VILDISHAL M 50/1000 TABLETS

(Vildagliptin and Metformin Hydrochloride Tablets 50mg/1000mg)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vildishal M 50/1000 Tablets (Vildagliptin and Metformin Hydrochloride Tablets 50mg/1000mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No	Name	Quantity per Tablet (mg)
Dry Mixing		
1	Metformin Hydrochloride BP	1000.00
2	Hydroxy Propyl Cellulose BP	80.00
Binder (Paste Preparation)		
3	Hydroxy Propyl Cellulose BP	10.00
4	Purified Water BP	--
Blending/Lubrication		
5	Vildagliptin IH	50.00
6	Magnesium Stearate BP	5.00
Coating		
7	Uniquecoat FCNAQ (EXW) IH (Hydroxy Propyl Methyl Cellulose USP, Polyethylene Glycol USP, Purified Talc USP, Titanium Dioxide BP)	38.010
8	Sunset Yellow Lake IH	2.00
9	Isopropyl Alcohol BP	--
10	Dichloromethane BP	--

Definitions:

BP: British Pharmacopoeia

USP: United State British Pharmacopoeia

IH: In-House Specifications

3. PHARMACEUTICAL FORM

Tablet (Oral)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- As an adjunct to diet and exercise to improve glycaemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablet.
- In combination with a sulfonylurea (SU) (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.

- As add-on to insulin as an adjunct to diet and exercise to improve glycaemic control in patients when stable doses of insulin and metformin alone do not provide adequate glycaemic control.
- As an initial therapy in patients with type 2 diabetes whose diabetes is not adequately controlled by diet and exercise alone.

4.2 Posology and method of administration

- The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability.
- The recommended starting dose of Vildagliptin + metformin should be based on the patient's current regimen of vildagliptin and/or metformin.
- Based on the patient's current dose of vildagliptin and/or metformin, Vildagliptin+metformin may be initiated at either 50 mg/500 mg or 50mg/850mg or 50mg/1000mg tablet strength twice daily, one tablet in the morning and the other in the evening. The recommended daily dose is 100mg vildagliptin plus 2000mg metformin.
- Patients receiving vildagliptin and metformin from separate tablets may be switched to fixed dose combination of Vildagliptin and metformin containing the same doses of each component.
- In treatment naïve patients, Vildagliptin + metformin may be initiated at 50mg/500 mg once daily and gradually titrated to a maximum dose of 50mg/1000 mg twice daily after assessing the adequacy of therapeutic response.
- In combination therapy with SU or insulin would provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.
- When used in combination with a SU, a lower dose of the SU may be considered to reduce the risk of hypoglycaemia.
- Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider. Doses higher than 100mg of vildagliptin are not recommended.

Dose in special population:

Elderly population: Elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products should have their renal function monitored regularly.

Pediatric patients: Not recommended in children below 18 years.

Hepatic impairment: Not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.

Renal impairment: The dose is administered as per GFR ml/min.

GFR ml/min	Metformin	Vildagliptin
60 -89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function	Maximal daily dose is 100 mg.
45- 59	Starting dose should not be more than 1000mg with a maximum daily dose of 2000 mg	Maximal daily dose is 50 mg
30 -44	Starting dose should not be more than 500mg with a maximum daily dose of 1000 mg	
< 30	Metformin is contraindicated	

Route of Administration: Tablets (Oral)

4.3 Contraindications

- Hypersensitivity to either vildagliptin or metformin or any of the component of the formulation.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma
- Severe renal failure (GFR < 30 ml/min) .
- Congestive heart failure.
- Acute conditions with the potential to alter renal function, such as:
  - Dehydration
  - Severe infection
  - Shock
  - Intravascular administration of iodinated contrast agents
- Acute or chronic disease which may cause tissue hypoxia, such as:
  - Cardiac or respiratory failure
  - Recent myocardial infarction
  - Shock
  - Hepatic impairment.
  - Acute alcohol intoxication, alcoholism
  - Breast-feeding

4.4 Special warnings and precautions for use

i. General.

ii. Pregnancy

iii. Nursing Mothers

iv. Any Other

- Vildagliptin + metformin is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes
- When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold vildagliptin + metformin and temporarily administer insulin. vildagliptin + metformin may be reinstituted after the acute episode is resolved

Vildagliptin:

- Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of vildagliptin therapy is recommended.
- In patients with NYHA functional class IV and III, use of vildagliptin is not recommended
- In keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.
- There are reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. Hence, consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
- Use of vildagliptin 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, 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.
- Patients receiving vildagliptin in combination with a sulphonylurea, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Metformin:

- Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
- In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

- Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.
- Patients and/or care-givers should be informed of the risk of lactic acidosis.
- GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function
- In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.
- Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable,
- Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.
- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.

