**SCHEDULING STATUS**

S3

## 1. NAME OF THE MEDICINE

SITAGLIPTIN 25 mg MEDFOUR (25 mg, film-coated tablets)

SITAGLIPTIN 50 mg MEDFOUR (50 mg, film-coated tablets)

SITAGLIPTIN 100 mg MEDFOUR (100 mg, film-coated tablets)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sitagliptin hydrochloride which is equivalent to 25, 50 or 100 mg, sitagliptin, respectively.

SITAGLIPTIN MEDFOUR is sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

SITAGLIPTIN 25 mg MEDFOUR: Round, biconvex, pink film-coated tablets. Approximate tablet dimensions 6,0 mm.

SITAGLIPTIN 50 mg MEDFOUR: Round, biconvex, light beige film-coated tablets. Approximate tablet dimensions 8,0 mm.

SITAGLIPTIN 100 mg MEDFOUR: Round, biconvex, beige film-coated tablets. Approximate tablet dimensions 10,0 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

***Monotherapy***

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

***Combination Therapy***

SITAGLIPTIN MEDFOUR is also indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist (e.g. thiazolidinedione) when diet and exercise, plus the single medicine do not provide adequate glycaemic control.

The combination of SITAGLIPTIN MEDFOUR and sulphonylureas has not been adequately studied.

### 4.2 Posology and method of administration

**Posology**

The dose of SITAGLIPTIN MEDFOUR in combination with metformin or a PPARγ agonist is 100 mg once daily. The dosage of metformin or PPARγ agonist should be maintained, and SITAGLIPTIN MEDFOUR administered concomitantly.

If a dose of SITAGLIPTIN MEDFOUR is missed, it should be taken as soon as the patient remembers. A double dose of SITAGLIPTIN MEDFOUR should not be taken on the same day.

**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 micromol/litre in men and ≤ 133 micromol/litre in women), no dosage adjustment for SITAGLIPTIN MEDFOUR is required.

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

For patients with severe renal insufficiency (CrCl < 30 mL/min, approximately corresponding to serum creatinine levels of > 265 micromol/litre in men and > 221 micromol/litre in women) or with end-stage renal disease requiring haemodialysis, the dose of SITAGLIPTIN MEDFOUR is 25 mg once daily.

SITAGLIPTIN MEDFOUR 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. SITAGLIPTIN MEDFOUR 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 SITAGLIPTIN MEDFOUR in patients younger than 18 years of age. Therefore, use of SITAGLIPTIN MEDFOUR in paediatric patients is not recommended.

**Method of administration**

Oral.

SITAGLIPTIN MEDFOUR can be taken with or without food.

**4.3 Contraindications**

- Hypersensitivity to sitagliptin hydrochloride or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8).
- A history of serious hypersensitivity reactions, such, as anaphylaxis and angioedema to SITAGLIPTIN MEDFOUR or other gliptins (DPP-4).
- SITAGLIPTIN MEDFOUR has not been studied in patients with severe hepatic insufficiency (see section 5.2).

**4.4 Special warnings and precautions for use**

*General*

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

*Acute pancreatitis*

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of SITAGLIPTIN MEDFOUR (with or without supportive treatment) but cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, SITAGLIPTIN MEDFOUR and other potentially suspect medicines

should be discontinued immediately. If acute pancreatitis is confirmed, SITAGLIPTIN MEDFOUR should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

*Hypoglycaemia when used in combination with other anti-hyperglycaemic medicines*

In clinical trials of sitagliptin (as contained in SITAGLIPTIN MEDFOUR) as monotherapy and as part of combination therapy with medicines not known to cause hypoglycaemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycaemia reported with sitagliptin (as contained in SITAGLIPTIN MEDFOUR) were similar to rates in patients taking placebo. Hypoglycaemia has been observed when SITAGLIPTIN MEDFOUR 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 (see section 4.2).

*Renal impairment*

SITAGLIPTIN MEDFOUR is renally excreted. To achieve plasma concentrations of SITAGLIPTIN MEDFOUR similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal impairment, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (see section 4.2 and 5.2).

When considering the use of SITAGLIPTIN MEDFOUR in combination with another anti-diabetic medicines, its conditions for use in patients with renal impairment should be checked.

