1.NAME OF THE MEDICINAL PRODUCT

Sitaglip 50 Tablet

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains Sitagliptin 50 mg
For a full list of excipients, see section 6.1.

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. CLINICALPARTICULARS

4.1 Therapeutic indications

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

4.2 Posology and method of administration

For Adult over 18 years, 100 mg dose is needed once daily. Dose of concomitant sulfonylurea or insulin may need to be reduced.

OR AS DIRECTED BY THE PHYSICIAN.

4.3 Contraindications:

Contraindicated to the patients with ketoacidosis, diabetic pre-coma, severe renal failure.

4.4 Special warnings and precautions for use:

Caution should be taken when treating he patients with:

- Acute pancreatitis
- Lactic acidosis
- Renal dysfunction
- Hypoglycaemia
- Bullous pemphigoid

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

Sitagliptin increases plasma concentration of digoxin. Being an antidiabetic its hypoglycaemic effect is enhanced by alcohol, anabolic steroids, and testosterone. On the other side, hypoglycaemic effect is antagonised by corticosteroids, diazoxide, loop diuretics, oestrogens, progestogens, etc.

4.6 Pregnancy and lactation:

Pregnancy: There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of Sitagliptin

Nursing Mother: No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of studied animals.

4.7 Effects on the ability to drive and operate machinery:

Sitagliptin has no or negligible influence on the ability to drive

4.8 Undesirable effect:

Gastro-intestinal disturbances; peripheral oedema; upper respiratory tract infection, nasopharyngitis; pain; less commonly dry mouth, anorexia, headache, drowsiness, dizziness, hypoglycaemia, osteoarthritis; also reported pancreatitis, rash, cutaneous vasculitis, and StevensJohnson syndrome.

4.9 Overdose:

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.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: DPP-4
Inhibitor ATC code: A10BH01

Mode of action:

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose- dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. 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. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha glucosidase inhibitors, and amylin analogues.

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 Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 µM•hr, Cmax 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.

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 isoenzymes 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 t½ 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystalline Cellulose (102)
Anhydrous Dibasic Calcium Phosphate
Croscarmellose Sodium
Sodium Stearyl Fumarate
Magnesium Stearate
Instamoistshield Aqua II (white) [IC-AMS-II-1675]
Opadry OY-B-37203 (Tan)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life:

Proposed shelf life (after pack): 36 months

6.4 Special precautions for storage:

Store below 30°C, Protected from light and moisture.

6.5 Nature and contents of container

Alu-Alu Blister

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

H2014/CTD1614/206

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

13th May 2014

10. DATE OF REVISION OF THE TEXT

01/03/2026