Pregnancy and nursing mothers

Vildagliptin+metformin should not be used during pregnancy and in nursing mother.

4.5 Interaction with other medicinal products and other forms of interaction

Vildagliptin:

- 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.
- 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.

Metformin:

- Concomitant use is not recommended with alcohol, Iodinated contrast agents.
- Close monitoring of renal function is necessary when starting or using NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics, in combination with metformin.
- Close monitoring of glycaemic control, dose adjustment within the recommended dose and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.
- More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.
- Co-administration of metformin with Inhibitors of Organic cation transporters (OCT1) (such as verapamil) or inducers of OCT1 (such as rifampicin) may reduce efficacy of metformin.
- Co-administration with inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Co-administration with inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.
- Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of vildagliptin+metformin may need to be adjusted during concomitant therapy and on its discontinuation.
- Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

Vildagliptin+metformin should not be used during pregnancy and in nursing mother.

4.7 Adverse Reactions

The commonly reported adverse reactions are tremor, dizziness, headache, nausea and hypoglycaemia; When combined with insulin the commonly reported adverse reactions are headache, nausea, gastroesophageal reflux disease, chills, blood glucose decreased; When combined with SU the commonly reported adverse reactions are dizziness, tremor, asthenia, hypoglycaemia, hyperhidrosis; The commonly reported adverse reactions with vildagliptin monotherapy is dizziness and with metformin

monotherapy are decreased appetite, dysgeusia, flatulence, nausea, vomiting, diarrhoea and abdominal pain.

4.8 Symptoms of Overdosage & Treatment

Vildagliptin:

Symptoms

At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced 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 experienced 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.

Metformin:

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological action:

It is combination of two antihyperglycemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes.

Vildagliptin:

Acts by 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) resulting in enhancement of sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion.

Metformin:

Acts via 3 mechanisms Viz., by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization (thus reducing insulin resistance) and by delaying intestinal glucose absorption.

Pharmacotherapeutic group: A combination therapy consisting of oral hypoglycaemic agent that is vildagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor and metformin, a biguanide.

ATC code: A10BD08

Pharmacological Category:

Oral hypoglycaemic agent

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A combination therapy consisting of oral hypoglycaemic agent that is vildagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor and metformin, a biguanide.

ATC code: A10BD08

It is combination of two antihyperglycemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes.

Vildagliptin:

Acts by 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) resulting in enhancement of sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion.

Metformin:

Acts via 3 mechanisms Viz., by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization (thus reducing insulin resistance) and by delaying intestinal glucose absorption.

5.2 Pharmacokinetic properties

Vildagliptin:

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%.The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. 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. Following oral administration, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. The elimination half-life is approximately 3 hours.

Metformin:

Absolute bioavailability is approximately 50-60% and the maximum plasma concentration is reached in approximately 2.5 hours. Plasma protein binding is negligible. Metformin is excreted unchanged in the

urine. No metabolites have been identified in humans. The apparent terminal elimination half-life is approximately 6.5 hours. Food decreases the extent and slightly delays the absorption of metformin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxy Propylcellulose BP, Magnesium Stearate BP, Uniquecoat FCNAQ (EXW) IH (Hydroxy Propyl Methyl Cellulose USP, Polyethylene Glycol USP, Purified Talc USP, Titanium Dioxide BP)

6.2 Incompatibilities

None.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

Vildishal M 50/1000 Tablets is available in Alu Alu blister pack of 10 Tablets. 3 such filled blisters are packed in a printed carton along with one leaflet.

7. MARKETING AUTHORISATION HOLDER

SHALINA HEALTHCARE DMCC

30th Floor, Almas Towers,

Jumeirah Lakes Towers Dubai-UAE.

8. MARKETING AUTHORISATION IN OTHER COUNTRIES

None