***Hypersensitivity Reactions:***

**There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin (as contained in SITAGLIPTIN MEDFOUR). These reactions included 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**

**contained in SITAGLIPTIN MEDFOUR), with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue SITAGLIPTIN MEDFOUR immediately. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated (see sections 4.3 and 4.8).**

*Bullous pemphigoid*

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

SITAGLIPTIN MEDFOUR contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicines and other forms of interaction**

*Effects of other medicines on SITAGLIPTIN MEDFOUR*

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

*In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of SITAGLIPTIN MEDFOUR 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 MEDFOUR 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 MEDFOUR 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 MEDFOUR is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of SITAGLIPTIN MEDFOUR 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 MEDFOUR did not meaningfully alter the pharmacokinetics of SITAGLIPTIN MEDFOUR 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 (as contained in SITAGLIPTIN MEDFOUR). Co-administration of a single 100 mg oral dose of sitagliptin (as contained in SITAGLIPTIN MEDFOUR) and a single 600 mg oral dose of ciclosporin increased the AUC and $C_{max}$ of sitagliptin (as contained in SITAGLIPTIN MEDFOUR) by approximately 29 % and 68 %, respectively. These changes in sitagliptin (as contained in SITAGLIPTIN MEDFOUR) pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin (as contained in SITAGLIPTIN MEDFOUR) was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

***Effects of SITAGLIPTIN MEDFOUR on other medicines***

*Digoxin:*

Sitagliptin (as contained in SITAGLIPTIN MEDFOUR) 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 MEDFOUR 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 adequate data from the use of SITAGLIPTIN MEDFOUR in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, SITAGLIPTIN MEDFOUR should not be used during pregnancy.

**Breastfeeding**

It is unknown whether SITAGLIPTIN MEDFOUR is excreted in human breast milk. Animal studies have shown excretion of SITAGLIPTIN MEDFOUR in breast milk. SITAGLIPTIN MEDFOUR should not be used during breastfeeding.

**Fertility**

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

**4.7 Effects on ability to drive and use machines**

Dizziness and somnolence have been reported with sitagliptin, which may influence the ability to drive and use machines.

In addition, patients should be alerted to the risk of hypoglycaemia when SITAGLIPTIN MEDFOUR 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 (see section 4.4).

*b. Tabulated list of adverse reactions*

*Table 1 The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin monotherapy and post-marketing experience*

| | |
|---|---|
| **Blood and lymphatic system disorders** | |
| *Less frequent* | Thrombocytopenia |
| **Immune system disorders** | |
| *Frequency unknown* | Hypersensitivity reactions including anaphylactic responses*,†, angioedema*,† |
| **Metabolism and nutrition disorders** | |
| *Frequent* | Hypoglycaemia† |
| **Nervous system disorders** | |

| | |
|---|---|
| *Frequent* | Headache |
| *Less frequent* | Dizziness |
| **Respiratory, thoracic and mediastinal disorders** | |
| *Frequency unknown* | Interstitial lung disease* |
| **Gastrointestinal disorders** | |
| *Less frequent* | Constipation |
| *Frequency unknown* | Vomiting*, acute pancreatitis*,†,‡, fatal and non-fatal haemorrhagic and necrotising pancreatitis*,† |
| **Skin and subcutaneous tissue disorders** | |
| *Less frequent* | Pruritus* |
| *Frequency unknown* | rash*,†, urticaria*,†, cutaneous vasculitis*,†, exfoliative skin conditions including Stevens-Johnson syndrome*,†, bullous pemphigoid* |
| **Skin and subcutaneous tissue disorders** | |
| *Less frequent* | Pruritus* |
| *Frequency unknown* | rash*,†, urticaria*,†, cutaneous vasculitis*,†, exfoliative skin conditions including Stevens-Johnson syndrome*,†, bullous pemphigoid* |
| **Musculoskeletal and connective tissue disorders** | |
| *Frequency unknown* | Arthralgia*, myalgia*, back pain*, arthropathy* |
| **Renal and urinary disorders** | |
| *Frequency unknown* | Impaired renal function*, acute renal failure* |

*Adverse reactions were identified through post-marketing surveillance.

† See section 4.4.

‡ See TECOS Cardiovascular Safety Study below.

