SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	Product Name : **VILDARIL 50** (Vildagliptin Tablets 50 mg)
	1.2 Strength : **VILDARIL 50** (Vildagliptin Tablets 50 mg) Each uncoated tablet contains: Vildagliptin 50 mg
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **VILDARIL 50 (**Vildagliptin Tablets 50 mg**)** Each uncoated tablet contains: Vildagliptin 50 mg Excipients q.s For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Tablet Vildaril 50: White to off white colored, circular flat beveled edged uncoated tablets, plain on both sides.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Vildaril is indicated in the treatment of type 2 diabetes mellitus in adults: **<u>As monotherapy</u>** • In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. **<u>As dual oral therapy in combination with</u>** • Metformin, in patients with insufficient glycemic control despite maximal tolerated dose of monotherapy with metformin, • A sulphonylurea, in patients with insufficient glycemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance, • A thiazolidinedione, in patients with insufficient glycemic control and for whom the use of a thiazolidinedione is appropriate. **<u>As triple oral therapy in combination with</u>** • A sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycemic control. Vildaril 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: Posology *Adults* The management of Antidiabetic therapy should be individualized. The maximum daily dose of Vildaril is 100 mg. For monotherapy, and for combination with metformin, with a TZD or with insulin (with or without metformin), the recommended dose of Vildaril is 50 mg or 100 mg daily. The dose 100 mg of Vildaril can be given as single dose of 100 mg given before evening meal or administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. Thus, the 100 mg daily doses of Vildaril were similarly effective when given once daily or in divided doses, indicating that complete suppression of DPP-4 activity over 24 hours is not necessary to achieve the maximum reduction in HbA1c. When used in dual combination with a sulphonylurea, the recommended dose of Vildaril is 50 mg once daily administered in the morning. In this patient population, Vildaril 100 mg daily was no more effective than Vildaril 50 mg once daily. Doses higher than 100 mg are not recommended. If a dose of Vildaril is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. ***Additional information on special populations*** *Elderly (≥ 65 years)* No dose adjustments are necessary in elderly patients *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 Vildaril is 50 mg once daily *Hepatic impairment* Vildaril should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN). *Pediatric population* Vildaril is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildagliptin in children and adolescents (< 18 years) have not been established. No data are available.
	4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning and precautions for use:

General

Vildaril is not a substitute for insulin in insulin-requiring patients. Vildaril should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment

There is limited experience in patients with ESRD on haemodialysis. Therefore Vildaril should be used with caution in these patients.

Hepatic impairment

Vildaril should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Vildaril in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildaril at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Vildaril therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildaril.

Following withdrawal of treatment with Vildaril and LFT normalisation, treatment with Vildaril should not be reinitiated.

Cardiac failure

A clinical trial of Vildaril in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with Vildaril was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with Vildaril is still limited and results are inconclusive.

There is no experience of Vildaril use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies. Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

	Acute pancreatitis Use of Vildaril has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, Vildaril should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. Hypoglycemia Sulphonylureas are known to cause hypoglycemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycemia.
	4.5 Interactions with other medicinal products and other forms of Interactions : 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 CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. Combination with pioglitazone, metformin and glyburide Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions. Digoxin (Pgp substrate), warfarin (CYP2C9 substrate) Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population. Combination with amlodipine, ramipril, valsartan or simvastatin Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with Vildagliptin. Combination with ACE-inhibitors There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. 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 sympathomimetic.
	4.6 Pregnancy and Lactation: Pregnancy There are no adequate data from the use of Vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, Vildaril should not be used during pregnancy.

	Breast-feeding It is unknown whether Vildagliptin is excreted in human milk. Animal studies have shown excretion of Vildagliptin in milk. Vildaril should not be used during breast-feeding. Fertility No studies on the effect on human fertility have been conducted for Vildaril.
	4.7 Effects on ability to drive and use machine: 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: Summary of the safety profile Safety data were obtained from a total of 3,784 patients exposed to Vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 weeks duration. Of these patients, 2,264 patients received Vildagliptin as monotherapy and 1,520 patients received Vildaril in combination with another medicinal product. 2,682 patients were treated with Vildaril 100 mg daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with Vildaril 50 mg once daily. The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose. Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for Vildagliptin 50 mg once daily, Vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice. Rare cases of angioedema have been reported on Vildagliptin at a similar rate to controls. A greater proportion of cases were reported when Vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing Vildagliptin treatment. Tabulated list of adverse reactions Adverse reactions reported in patients who received Vildaril in double-blind studies as monotherapy and add-on therapies are listed below for each indication by system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Combination with metformin

Table 1 Adverse reactions reported in patients who received Vildaril 100 mg daily in combination with metformin in double-blind studies (N=208)

Metabolism and nutrition disorders	
Common	Hypoglycemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Description of selected adverse reactions

In controlled clinical trials with the combination of Vildagliptin 100 mg daily + metformin, no withdrawal due to adverse reactions was reported in either the Vildagliptin 100 mg daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycemia was common in patients receiving Vildagliptin 100 mg daily in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycemic events were reported in the Vildaril arms.

