For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ENCELIN M OD/TORGLIP M OD

BOX WARNING

Lactic acidosis

Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmias. The onset of metformin associated lactic acidosis is often subtle and accompanied by non-specific symptoms such as malaise, myalgias, respiratory distress, somnolence and abdominal pain. Metformin associated lactic acidosis was characterised by elevated blood lactate levels (>5 mmol/litre), anion gap acidosis (without evidence of ketonuria or ketonemia), an increase in lactate/pyruvate ratio, and metformin in plasma levels generally >5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g. carbonic anhydrase inhibitors like topiramate), age 65 years or greater, having a radiological study

with contrast, surgery and other procedures, hypoxic states (e.g. acute congestive heart failure), excessive alcohol intake and hepatic impairment. If lactic acidosis is suspected, discontinue Vildagliptin and metformin hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name

Vildagliptin & Metformin Hydrochloride (SR) Tablets

2. Qualitative and quantitative Composition:

ENCELIN M OD 100/500 / TORGLIP M OD 100/500

Each film coated bilayered tablet contains:

Vildagliptin I.P. ……100 mg

(As Sustained Release)

Metformin Hydrochloride I.P….. 500 mg

(As Sustained Release)

Colour: Sunset Yellow Lake

(In Vildagliptin layer)

The excipients used are Methocel K100 M, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Magnesium Stearate, Polyvinylpyrrolidone K30, Isopropyl alcohol, Talcum, HPMC, Ethyl Cellulose & Methylene Dichloride.

ENCELIN M OD 100/1000 / TORGLIP M OD 100/1000

Each film coated bilayered tablet contains:

Vildagliptin I.P. ……100 mg

(As Sustained Release)

Metformin Hydrochloride I.P…... 1000 mg

(As Sustained Release)

Colour: Ferric Oxide Yellow USP-NF

(In Vildagliptin layer).

The excipients used are Methocel K100 M, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Magnesium Stearate, Polyvinylpyrrolidone K30, Isopropyl alcohol, Talcum, HPMC, Ethyl Cellulose & Methylene Dichloride

3. Dosage form and strength

Dosage form: Tablets

Strength: Vildagliptin I.P. 100 mg, Metformin Hydrochloride I.P. 500 and 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is used for the treatment of type-II diabetes mellitus inadequately controlled on metformin monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet daily. Each film coated bilayered tablet contains a fixed dose of Vildagliptin & Metformin Hydrochloride (SR) Tablets.

Method of Administration

It should be given orally once daily.

4.3 Contraindications

- Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients
- Metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma.
- Radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

4.4 Special warnings and precautions for use

General

Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin 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, 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 test results returned to normal after discontinuation of treatment. Liver function tests 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 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 vildagliptin therapy is recommended.

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

Pancreatitis

In post-marketing experience, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of vildagliptin. If pancreatitis is suspected, vildagliptin and other potentially suspect medicinal products should be discontinued.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (e.g. due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products and seek immediate medical attention. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with metformin-containing products

Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, 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.

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause prerenal azotmeia. If such events occur in patients receiving metformin-containing products, the medication should be promptly discontinued.

4.5 Drugs interactions

No clinically relevant pharmacokinetic interactions have been observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily). Drug interactions for each component of Vildagliptin + Metformin has been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin

Vildagliptin has low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medicationsmetabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug- drug interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

The following is known about metformin:

Furosemide

Furosemide increased Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased Cmax, blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine

Nifedipine increased absorption, Cmax and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide

Glyburide produced no changes in metformin PK/PD parameters. Decreases in Cmax, blood AUC of glyburide were observed, but were highly variable. Therefore, the clinical significance of this finding was unclear.

Iodinated contrast agents

Metformin-containing products (such as Galvus Met) must 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.

Drugs that reduce metformin clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin.

Other

Some drugs can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin-containing products (such as Vildagliptin + Metformin), close monitoring of renal function is necessary. Certain drugs tend to cause hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Avoid consumption of alcohol and

medicinal products containing alcohol.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Patients with renal impairment: A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3 to 6 months. The maximum daily dose of metformin should preferably be divided into 2 to 3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin-containing products in patients with GFR< 60 ml/min. Vildagliptin + Metformin is contraindicated in patients with GFR< 30 ml/min because of its metformin component.

