PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DIBESTOR 25 (25 mg film-coated tablets)

DIBESTOR 50 (50 mg film-coated tablets)

DIBESTOR 100 (100 mg film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DIBESTOR 25: Each film-coated tablet contains 25 mg sitagliptin (as Sitagliptin hydrochloride monohydrate).

DIBESTOR 50: Each film-coated tablet contains 50 mg sitagliptin (as Sitagliptin hydrochloride monohydrate).

DIBESTOR 100: Each film-coated tablet contains 100 mg sitagliptin (as Sitagliptin hydrochloride monohydrate).

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

DIBESTOR 25 mg film-coated tablets

Film-coated, round, biconvex, orange tablets, one side engraving “25”.

MND Matjila

DIBESTOR 50 mg film-coated tablets

Film-coated, round, biconvex, orange tablets, one side engraving “50”.

DIBESTOR 100 mg film-coated tablets

Film-coated, round, biconvex, orange tablets, one side engraving “100”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy

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

Combination Therapy

DIBESTOR is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ (peroxisome proliferator-activated receptor gamma) agonist (e.g. thiazolidinedione) when diet and exercise, plus the single agent 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

The dose is 100 mg once daily when taken in combination with metformin or a PPARγ agonist.

The dosage of metformin or PPARγ agonist should be maintained, and **DIBESTOR** administered concomitantly.

MND Matjila

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

Special populations

Patients with renal insufficiency

No dosage adjustment for **DIBESTOR** is required for patients with mild renal insufficiency. Mild renal insufficiency is defined as creatinine clearance [CrCl] ≥ 50 ml/min, approximately corresponding to serum creatinine levels of ≤ 150 µmol/litre in men and ≤ 133 µmol/litre in women.

The dose of **DIBESTOR** is 50 mg once daily 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). This dose should be decreased if CrCl decreases to < 30ml/min.

The dose of **DIBESTOR** is 25 mg once daily 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 end-stage renal disease requiring haemodialysis. **DIBESTOR** may be administered without regard to the timing of haemodialysis.

Patients with hepatic insufficiency

MND Matjila

Sitagliptin has not been studied in patients with severe hepatic insufficiency. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency.

Elderly

No dosage adjustment is necessary for elderly patients.

Paediatric population

The safety and efficacy of **DIBESTOR** in children aged under 18 years has not yet been established. Therefore, use of **DIBESTOR** in paediatric patients is not recommended.

Method of administration

For oral use.

DIBESTOR may be taken with or without food.

4.3 Contraindications

Hypersensitivity to sitagliptin, other gliptins or to any of the excipients (see section 6.1)

4.4 Special warnings and precautions for use

General

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

Acute pancreatitis

MND Matjila

Patients should be told of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. A risk of developing acute pancreatitis has been associated with the use of DPP-4 inhibitors. After discontinuation of sitagliptin a resolution of pancreatitis has been observed (with or without supportive treatment). Cases of haemorrhagic or necrotising pancreatitis and/or death have been reported. **DIBESTOR** and other potentially suspect medicines should be discontinued if pancreatitis is suspected. If acute pancreatitis is confirmed, **DIBESTOR** 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. 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, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue DIBESTOR immediately and institute an alternative class of medicines for treatment for diabetes (see sections 4.3 and 4.8).

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicines

Hypoglycaemia has been observed when sitagliptin was used in combination with sulphonylurea or insulin. Clinical trials have indicated sitagliptin as monotherapy and as part of combination therapy with medicines not known to cause hypoglycaemia (i.e. PPARγ agonist and/or metformin), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. Therefore,

MND Matjila

to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered (see section 4.2).

Renal impairment

Sitagliptin is renally excreted. Lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2) to achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function.

Conditions for use in patients with renal impairment should be checked, when considering the use of sitagliptin in combination with another anti-diabetic medicine.

Bullous pemphigoid

There have been reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. **DIBESTOR** should be discontinued if bullous pemphigoid is suspected.

Sodium

This medicine 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

Sitagliptin does not have clinically meaningful effects on the pharmacokinetics of the following: simvastatin, metformin, warfarin, glyburide and oral contraceptives. Based on this, sitagliptin does not inhibit CYP isoenzymes CYP3A4, 2C8 or 2C9.

