# SUMMARY OF PRODUCT CHARACTERISTICS

## *1. NAME OF DRUG PRODUCT*

Vilget Tablets 50mg

## 2. *QUALITATIVE AND QUANTITATIVE COMPOSITION*

Each tablet contains:
Vildagliptin .....50mg

*Excipient with known effect*
Each tablet contains 40 mg lactose anhydrous.
For the full list of excipients, please refer to Section 6.1

## 3. *PHARMACEUTICAL FORM*

White colored round shaped tablet, plain on both sides.

## 4. *CLINICAL PARTICULARS*

### 4.1 Therapeutic indications

Vilget (Vildagliptin) is indicated for the treatment of type 2 diabetes mellitus in adults:

***As monotherapy***
- In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

***As dual oral therapy in combination with***
- Metformin, in patients with insufficient glycemic control despite maximal tolerated dose of monotherapy with metformin.

- Sulfonylurea, in patients with insufficient glycemic control despite maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance.

- Thiazolidinedione, in patients with insufficient glycemic control and for whom the use of a thiazolidinedione is appropriate.

***As triple oral therapy in combination with***
- Sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycemic control.

Vilget (Vildagliptin) is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycemic control.

### 4.2 Posology and method of administration

The recommended dose of Vilget (Vildagliptin) is 50mg once or twice daily. The maximum dose of Vilget (Vildagliptin) is 100mg. Vilget (Vildagliptin) can be administered orally with or without food.

**Adult**
When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulfonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of Vilget (Vildagliptin) is 100mg, administered as one dose of 50mg in the morning and one dose of 50mg in the evening. When used in dual combination with a sulfonylurea, the recommended dose of Vilget (Vildagliptin) is 50mg once daily administered in the morning.

If a dose of Vilget (Vildagliptin) is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

**Special Population**
*Patients with renal impairment*
No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Vilget (Vildagliptin) is 50mg once daily.

*Patients with hepatic impairment*
Vilget (Vildagliptin) should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN).

*Elderly (≥ 65 years)*
No dose adjustments are necessary in elderly patients.

*Pediatrics*
Vilget (Vildagliptin) is not recommended for use in children and adolescents (<18 years).

### 4.3 Contraindications

Vildagliptin is contraindicated in patients with known hypersensitivity to vildagliptin or to any excipient of the product.

### 4.4 Special warnings and special precautions for use

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

*Renal impairment*
Vildagliptin should be used with caution in patients with ESRD or hemodialysis.

*Liver enzyme monitoring*
Rare cases of hepatic dysfunction (including hepatitis) have been reported. Liver function tests should be performed prior to the initiation of treatment. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin.

*Cardiac failure*
Vildagliptin use is not recommended in patients with NYHA functional class IV.

*Skin disorders*
In diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

*Acute pancreatitis*
Use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued and if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

*Hypoglycemia*
Sulfonylureas are known to cause hypoglycemia. Patients receiving vildagliptin in combination with a sulfonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulfonylurea may be considered to reduce the risk of hypoglycemia.

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicaments and other forms of interaction

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. As with other oral antidiabetic medicinal products the hypoglycemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

### 4.6 Uses in Pregnancy and Lactation

**Pregnancy**
There are no adequate data from the use of vildagliptin in pregnant women. Due to lack of human data, vildagliptin should not be used during pregnancy.

**Lactation**
It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.

### 4.7 Effects on ability to drive and operate machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

### 4.8 Undesirable effects

The following adverse reactions have been reported during the use of vildagliptin:

***Monotherapy***
*Common:* Dizziness.
*Uncommon:* Hypoglycemia, headache, edema peripheral, constipation & arthralgia.
*Very Rare:* Upper respiratory tract infection & nasopharyngitis.

***Combination with Metformin***
*Common:* Hypoglycemia, tremor, headache, dizziness & nausea.
*Uncommon:* Fatigue.

***Combination with Sulfonylurea***
*Common:* Hypoglycemia, tremor, headache, dizziness & asthenia.
*Uncommon:* Constipation.
*Very Rare:* Nasopharyngitis.

***Combination with Thiazolidinedione***
*Common:* Weight increase & edema peripheral.
*Uncommon:* Hypoglycemia, headache & asthenia.

***Combination with Metformin and Sulfonylurea***
*Common:* Hypoglycemia, dizziness, tremor, hyperhidrosis & asthenia.

***Combination with Insulin***
*Common:* Decreased blood glucose, headache, chills, nausea, gastroesophageal reflux disease.
*Uncommon:* Diarrhea & flatulence.

### 4.9 OVERDOSAGE

In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by hemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis.

## *5. PHARMACOLOGICAL PROPERTIES*

### 5.1 Pharmacokinetic properties

*Absorption*
Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. The absolute bioavailability is 85%.

Effect of Food: Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased $C_{max}$ (19%).

*Distribution*
The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration ($V_{ss}$) is 71 litres, suggesting extravascular distribution.

*Metabolism*
Metabolism is the major elimination pathway for vildagliptin, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent.

*Elimination*
Following oral administration of [$^{14}$C] vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the feces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. The elimination half-life after oral administration is approximately 3 hours.

**Special Population**
*Hepatic impairment*
The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment were increased by 22%.

*Renal impairment*
Vildagliptin AUC increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively. AUC of the metabolites LAY151 and BQS867 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. Patients with end stage renal disease (ESRD) have vildagliptin exposure similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment.

### 5.2 Pharmacodynamic properties

**Pharmacotherapeutic group:** Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors. **ATC code:** A10BH02

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

### 5.3 Preclinical safety data

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on Cmax).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional in vitro and in vivo tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-fetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

## *6. PHARMACEUTICAL PARTICULARS*

### 6.1 List of Excipients

Microcrystalline Cellulose (Avicel PH-102 DC Grade), Lactose Anhydrous, Sodium Starch Glycolate and Magnesium Stearate.

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf-life**

2 Years
The expiration dates refers to the product correctly stored in the required conditions.

**6.4 Special precautions for storage**

- Do not store above 30°C
- Protect from sunlight & moisture.
- The expiration date refers to the product correctly stored at the required conditions.

**6.5 Nature and contents of container**

Vilget Tablets 50mg are packed in Alu-Alu blister packs of 4 x 7's in a unit carton along with the package insert.

**6.6 Special precautions for disposal**

No special requirements.

**6.7 Instructions for use/handling**

Keep out of reach of children.
To be dispensed on prescription only.

## *7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION*

Getz Pharma (Pvt.) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

## *8. DRUG PRODUCT MANUFACTURER*

Getz Pharma (Pvt.) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

## *9. NAFDAC REGISTRATION NUMBER*

B4-9698