*Table 2 The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin with Metformin and sitagliptin with a PPARγ Agent (pioglitazone)*

| **Frequency of adverse reaction by treatment regimen** | **Sitagliptin with Metformin** | **Sitagliptin with a PPARγ Agent (pioglitazone)** |
|---|---|---|
| **Investigations** | | |
| *Less frequent* | Decreased blood glucose levels | |
| **Nervous system disorders** | | |
| *Less frequent* | Somnolence | |
| **Gastrointestinal disorders** | | |
| *Frequent* | Nausea | Flatulence |
| *Less frequent* | Diarrhoea, Upper abdominal pain | |
| **Metabolism and nutrition disorders** | | |
| *Frequent* | | Hypoglycaemia |
| **General disorders** | | |
| *Frequent* | | Peripheral oedema |

In addition, in monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine-related reported in patients treated with sitagliptin in excess (> 0,2 % and difference more than 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

*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 more commonly in patients treated with sitagliptin (e.g. SITAGLIPTIN MEDFOUR) 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 (not reaching the 5 % level but occurring with an incidence of > 0,5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin (e.g. SITAGLIPTIN MEDFOUR) with other anti-diabetic medicines than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very 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)).

*TECOS Cardiovascular Safety Study*

The Trial Evaluating Cardiovascular Outcomes with sitagliptin (TECOS) included patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1,73 $m^2$), and patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2,7 % in sitagliptin-treated patients and 2,5 % in

placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1,0 % in sitagliptin-treated patients and 0,7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0,3 % in sitagliptin-treated patients and 0,2 % in placebo-treated patients.

*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 providers 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.

**4.9 Overdose**

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (as contained in SITAGLIPTIN MEDFOUR). There is no experience with doses above 800 mg in clinical studies.

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 MEDFOUR 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 MEDFOUR is dialysable by peritoneal dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A.21.2 Oral Hypoglycaemics

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

**Mechanism of action**

Sitagliptin 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 medicine 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 peptide (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.

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

### 5.2 Pharmacokinetic properties

**Absorption**

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median $T_{max}$) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8,52 μM•hr, $C_{max}$ was 950 nM. The absolute bioavailability of sitagliptin is approximately

87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for $C_{max}$ and $C_{24hr}$ ($C_{max}$ increased in a greater than dose-proportional manner and $C_{24hr}$ increased in a less than dose-proportional manner).

**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.

*In vitro* data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

**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. Sitagliptin accumulates only minimally with multiple doses. The 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. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50 = 160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

**Characteristics in patients**

The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

*Renal impairment*

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment 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 (ESRD) were assessed using population pharmacokinetic analyses.

Patients with mild renal impairment did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2,3-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment, and an approximately 3,8-fold increase was observed in patients with severe renal impairment and 4,5-fold increase was observed in patients with end-stage renal disease on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was 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 impairment, as well as in ESRD patients requiring dialysis (see section 4.2).

*Hepatic impairment*

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). 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. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child- Pugh score > 9). (see section 4.3)

*Elderly*

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II

data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

*Paediatric*

No studies with sitagliptin have been performed in paediatric patients.

*Other patient characteristics:*

No dose adjustment is necessary based on gender or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

**5.3 Preclinical safety data**

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at

systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Calcium hydrogen phosphate, anhydrous

Cellulose, microcrystalline

Croscarmellose sodium

Magnesium stearate

Sodium stearyl fumarate

*Film coating:*

Iron oxide yellow (E172)

Iron oxide red (E172)

Macrogol 3350

Polyvinyl alcohol-part, hydrolysed

Talc

Titanium dioxide (E171)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

30 months.

**6.4 Special precautions for storage**

Store at or below 25 °C.

Keep the tablets in the blister in the outer carton until required for use.

**6.5 Nature and contents of container**

SITAGLIPTIN 25 mg/50 mg/100 mg MEDFOUR are packed in PVC/PE/PVdC-aluminium blisters.

The blisters strips are packed in outer cardboard cartons with package leaflet.

Pack sizes: 14, 28, 30, 56, 60, 84, 90, 98, 180 or 196. Not all pack sizes may be marketed.

**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

Medfour Healthcare CC.

31 Burger Street,

Baillie Park,

Potchefstroom

2531

## 8. REGISTRATION NUMBER(S)

SITAGLIPTIN 25 mg MEDFOUR: 55/21.2/0441

SITAGLIPTIN 50 mg MEDFOUR: 55/21.2/0442

SITAGLIPTIN 100 mg MEDFOUR: 55/21.2/0443

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

## 10. DATE OF REVISION OF THE TEXT