In clinical trials, weight did not change from baseline when Vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for Vildaril and placebo, respectively).

Clinical trials of up to more than 2 years' duration did not show any additional safety signals or unforeseen risks when Vildaril was added on to metformin.

Combination with a sulphonylurea

Table 2 Adverse reactions reported in patients who received Vildaril 50 mg in combination with a sulphonylurea in double-blind studies (N=170)

Infections and infestations	
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Common	Asthenia
Gastrointestinal disorders	

Uncommon	Constipation

Combination with a thiazolidinedione

Table 3 Adverse reactions reported in patients who received Vildaril 100 mg daily in combination with a thiazolidinedione in double-blind studies (N=158)

Metabolism and nutrition disorders	
Common	Weight increase
Uncommon	Hypoglycemia
Nervous system disorders	
Uncommon	Headache
Uncommon	Asthenia
Vascular disorders	
Common	Oedema peripheral

Monotherapy

Table 4 Adverse reactions reported in patients who received Vildaril 100 mg daily as monotherapy in double-blind studies (N=1,855)

Infections and infestations	
Very rare	Upper respiratory tract infection
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Uncommon	Hypoglycemia
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Edema peripheral
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia

Combination with metformin and a sulphonylurea

Table 5 Adverse reactions reported in patients who received Vildaril 50 mg twice daily in combination with metformin and a sulphonylurea (N=157)

Metabolism and nutritional disorders	
Common	Hypoglycemia

Nervous system disorders	
Common	Dizziness, tremor
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
General disorders and administration site conditions	
Common	Asthenia

Combination with insulin

Table 6 Adverse reactions reported in patients who received Vildaril 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (N=371)

Metabolism and nutrition disorders	
Common	Decreased blood glucose
Nervous system disorders	
Common	Headache, chills
Gastrointestinal disorders	
Common	Nausea, gastro-esophageal reflux disease
Uncommon	Diarrhea, flatulence

Post-marketing experience

Table 7 Post-marketing adverse reactions

Gastrointestinal disorders	
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis (reversible upon discontinuation of the medicinal product) Abnormal liver function tests (reversible upon discontinuation of the medicinal product)
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Skin and subcutaneous tissue disorders	
Not known	Urticaria Exfoliative and bullous skin lesions, including bullous pemphigoid

4.9 Overdosage:
Information regarding overdose with Vildagliptin is limited.
Symptoms

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Vildaril for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, edema and a

	transient increase in lipase levels. At 600 mg, one subject experienced edema of the feet and hands, and increases in creatinine phosphokinase (CPK), aspartate aminotransferase (AST), and C - reactive protein (CRP) and myoglobin levels. Three other subjects experienced edema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product. Management In the event of an overdose, supportive management is recommended. Vildaril cannot be removed by hemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl peptidase 4 (DPP-4) inhibitors. Mechanism of action 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). **Pharmacodynamic effects** By increasing the endogenous levels of these incretin hormones, Vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with Vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycemic) individuals, Vildaril does not stimulate insulin secretion or reduce glucose levels. By increasing endogenous GLP-1 levels, Vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The enhanced increase in the insulin/glucagon ratio during hyperglycemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia. The known effect of increased GLP-1 levels delaying gastric emptying is not observed with Vildaril treatment.
	5.2 Pharmacokinetics Properties: Absorption Following oral administration in the fasting state, Vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. 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%). However, the

	magnitude of change is not clinically significant, so that Vildaril can be given with or without food. The absolute bioavailability is 85%. Distribution The plasma protein binding of Vildagliptin is low (9.3%) and Vildaril 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. Biotransformation Metabolism is the major elimination pathway for Vildagliptin in humans, 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). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of Vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of Vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildaril is not metabolised by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of Vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies demonstrated that Vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, Vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5. Elimination Following oral administration of [^{14}C] Vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged Vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of Vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.
	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 C_{max}). 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, diarrhea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established. Vildaril 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-foetal 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, Sodium Starch Glycolate Type B, Hydrophobic Colloidal Silica and Magnesium Stearate.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C. Protect from Moisture.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Patient Information Leaflet.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited B-4/5/6, M.I.D.C. Area, Paithan,

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8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Dec 07, 2020