SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Sitagliptin 25 mg Adco, film-coated tablets
Sitagliptin 50 mg Adco, film-coated tablets
Sitagliptin 100 mg Adco, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sitagliptin 25 mg Adco: Each film-coated tablet contains 28,345 mg of sitagliptin hydrochloride monohydrate (equivalent to 25 mg of sitagliptin), as active substance.
Sitagliptin 50 mg Adco: Each film-coated tablet contains 56,69 mg of sitagliptin hydrochloride monohydrate (equivalent to 50 mg of sitagliptin), as active substance.
Sitagliptin 100 mg Adco: Each film-coated tablet contains 113,38 mg of sitagliptin hydrochloride monohydrate (equivalent to 100 mg of sitagliptin), as active substance.
Sitagliptin Adco is sugar free.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Sitagliptin 25 mg Adco: Round, orange, round, convex, film-coated tablets with “25” embossed on one side. The diameter of the tablets is about 6 mm.
Sitagliptin 50 mg Adco: Round, orange, convex, film-coated tablets with “50” embossed on one side. The diameter of the tablets is about 8 mm.
Sitagliptin 100 mg Adco: Round, orange convex, film-coated tablets with “100” embossed on one side. The diameter of the tablets is about 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy

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

Combination Therapy

Sitagliptin Adco 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 Adco and sulphonylureas has not been adequately studied.

4.2 Posology and method of administration

Posology

The dose of Sitagliptin Adco 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 Adco administered concomitantly.
If a dose of Sitagliptin Adco is missed, it should be taken as soon as the patient remembers. A double dose of Sitagliptin Adco 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 Adco 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 Adco 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 Adco is 25 mg once daily.
Sitagliptin Adco 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 Adco 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 Adco in patients younger than 18 years of age. Therefore, use of Sitagliptin Adco in paediatric patients is not recommended.

Method of administration

Oral.
Sitagliptin Adco 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.
- A history of serious hypersensitivity reactions, such, as anaphylaxis and angioedema to

Sitagliptin Adco or other gliptins (DPP-4).
- Sitagliptin Adco has not been studied in patients with severe hepatic insufficiency (see section 5.2).

4.4 Special warnings and precautions for use

General

Sitagliptin Adco 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 Adco (with or without supportive treatment) but cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sitagliptin Adco and other potentially suspect medicines should be discontinued immediately. If acute pancreatitis is confirmed, Sitagliptin Adco 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 Adco) 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 Adco) were similar to rates in patients taking placebo. Hypoglycaemia has been observed when Sitagliptin Adco 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 Adco is renally excreted. To achieve plasma concentrations of Sitagliptin Adco 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 Adco in combination with another antidiabetic 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 Adco). 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 Adco) with some reports occurring after the first dose. If a hypersensitivity reaction is

suspected, discontinue Sitagliptin Adco 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 Adco should be discontinued.

Sitagliptin Adco 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 Adco

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 as in Sitagliptin Adco 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 Adco 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 Adco 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 as in Sitagliptin Adco is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of Sitagliptin as in Sitagliptin Adco 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 Adco did not meaningfully alter the pharmacokinetics of Sitagliptin Adco 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 Adco). Co-administration of a single 100 mg oral dose of sitagliptin (as contained in Sitagliptin Adco) and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin (as contained in Sitagliptin Adco) by approximately 29 % and 68 %, respectively. These

changes in sitagliptin (as contained in Sitagliptin Adco) pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin (as contained in Sitagliptin Adco) was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of Sitagliptin Adco on other medicines
Digoxin:
Sitagliptin (as contained in Sitagliptin Adco) 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 Adco 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 Adco in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). Sitagliptin Adco should not be used during pregnancy.

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

Fertility
Animal data do not suggest an effect of treatment with Sitagliptin Adco on male and female fertility. No human data is available.

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 Adco 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*
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 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 medicine (pioglitazone)

Frequency of adverse reaction by treatment regimen	**Sitagliptin with Metformin**	**Sitagliptin with a PPARγ medicine (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 and administration site conditions		
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 Adco) 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 Adco) 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)).

Cardiovascular Safety Study
A clinical study was conducted that 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. 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
Single doses of up to 800 mg sitagliptin are generally well tolerated. There is no experience with doses above 800 mg.

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 Adco 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 Adco 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

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

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. 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.

Characteristics in patients

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.

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 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 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 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.

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:
OPADRY II 85F230000 (orange) consisting of:
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 4 000
Polyvinyl alcohol-part, hydrolysed
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 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 Adco, Sitagliptin 50 mg Adco and Sitagliptin 100 mg Adco are packed in

PVC/PVDC-aluminium blisters.
The blisters strips are packed in outer cardboard cartons with package leaflet.
Pack sizes: 28 count PVC/PVDC-aluminium blisters

6.6 Special precautions for disposal and other handling
Any unused medicine or waste material should be disposed of in accordance with local requirements.
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
Sitagliptin 25 mg Adco: 57/21.2/0109
Sitagliptin 50 mg Adco: 57/21.2/0110
Sitagliptin 100 mg Adco: 57/21.2/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29 July 2025

10. DATE OF REVISION OF THE TEXT