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of vildagliptin + metformin is available, individual components should be used instead of the fixed dose combination.

Patients with hepatic impairment: Vildagliptine + Metformin combination is 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 (ULN).

Elderly patients: As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products should have their renal function monitored regularly. The use or dosage of Vildagliptine + Metformin combination should be based on renal function.

Paediatric patients: The safety and effectiveness of Vildagliptine + Metformin combination in paediatric patients have not been established. Therefore, this is not recommended for use in children below 18 years of age.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 Vildagliptin in combination with another medicinal product. 2,682 patients were treated with Vildagliptin 100 mg daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with Vildagliptin 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Information regarding overdose with Vildagliptin is limited.

Symptoms

Information on the likely symptoms of overdose was taken from a reported rising dose tolerability study in healthy subjects given Vildagliptin for 10 days. 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 reported 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 Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of the accumulated drug from patients in whom metformin hydrochloride overdosage is suspected. In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

5. Pharmacological properties

5.1 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).

Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

5.2 Pharmacodynamic properties

Vildagliptin

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 (Homeostasis Model Assessment), 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.

Metformin

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike sulphonylureas, metformin hydrochloride does not cause hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances), and does not cause hyperinsulinaemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. In humans metformin hydrochloride has favourable effects on lipid metabolism, independent of its action on glycaemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

5.3 Pharmacokinetic properties

Absorption

Vildagliptin:

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin Hydrochloride:

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration

in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of the time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered under fasting conditions. The clinical relevance of these decreases is unknown.

Distribution

Vildagliptin:

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 (Vss) is 71 L, suggesting extravascular distribution.

Metformin Hydrochloride:

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally<1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Biotransformation

Vildagliptin:

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). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in a reported in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. In- vitro studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Metformin Hydrochloride:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans

Elimination

Vildagliptin:

Following oral administration of [14C]-vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After an 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.

Metformin Hydrochloride:

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is

excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6. Nonclinical properties

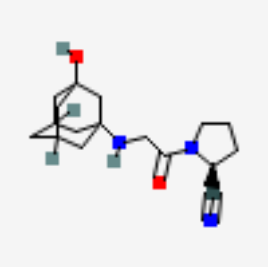
6.1 Animal Toxicology or Pharmacology

No studies were conducted

7. Description

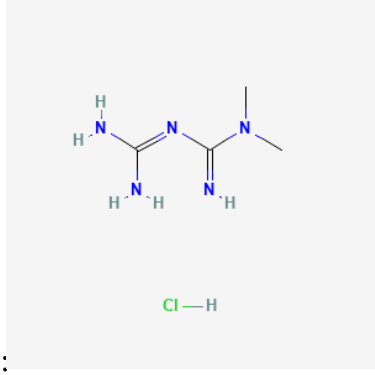
Vildagliptin:

Vildagliptin is (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile. The empirical formula is $C_{17}H_{25}N_3O_2$ and its molecular weight is 303.4g/mol. The chemical structure of Vildagliptin is:



Metformin Hydrochloride:

Metformin Hydrochloride is 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride. The empirical formula is C4H12ClN5 and molecular weight is 165.62g/mol. The chemical structure is



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ENCELIN M OD 100/500 /TORGLIP M OD 100/500

Vildagliptin & Metformin Hydrochloride Tablets are One side white coloured & other side light pink coloured, elongated, biconvex, bi-layered, film coated tablets, plain on both sides.

The excipients used are Methocel K100 M, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Magnesium Stearate, Polyvinylpyrrolidone K30, Isopropyl alcohol, Talcum, HPMC, Ethyl Cellulose & Methylene Dichloride.

ENCELIN M OD 100/1000 /TORGLIP M OD 100/1000

Vildagliptin & Metformin Hydrochloride Tablets are One side white coloured & other side light yellow coloured, elongated, biconvex, bi-layered, film coated tablets, scored on one side.

The excipients used are Methocel K100 M, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Magnesium Stearate, Polyvinylpyrrolidone K30, Isopropyl alcohol, Talcum, HPMC, Ethyl Cellulose & Methylene Dichloride

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

ENCELIN M OD/TORGLIP M OD are available in blister pack of 10 tablets

8.4 Storage and handing instructions

Store protected from moisture at a room temperature not exceeding 30°C.

