For the use of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

SUCRALO

Vildagliptin Tablets 50 mg

COMPOSITION

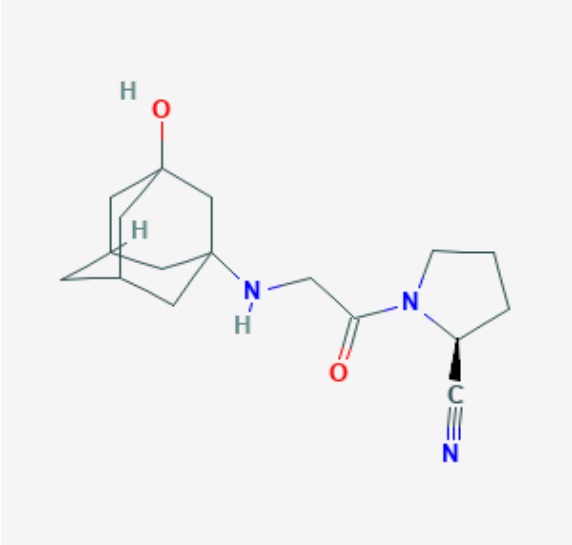
Each tablet contains:
Vildagliptin …50 mg

Excipients:
Lactose Anhydrous, Cellulose Microcrystalline (Avicel PH 102), Sodium starch glycolate, Magnesium stearate

DESCRIPTION

White to off white colored, round tablets debossed with '50' on one side and 'V' on other side

SUCRALO contains Vildagliptin. Vildagliptin is a cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. It is described chemically as (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile. Vildagliptin has molecular formulae $C_{17}H_{25}N_3O_2$ and molecular weight is 303.4. Vildagliptin has the following structural formula:



STRUCTURAL FORMULAE OF VILDAGLIPTIN

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

- **Pharmacodynamics**

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

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor.

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).

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 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assesment-β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin 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 hyperglycaemia 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 vildagliptin treatment.

- **Pharmacokinetics**

Absorption
Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations reported 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 has been reported to result in a decreased C_{max} (19%). However, the magnitude of change is not

clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85%.

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.

Biotransformation
Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the 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. Vildagliptin is not metabolized 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. 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 has been reported to be excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of 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 litres/hour and 13 litres/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of the dose.

Linearity / non-linearity
The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

Special Populations

Gender
No clinically relevant differences in the pharmacokinetics of vildagliptin has been reported between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin has been reported to be unaffected by gender.

Elderly
In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) has been reported to be increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18 to 40 years). These changes are, however, not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic Impairment
The effect of impaired hepatic function on the pharmacokinetics of vildagliptin has been reported in patients with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment has been reported to be decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment has been reported to be increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. No correlation between the severity of the hepatic disease and changes in exposure to vildagliptin has been reported.

Renal Impairment

Vildagliptin AUC has been reported to increase on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151 and BQS867 has been reported to increase on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. Limited reported data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations were approximately 2-3-fold higher than in patients with severe renal impairment.

Vildagliptin has been reported to be removed by haemodialysis to a limited extent (3% over a 3 to 4-hour haemodialysis session starting 4 hours post dose).

Ethnic Group
Limited reported data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

INDICATIONS

SUCRALO is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- as monotherapy
- as combination therapy
  - Initial combination with metformin when diabetes is not adequately controlled by diet and exercise alone
  - in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control.

DOSE AND METHOD OF ADMINISTRATION

Adults

When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

When used as initial combination therapy with metformin, the recommended dose of vildagliptin is 50 mg once or twice daily.

Doses higher than 100 mg are not recommended.

If a dose of vildagliptin 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 reported.

Vildagliptin can be administered with or without a meal**.**

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 vildagliptin is 50 mg once daily**.**

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

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

Paediatric population
Vildagliptin 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 reported.

CONTRAINDICATIONS

Vildagliptin is contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients of the formulation.

WARNINGS AND PRECAUTIONS

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

Renal impairment
There is limited reported data in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore, vildagliptin should be used with caution in these patients**.**

Hepatic impairment
Vildagliptin 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 tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin 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 LFTs until the abnormality(ies) return(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of therapy with vildagliptin is recommended.