MND Matjila

According to *in vitro* data, sitagliptin is also not expected to induce CYP3A4 or to inhibit CYP2D6, 1A2, 2C19 or 2B6. There is limited information on multiple dose co-administration of these medicines.

Although there was a slight increase in the mean peak medicine concentration (C_{max} 18 %) and area under the curve (AUC 11 %) of digoxin with the co-administration of sitagliptin; these increases are not considered likely to be clinically significant. No dosage adjustment of digoxin or **DIBESTOR** is recommended. Patients receiving digoxin should be monitored appropriately.

In subjects with co-administration of a single 100 mg oral dose of **DIBESTOR** and a single 600 mg oral dose of ciclosporin (a potent probe inhibitor of p-glycoprotein), the C_{max} and AUC of **DIBESTOR** were increased approximately 68 % and 29 % respectively. No dosage adjustment for **DIBESTOR** is recommended when co-administered with ciclosporin or other p-glycoprotein inhibitors (e.g. ketoconazole), as the observed changes in **DIBESTOR** pharmacokinetics are not considered likely to be clinically significant.

The risk for clinically meaningful interactions by co-administered medicines is low as described by the clinical data below.

In vitro studies showed that CYP3A4 is the primary enzyme responsible for the limited metabolism of sitagliptin, with contribution from CYP2C8. Metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin, in patients with normal renal function. However, 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). Therefore, in patients with severe renal impairment or ESRD, it is possible that potent CYP3A4 inhibitors (i.e.

MND Matjila

itraconazole, ketoconazole, clarithromycin, ritonavir) could alter the pharmacokinetics of sitagliptin. A clinical study has not been assessed the effect of potent CYP3A4 inhibitors in the setting of renal impairment.

In vitro transport studies showed that sitagliptin is a substrate for organic anion transporter-3 (OAT3) and p-glycoprotein. *In vitro*, Probenecid inhibited OAT3 mediated transport of sitagliptin. The risk of clinically significant interactions is low. *In vivo,* concomitant administration of OAT3 inhibitors has not been evaluated.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

DIBESTOR is not recommended for use in pregnancy as there are no studies in pregnant woman.

Breastfeeding

DIBESTOR should not be used by a woman who are breastfeeding as it is not known whether **DIBESTOR** is excreted in human breast milk. Animal studies indicate sitagliptin is excreted in breast milk

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

MND Matjila

DIBESTOR may cause dizziness and somnolence, therefore patients taking **DIBESTOR** should not drive or use machines until their individual susceptibility to dizziness and somnolence is known.

4.8 Undesirable effects

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Frequency not known	hypersensitivity reactions including anaphylactic responses
Metabolism and nutrition disorders	Frequent	Hypoglycaemia (when taken with **PPARγ Agent)**
Nervous system disorders	Frequent	Headache
	Less Frequent	Dizziness, somnolence (when taken with Metformin)
Respiratory, thoracic and mediastinal disorders	Frequency not known	interstitial lung disease
Gastrointestinal disorders	Frequent	Nausea, flatulence (when taken with **PPARγ Agent)**
	Less Frequent	Diarrhoea, upper abdominal pain (when taken with Metformin), Constipation
	Frequency not known	Vomiting, acute pancreatitis, fatal and non-fatal haemorrhagic and necrotizing pancreatitis

MND Matjila

MedDRA system organ class	**Frequency**	**Adverse reactions**
Skin and subcutaneous tissue disorders	Less Frequent	Pruritus
	Frequency not known	Angiodema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigiod
Musculoskeletal and connective tissue disorders	Frequency not known	Arthralgia, myalgia, back pain, arthropathy
Renal and urinary disorders	Frequency not known	Impaired renal function, acute renal failure
General disorders and administration site conditions	Frequent	Peripheral oedema (when taken with Metformin)
Investigations	Less frequent	Decreased blood glucose levels (when taken with 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.

MND Matjila

4.9 Overdose

In the event of an overdose the usual supportive measures can be implemented e.g. employ clinical monitoring (including obtaining an electrocardiogram), remove unabsorbed material from the gastrointestinal tract and institute supportive therapy if required.

