SUMMARY OF PRODUCT CHARACTERISTIC
SITABETIC 50 TABLET
(Sitagliptin Tablets, 50 mg)

1. NAME OF THE MEDICINAL PRODUCT

SITABETIC 50 TABLET (Sitagliptin Tablets, 50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of the Ingredient	Quantity per Tablet
Sitaglitpin Phosphate	64.25 mg (equivalent to Sitaglitpin 50.00 mg)
Microcrystalline Cellulose (PH 102)	116.75 mg
Anhydrous Dibasic Calcium Phosphate	10.00 mg
Croscarmellose Sodium	6.00 mg
Sodium Stearyl Fumarate	2.00 mg
Magnesium Stearate	1.00 mg
Insta moistshield Aqua II (White) [IC-AMS-II-1675]	5.50 mg
Opadry OY-B-37203 (Tan)	0.50 mg

3. PHARMACEUTICAL FORM

Oral Tablet

Light pink, round, bi-convex film coated tablet engraved with 'ACME' on one face and a break line on the other face.

4. CLINICAL PRECAUTION

4.1. Therapeutic Indications:

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is also indicated for use in combination with Metformin, Sulfonylurea or Thiazolidinediones when diet and exercise plus the single agent does not provide adequate glycemic control.

4.2. Posology and method of administration

The recommended dose of Sitagliptin Tablets is 100 mg once daily. Sitagliptin Tablets can be taken with or without food.

Patients with Renal Insufficiency: For patients with mild renal insufficiency, no dosage adjustment for Sitagliptin Tablets is required. For patients with moderate renal insufficiencey, the dose of Sitagliptin Tablets is 50 mg once daily. For patients with severe renal insufficiency
or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin Tablets is 25 mg once daily.

Pediatric Use: Safety and effectiveness of Sitagliptin in pediatric patients under 18 years of age have not been established.

***Geriatric Use*:** No dosage adjustment is required based solely on age. The drug is

excreted by the kidney. As elderly patients are more likely to have decreased renal function, caution should be taken in dose selection in the elderly.

Or as directed by the physician.

4.3. Contraindication

History of a serious hypersensitivity reaction to Sitagliptin, such as anaphylaxis or angioedema and exfoliative skin conditions Including Stevens-Johnson syndrome.

4.4. Special warning and precautions for use

If pancreatitis is suspected, Sitagliptin should promptly be discontinued and appropriate management should be initiated. Dosage adjustment should recommend in patients with moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function should recommend prior to initiating Sitagliptin. When Sitagliptin is used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. If a hypersensitivity reaction is suspected, Sitagliptin should discontinue**.**

4.5. Interaction with other medicinal products and other forms of interaction

Co-administration of Digoxin and Sitagliptin may slightly increase the mean peak drug concentration of Digoxin. But no dosage adjustment of Digoxin or Sitagliptin is recommended.

4.6 Fertility, pregnancy and lactation general principle

***Pregnancy*:**
Pregnancy Category: B.
Safety of Sitagliptin in pregnant women has not been established. Sitagliptin should be used during pregnancy only if the potential benefit justifies the potential risk of the fetus.

***Nursing mother*:**
It is not known whether Sitagliptin is excreted in human milk, because many drugs are excreted in human milk, caution should be exercised when Sitagliptin is administered to a nursing woman.

***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 medicines

Sitagliptin 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 Sitagliptin is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effect

The most common adverse reactions are; upper respiratory tract infection, nasopharyngitis and headache. Hypoglycemia may occur in patients treated with the combination of Sitagliptin and sulfonylurea and add-on to insulin.

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.
There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.
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

Pharmacotherapeutic group: [Dipeptidyl peptidase 4 (DPP-4) inhibitors]

ATC code: A10BH01

Mechanism of action:
Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. 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 by intracellular signaling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher

insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.
In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

5.2. Pharmacokinetics 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.

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:
Sitaglitpin Phosphate
Microcrystalline Cellulose (PH 102)
Anhydrous Dibasic Calcium Phosphate
Croscarmellose Sodium
Sodium Stearyl Fumarate
Magnesium Stearate

Film coating:
Insta moistshield Aqua II (White) [IC-AMS-II-1675]
Opadry OY-B-37203 (Tan)

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

2 years

6.4. Special precautions for storage

Store this medicine in a cool, dry place (below 30°C) and out of direct sunlight.

6.5. Nature and content of container

Aluminium–Aluminium blister pack, each blister contains 10 Tablets.
The blisters are further packed in Paperboard carton (Each carton contains 3 blisters with 1 package insert).

6.6. Special precaution for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER THE ACME LABORATORIES LTD

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8. APPLICANT
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