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

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

Cardiac failure
Treatment with vildagliptin has not been reported to be 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 vildagliptin is still limited and the results are inconclusive**.**

There is no reported experience of vildagliptin use in patients with NYHA functional class IV and therefore use of vildagliptin is not recommended in these patients.

Skin disorders
Skin lesions, including blistering and ulceration have been reported in extremities of monkeys. Although skin lesions have not been reported at an increased incidence in humans, there is 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 vildagliptin has been reported to be associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis.

If pancreatitis is suspected, vildagliptin 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.

Hypoglycaemia
Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Severe and Disabling Arthralgia
Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Excipients
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.

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

USE IN SPECIAL POPULATIONS

Pregnancy
No adequate data from the use of vildagliptin in pregnant women has been reported. Reproductive toxicity at high doses have been reported in animals. The potential risk for humans is unknown. Due to lack of human data, vildagliptin should not be used during pregnancy.

Breast-feeding
It is unknown whether vildagliptin is excreted in human milk. Excretion of vildagliptin in milk have been reported in animals. Vildagliptin should not be used during breast-feeding.

Fertility
There are no reported data on the effect of vildagliptin on human fertility.

DRUG INTERACTIONS

Vildagliptin has 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
No clinically relevant pharmacokinetic interactions have been reported with these oral antidiabetics.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)
No clinically relevant pharmacokinetic interactions have been reported in healthy subjects. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin
No clinically relevant pharmacokinetic interactions have been reported after co-administration of amlodipine, ramipril, valsartan and simvastatin with vildagliptin in healthy subjects.

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 hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

UNDESIRABLE EFFECTS

Summary of the safety profile
Safety data has been reported from 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) for at least 12 weeks duration.

The majority of reported adverse reactions with vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) were mild and transient, not requiring treatment discontinuations. No association has been reported 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 has been generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. 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) has been reported to be 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 has been 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

Combination with metformin

Table: Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with metformin

Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor, dizziness, headache
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Combination with a sulphonylurea

Table: Adverse reactions reported in patients who received vildagliptin 50 mg in combination with a sulphonylurea

Infections and infestations	
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor, headache, dizziness, asthenia
Gastrointestinal disorders	
Uncommon	Constipation

Combination with a thiazolidinedione

Table: Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with a thiazolidinedione

Nervous system disorders	
Uncommon	Headache, asthenia
Metabolism and nutrition disorders	

Common	Weight increase
Uncommon	Hypoglycaemia
Vascular disorders	
Common	Oedema peripheral

The incidence of peripheral oedema when vildagliptin 100 mg daily was added to a maximum dose of background pioglitazone (45 mg once daily) has been reported to be 7.0%, compared to 2.5% for background pioglitazone alone.

Monotherapy

Table: Adverse reactions reported in patients who received vildagliptin 100 mg daily as monotherapy

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

No additional safety signals or unforeseen risks with vildagliptin monotherapy has been reported.

Combination with metformin and a sulphonylurea

Table: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea

Metabolism and nutritional disorders	
Common	Hypoglycaemia
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: Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin).

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

Post-marketing experience

Table: 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

OVERDOSE

Signs and symptoms

Information regarding overdose with vildagliptin is limited.

At 400 mg, three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels has been reported. At 600 mg, one subject has been reported to experience oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP), and myoglobin levels. Three other subjects has been reported to experience oedema 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. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

STORAGE
Store below 30°C, protect from moisture

Pack Style:

- Cold form blister pack of 10 tablets and 3 x 10 tablets packed in carton along with pack insert
- Desiccant embedded cold form blister pack of 10 tablets and 3 x 10 tablets packed in carton along with pack insert

Manufacturer
Sun Pharmaceutical Industries Ltd.
Village Ganguwala, Paonta Sahib – 173 025,
District Sirmour, Himachal Pradesh. INDIA.

Product Registration Holder
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Malaysia.

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27-Jun-2023

Note:
The pack insert font size will be min size: 7, as measure in Times New Roman