Keep the medicine out of reach of children

9. Patient Counselling Information

Package leaflet: Information for the user

ENCELIN M OD/TORGLIP M OD

Vildagliptin & Metformin Hydrochloride (SR) Tablets

Vildagliptin (As sustained release) and Metformin Hydrochloride (As sustained release) Tablets

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What ENCELIN M OD/TORGLIP M OD is and what it is used for

Vildagliptin Sustained Release and Metformin Tablets contains active substances – Vildagliptin and Metformin Hydrochloride sustained release, both belong to a group of medicines called oral antidiabetics.

It is indicated for the treatment of type-II diabetes mellitus inadequately controlled on metformin monotherapy

9.2 What you need to know before you take ENCELIN M OD/TORGLIP M OD

Do not take ENCELIN M OD / TORGLIP M OD

- If you are allergic to vildagliptin, metformin or any of the other ingredients of this medicine. If you think you may be allergic to any of these, talk to your doctor before taking Encelin M OD/Torglip M OD.
- If you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called ketone bodies accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell. - if you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems.
- If you have severely reduced kidney function.
- If you have a severe infection or are seriously dehydrated (have lost a lot of water from your body).
- If you are going to have a contrast x-ray (a specific type of x-ray involving an injectable dye).
- If you have liver problems.
- If you drink alcohol excessively (whether every day or only from time to time).
- If you are breast-feeding

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking ENCELIN M OD/TORGLIP M OD:

Renal impairment

There is limited experience in patients with 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 test results returned to normal after discontinuation of treatment. Liver function tests 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 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 vildagliptin therapy is recommended.

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

Pancreatitis

In post-marketing experience, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of vildagliptin. If pancreatitis is suspected, vildagliptin and other potentially suspect medicinal products should be discontinued.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (e.g. due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products and seek immediate medical attention. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with metformin-containing products

Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, 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.

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause prerenal azotmeia. If such events occur in patients receiving metformin-containing products, the medication should be promptly discontinue.

Stop taking Encelin M OD/Torglip M OD for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Lactic acidosis is a medical emergency and must be treated in a hospital.

Encelin M OD/Torglip M OD is not a substitute for insulin. Therefore, you should not receive Encelin M OD/Torglip M OD for the treatment of type 1 diabetes.

Talk to your doctor, pharmacist or nurse before taking Encelin M OD/Torglip M OD if you have or have had a disease of the pancreas.

Talk to your doctor, pharmacist or nurse before taking Encelin M OD/Torglip M OD if you are taking an anti-diabetic medicine known as a sulphonylurea. Your doctor may want to reduce your dose of the sulphonylurea when you take it together with Encelin M OD/Torglip M OD in order to avoid low blood glucose (hypoglycaemia).

If you have previously taken vildagliptin but had to stop taking it because of liver disease, you should not take this medicine.

Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking Encelin M

OD/Torglip M OD. Should these occur, you should promptly consult your doctor.

If you need to have major surgery you must stop taking Encelin M OD/Torglip M OD during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Encelin M OD/Torglip M OD.

A test to determine your liver function will be performed before the start of Encelin M OD/Torglip M OD treatment, at three-month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible.

During treatment with Encelin M OD/Torglip M OD, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or have worsening renal function.

Your doctor will test your blood and urine for sugar regularly.

Children and adolescents

The use of ENCELIN M OD/TORGLIP M OD in children and adolescents up to 18 years of age is not recommended.

Other medicines and ENCELIN M OD/TORGLIP M OD

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Encelin M OD/Torglip M OD before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Encelin M OD/Torglip M OD.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Encelin M OD/Torglip M OD. It is especially important to mention the following:

- glucocorticoids generally used to treat inflammation
- beta-2 agonists generally used to treat respiratory disorders
- other medicines used to treat diabetes
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- certain medicines affecting the thyroid
- certain medicines affecting the nervous system
- certain medicines used to treat angina (e.g. ranolazine)
- certain medicines used to treat HIV infection (e.g. dolutegravir)
- certain medicines used to treat a specific type of thyroid cancer (medullary thyroid cancer) (e.g. vandetanib)
- certain medicines used to treat heartburn and peptic ulcers (e.g cimetidine)

ENCELIN M OD/TORGLIP M OD with alcohol

Avoid excessive alcohol intake while taking ENCELIN M OD/TORGLIP M OD since this may increase the risk of lactic acidosis.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine

Do not use ENCELIN M OD/TORGLIP M OD if you are pregnant or breast-feeding.

