIN should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, as in METPLITIN.

These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, as in METPLITIN, with some reports occurring after the first dose.

If a hypersensitivity reaction is suspected, discontinue METPLITIN immediately and institute an alternative class of medicines for treatment for diabetes.

Hypoglycaemia

Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea.

Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

Renal insufficiency

Sitagliptin is renally excreted. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring haemodialysis (see Section 4.2). When considering the use of sitagliptin in combination with another anti-diabetic medicine, its conditions for use in patients with renal impairment should be checked.

Bullous pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, METPLITIN should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on sitagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicines are low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3).

OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo.*

Metformin: Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin.

Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicines

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0,25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dose adjustment of digoxin is

recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein in vivo.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies in pregnant women; therefore, METPLITIN is not recommended for use in pregnancy.

Breastfeeding

Sitagliptin is secreted in the milk of lactating rats. It is not known whether METPLITIN is secreted in human milk. Therefore, METPLITIN should not be used by a woman who is breastfeeding.

Fertility

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines

METPLITIN has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported.
In addition, patients should be alerted to the risk of hypoglycaemia when METPLITIN is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

a. Summary of the safety profile

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported.

Hypoglycaemia has been reported in combination with sulphonylurea and insulin.

b. Tabulated list of adverse reactions

Adverse drug reactions are classified by system organ class and frequency; within each frequency grouping, and listed in the table below.

Adverse reaction	**Frequency of adverse reaction**
Blood and lymphatic system disorders	
thrombocytopenia	Less frequent
Immune system disorders	
hypersensitivity reactions including anaphylactic responses[*,†]	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia[†]	Frequent
Nervous system disorders	
headache	Frequent
dizziness	Less frequent
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease[*]	Frequency not known
Gastrointestinal disorders	
constipation	Less frequent
vomiting*, acute pancreatitis[*,†], fatal and non-fatal haemorrhagic and necrotising pancreatitis[*,†]	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus[*]	Less frequent
angioedema[*,†], rash[*,†], urticaria[*,†], cutaneous vasculitis[*,†], exfoliative skin conditions including Stevens-Johnson syndrome[*,†], bullous pemphigoid[*]	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia[*], myalgia[*], back pain[*], arthropathy[*]	Frequency not known
Renal and urinary disorders	
impaired renal function[*], acute renal failure[*]	Frequency not known

General disorders and administration site conditions peripheral oedema	Frequent

† See section 4.4.

c. Description of selected adverse reactions

In addition to the medicine-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and frequently in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other antidiabetic medicines than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequent with the combination of sulphonylurea and metformin), influenza (frequent with insulin (with or without metformin)), nausea and vomiting (frequent with metformin), flatulence (frequent with metformin or pioglitazone), constipation (frequent with the combination of sulphonylurea and metformin), peripheral oedema (frequent with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (less frequent with metformin), and dry mouth (less frequent with insulin (with or without metformin)).

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in humans.

In the event of an overdose, it is reasonable to employ the usual supportive measures e.g., remove

unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13,5 % of the dose was removed over a 3- to 4- hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.21.2 Oral Hypoglycaemics

Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH01

Mechanism of action

Sitagliptin hydrochloride is an orally-active, potent and selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Incretin hormones physiologically regulate blood glucose levels by increasing insulin response from pancreatic beta cells and suppressing glucagon secretion from pancreatic alpha cells, when blood glucose levels are normal or elevated. These effects are not observed when blood glucose levels are low. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon, along with higher insulin levels lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels.

Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma ($PPAR_{\gamma}$) agonists, alpha-glucosidase inhibitors and amylin analogues.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin hydrochloride had no effect on the pharmacokinetics of sitagliptin.

Distribution

The mean volume of distribution at steady-state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine. Following a [^{14}C] sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin was approximately 12,4 hours and renal clearance was approximately 350 ml/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor did not reduce the renal clearance of sitagliptin.

Special populations

Type 2 diabetes

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy

subjects.

Renal insufficiency

A study was conducted to evaluate the pharmacokinetics of sitagliptin (50 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency, classified on the basis of creatinine clearance as mild (50 to < 80 ml/min), moderate (30 to < 50 ml/min) and severe (< 30 ml/min), as well as patients with end-stage renal disease on haemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\underline{\text{CrCl} = [140 - \text{age (years)}] \times \text{weight (kg)} \{\times 1{,}2\}}$$

$$[\text{serum creatinine } (\mu\text{mol/l})]$$

For female patients: 0,85 x value calculated for males

Compared to normal healthy control subjects, an approximate 1,6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. An approximately 2,3-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, an approximately 3,8-fold increase was observed in patients with severe renal insufficiency and an approximately 4,5-fold increase was observed in patients with end-stage renal disease on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was not meaningfully removed by haemodialysis (13,5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in end-stage renal disease patients requiring haemodialysis (see Section 4.2, Patients with renal insufficiency).

Hepatic insufficiency

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21 % and 13 %, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin hydrochloride. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Gender

Based on pharmacokinetic analysis, gender had no clinically meaningful effect on the pharmacokinetics of

sitagliptin.

Elderly

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric

No studies have been performed in paediatric patients.

Body Mass Index (BMI)

Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of pharmacokinetic data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Calcium hydrogen phosphate

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Povidone (K-30)

Purified water

Film-coating:

25 mg:

Opadry II White 85F18422 contains:

Macrogol (3350)/PEG

Polyvinyl alcohol-part, hydrolysed

Titanium dioxide

Talc

50 mg:

Opadry II Yellow 85F520260 contains:

Iron oxide yellow

Macrogol (3350)/PEG

Polyvinyl alcohol-part, hydrolysed

Titanium dioxide

Talc

100 mg:

Opadry II Brown 85F565140 contains:

Iron oxide red

Iron oxide yellow

Macrogol (3350)/PEG

Polyvinyl alcohol-part, hydrolysed

Titanium dioxide

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep out of reach of children.

Keep the tablets in the blisters and the blisters in the outer carton until required for use.

6.5 Nature and contents of container

METPLITIN are packed in OPA/Alu/PVC-Alu cold formable foil and hard tempered aluminium foil with heat seal lacquer coating or clear PVC (polyvinyl chloride) foil laminated with aclar and hard tempered aluminium foil with heat seal lacquer coating: blister packs of 28, 30, 56, 60 tablets with blisters containing 7, 10 or 14

tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

METPLITIN 25 mg: 56/21.2/0996

METPLITIN 50 mg: 56/21.2/0997

METPLITIN 100 mg: 56/21.2/0998

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 May 2024

10. DATE OF REVISION OF TEXT