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

Single doses of up to 800 mg sitagliptin were generally well tolerated in controlled clinical studies in healthy subjects. At a dose of 800 mg minimal increases in QTc was observed and was found not be clinically relevant.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.21.2 Oral Hypoglycaemics

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

Sitagliptin is an orally-active, selective and potent inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of medicines that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). When blood glucose levels are normal or elevated, incretin hormones physiologically regulate blood glucose levels by suppressing glucagon secretion from pancreatic alpha cells and increasing insulin response from

MND Matjila

pancreatic beta cells. When blood glucose levels are low, these effects are not observed.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed. The absolute bioavailability of sitagliptin is approximately 87 %, mean plasma AUC of sitagliptin was 8.52 μM•hr, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, C_{max} was 950 nM.

Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, therefore **DIBESTOR** may be administered with or without food.

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

Distribution

The fraction of sitagliptin reversibly bound to plasma proteins is 38 %.

A single 100-mg intravenous dose of sitagliptin given to healthy subjects has a mean volume of distribution at steady state of approximately 198 litres.

Biotransformation

Approximately 79 % of sitagliptin is excreted unchanged in the urine.

MND Matjila

Approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin, following a [^{14}C] sitagliptin oral dose. Although not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin, six metabolites were detected at trace levels. As indicated by *vitro* studies the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

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

Elimination

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in urine (87 %) or faeces (13 %) or within one week of dosing. Following a 100-mg oral dose of sitagliptin the apparent terminal $t_{1/2}$ was approximately 12.4 hours. The renal clearance was approximately 350 mL/min. Minimal accumulation is observed with multiple doses.

Renal excretion involving active tubular secretion is the primary route of elimination. The clinical relevance of hOAT-3 in sitagliptin transport has not been established, but sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3). This may be involved in the renal elimination of sitagliptin. Sitagliptin is also a substrate of p-glycoprotein. Although this may also be involved in mediating the renal elimination of sitagliptin, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for PEPT1/2, OAT1 or OCT2 transporters. *In vitro*, sitagliptin did not inhibit p-glycoprotein (up to 250 µM) or OAT3 (IC50=160 µM) mediated transport at therapeutically relevant plasma concentrations. Sitagliptin may be a mild inhibitor of p-glycoprotein as in a clinical study sitagliptin had a small effect on plasma digoxin concentrations

MND Matjila

Characteristics in patients

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

Renal impairment

The effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses. In addition, 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 mild, moderate, and severe renal impairment, as well as patients with ESRD 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, plasma AUC of sitagliptin was increased by approximately 1.6-fold and 1.2-fold in patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min) and with mild renal impairment (GFR ≥ 60 to < 90 mL/min), respectively. Dosage adjustment in these patients is not necessary because increases of this magnitude are not clinically significant.

Plasma AUC of sitagliptin was increased approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including in patients with ESRD on haemodialysis, and approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to <45 mL/min). Sitagliptin was modestly removed by

MND Matjila

haemodialysis (over a 3- to 4-hour haemodialysis session starting 4 hours post dose). Lower dosages are recommended in patients with GFR < 45 mL/min to achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function (see section4.2).

Hepatic impairment

Because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin. No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9).

Elderly

Compared to younger subjects, elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin.

Age did not have a clinically significant impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data, so no dose adjustment is required based on age.

Other patient characteristics

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

MND Matjila

Paediatric population

No studies with sitagliptin have been performed in paediatric patients with age <10 years. In paediatric patients (10 to 17 years of age) with type 2 diabetes the pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated. The dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. Based on the flat PK/PD relationship between the dose of 50 mg and 100 mg, this is not considered to be a clinically meaningful difference compared to adult patients

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Calcium phosphate anhydrous

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Sodium stearyl fumarate

Film coat:

Macrogol 4000

Polyvinyl alcohol

Red iron oxide E172

Talc

Titanium dioxide

Yellow iron oxide E172

6.2 Incompatibilities

MND Matjila

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture. Store in the original package/container. Keep the blister strips in the original carton until required for use.

6.5 Nature and contents of container

Blisters PVC/PVDC/Aluminium in outer carton.

7, 10, 14, 28, 30, 56, 60, 90, 120 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

3 Gwen Lane, 4th Floor,

Sandton, 2031

South Africa

8 REGISTRATION NUMBER(S)

Dibestor 25 56/21.2/1044

Dibestor 50 56/21.2/1045

MND Matjila

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 June 2025

10 DATE OF REVISION OF THE TEXT

MND Matjila