Driving and using machines

If you feel dizzy while taking this medicine, do not drive or use machines.

9.3 How to take ENCELIN M OD/TORGLIP M OD

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will prescribe the strength that is right for you.

Taking this medicine

• Swallow the tablet whole with half a glass of water.

If you take more ENCELIN M OD/TORGLIP M OD than you should

Contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take ENCELIN M OD/TORGLIP M OD

If you forget to take a tablet, take it with your next meal unless you are due to take one then anyway. Do not take a double dose (two tablets at once) to make up for a forgotten tablet.

If you stop taking Encelin M OD/Torglip M OD

Continue to take this medicine as long as your doctor prescribes it so that it can continue to control your blood sugar. Do not stop taking Encelin M OD/Torglip M OD unless your doctor tells you to. If you have any questions about how long to take this medicine, talk to your doctor.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Stop taking this medicine and consult your doctor immediately if any of the following occur –you may need medical treatment.

You should stop taking Encelin M OD/Torglip M OD and see your doctor immediately if you experience the following side effects:

- **Lactic acidosis (very rare: may affect up to 1 user in 10,000):** Encelin M OD/Torglip M OD may cause a very rare, but very serious side effect called lactic acidosis. If this happens you must stop taking Encelin M OD/Torglip M OD and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.
- **Angioedema (rare: may affect up to 1 in 1,000 people):** Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate a reaction called “angioedema”.
- **Liver disease (hepatitis) (rare):** Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis). •
- **Inflammation of the pancreas (pancreatitis) (frequency not known):** Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to your back, as well as nausea and vomiting.

Other side effects

ENCELIN M OD/TORGLIP M OD:

- Very common (may affect more than 1 in 10 people): nausea, vomiting, diarrhoea, pain in and around the stomach (abdominal pain), loss of appetite.
- Common (may affect up to 1 in 10 people): dizziness, headache, trembling that cannot be controlled, metallic taste, low blood glucose.
- Uncommon (may affect up to 1 in 100 people): joint pain, tiredness, constipation, swollen hands, ankle or feet (oedema).
- Very rare (may affect up to 1 in 10,000 people): sore throat, runny nose, fever; signs of a high level of lactic acid in the blood (known as lactic acidosis) such as drowsiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heart beat or deep, rapid breathing; redness of the skin, itching; decreased vitamin B12 levels (paleness, tiredness, mental symptoms such as confusion or memory disturbances).

ENCELIN M OD/TORGLIP M OD and a sulphonylurea:

- Common: dizziness, tremor, weakness, low blood glucose, excessive sweating.

Some patients have had the following side effects while taking ENCELIN M OD/TORGLIP M OD and insulin:

- Common: headache, chills, nausea (feeling sick), low blood glucose, heartburn.
- Uncommon: diarrhoea, flatulence.

Frequency not known (cannot be estimated from the available data): itchy rash, inflammation of the pancreas, localised peeling of skin or blisters, muscle pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store ENCELIN M OD/TORGLIP M OD

Store protected from moisture at a room temperature not exceeding 30°C.

Keep the medicine out of reach of children

9.6 Contents of the pack and other information

What ENCELIN M OD/TORGLIP M OD contains

The active substances are Vildagliptin and Metformin Tablets.

The excipients used are Hydroxypropylmethyl Cellulose 200M (HPMC K 200M), Povidone K 30, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicon dioxide, Magnesium Stearate, Calcium Stearate, Hypromellose, Polyethylene Glycol, Lactose monohydrate, Pregelatinized Starch, Ferric Oxide Yellow, Dicalcium phosphate anhydrous, carbomer (Biopal 974P).

What ENCELIN M OD/TORGLIP M OD looks like and contents of the pack

ENCELIN M OD/TORGLIP M OD is available in blister pack of 10 tablets

10. Details of manufacturer

Synokem Pharmaceutical Ltd.

Plot No-56-57, Sector-6A, I.I.E (SIDCUL), Ranipur (BHEL),

Haridwar-249403 (Uttarakhand)

11. Details of permission or licence number with date

Lic.No. 27/UA/2018 issued on 11.01.2023

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ENCELIN M OD/TORGLIP M OD/Jan 23/01/PI