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

ENCELIN 50
(VILDAGLIPTIN TABLETS**)**

1. Generic Name

Vildagliptin Tablets I.P.

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Vildagliptin I.P.…….50 mg

Colour : Yellow oxide of Iron

Excipients……..…….q.s.

The other ingredients are microcrystalline cellulose, lactose, sodium starch glycollate, ferric oxide yellow, polyvinyl pyrrolidone, isopropyl alcohol, magnesium stearate.

3. Dosage form and strength

Dosage form: Uncoated Tablets

Strength: 50 mg

4. Clinical particulars

4.1 Therapeutic indication

As an adjunct to diet and exercise to improve glycemic control in patients with type-II diabetes mellitus.

4.2 Posology and method of administration

Posology

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.

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 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 Vildagliptin is 50 mg once daily.

Hepatic impairment

Vildagliptin 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).

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 established. No data are available.

Method of administration

Oral use

Vildagliptin can be administered with or without a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

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.

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

Cardiac failure

A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin 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 vildagliptin is still limited and results are inconclusive.

There is no experience of vildagliptin 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 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.

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.

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.

4.5 Drugs interactions

Combinations not recommended

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

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

Pregnancy

There are no adequate data from the use of vildagliptin in pregnant women. Reported studies in animals have shown reproductive toxicity at high doses. 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. Reported animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for vildagliptin.

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 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 reported 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 (ACEInhibitor). 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 vildagliptin in reported 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 vildagliptin 100 mg daily in combination with metformin in double-blind studies (N=208)

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

Description of selected adverse reactions

In reported 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 reported clinical trials, the incidence of hypoglycaemia 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 hypoglycaemic events were reported in the vildagliptin arms.

In reported 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 vildagliptin and placebo, respectively).

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

Combination with a sulphonylurea

Table 2 Adverse reactions reported in patients who received vildagliptin 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

Description of selected adverse reactions

In reported controlled clinical trials with the combination of vildagliptin 50 mg + a sulphonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + sulphonylurea vs 0% in the placebo + sulphonylurea treatment group.

In reported clinical trials, the incidence of hypoglycaemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.

In reported clinical trials, weight did not change from baseline when vildagliptin 50 mg daily was added to glimepiride (-0.1 kg and -0.4 kg for vildagliptin and placebo, respectively).

Combination with a thiazolidinedione

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

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

Description of selected adverse reactions

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

In reported clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.6%) but common in patients receiving placebo + pioglitazone (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study reported, the absolute weight increases with placebo, vildagliptin 100 mg daily were 1.4 and 2.7 kg, respectively.

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

Monotherapy

Table 4 Adverse reactions reported in patients who received vildagliptin 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	Hypoglycaemia
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Oedema peripheral
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia

Description of selected adverse reactions

In addition, in controlled monotherapy trials with vildagliptin the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.5%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with metformin and a sulphonylurea

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

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

Description of selected adverse reactions

There were no withdrawals due to adverse reactions reported in the vildagliptin + metformin + glimepiride treatment group versus 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycaemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride group versus 1.9% for the placebo + metformin + glimepiride group). One severe hypoglycaemic event was reported in the vildagliptin group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

Combination with insulin

Table 6 Adverse reactions reported in patients who received vildagliptin 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-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Description of selected adverse reactions

In reported controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no withdrawals in the placebo group.

The incidence of hypoglycaemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4% in the placebo group). Two patients reported severe hypoglycaemic events in the vildagliptin group, and 6 patients in the placebo group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

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

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

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 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 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.

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).

5.2 Pharmacodynamic properties

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 DPP-4 inhibitor.

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 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.

Clinical efficacy and safety

More than 15,000 patients with type 2 diabetes participated in reported double-blind placebo- or active-controlled clinical trials of up to more than 2 years' treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily were ≥ 65 years. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 8).

In reported clinical trials, the magnitude of HbA_{1c} reductions with vildagliptin was greater in patients with higher baseline HbA_{1c}.

In a 52-week double-blind controlled reported trial, vildagliptin (50 mg twice daily) reduced baseline HbA_{1c} by -1% compared to -1.6% for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week double-blind controlled reported trial, vildagliptin (50 mg twice daily) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20% with vildagliptin and -1.48% with rosiglitazone in patients with mean baseline HbA_{1c} of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1% respectively).

In a reported clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day). After two years, mean reduction in HbA_{1c} was -0.5% for vildagliptin and -0.6% for gliclazide, from a mean baseline HBA_{1c} of 8.6%. Statistical non-inferiority was not achieved. Vildagliptin was associated with fewer hypoglycaemic events (0.7%) than gliclazide (1.7%).

In a 24-week reported trial, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2020 mg).

Mean reductions from baseline HbA_{1c} of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.

In a reported clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA_{1c} of 7.3%. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 52-week reported trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1928 mg/day). After 1 year, mean reductions in HbA_{1c} were -0.81% with vildagliptin added to metformin (mean baseline HbA_{1c} 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA_{1c} 8.5%); statistical non-inferiority was achieved (95% CI -0.11 – 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.

In a 24-week reported trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA_{1c} by -1.82%, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA_{1c} of 8.6%. The decrease in HbA_{1c} observed in patients with a baseline ≥10.0% was greater.

A 24-week, multi-centre, randomised, double-blind, placebo-controlled reported trial was conducted to evaluate the treatment effect of vildagliptin 50 mg once daily compared to placebo in 515 patients with type 2 diabetes and moderate renal impairment (N=294) or severe renal impairment (N=221). 68.8% and 80.5% of the patients with moderate and severe renal impairment respectively were treated with insulin (mean daily dose of 56 units and 51.6 units respectively) at baseline. In patients with moderate renal impairment vildagliptin significantly decreased HbA_{1c} compared with placebo (difference of -0.53%) from a mean baseline of 7.9%. In patients with severe renal impairment, vildagliptin significantly decreased HbA_{1c} compared with placebo (difference of -0.56%) from a mean baseline of 7.7%.

A 24-week reported randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥1500 mg daily) and glimepiride (≥4 mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA_{1c} compared with placebo.The placebo-adjusted mean reduction from a mean baseline HbA_{1c} of 8.8% was -0.76%.

A 24-week reported randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA_{1c} compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA_{1c} 8.8% was -0.72%. In the

subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA_{1c} was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).

In another 24-week reported study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA_{1c} when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).

A 52-week reported multi-centre, randomised, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (NYHA functional class I-III) to evaluate the effect of vildagliptin 50 mg twice daily (N=128) compared to placebo (N=126) on left-ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were balanced overall. There were more cardiac events in vildagliptin treated patients with NYHA class III heart failure compared to placebo. However, there were imbalances in baseline cardiovascular risk favouring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA_{1c} compared with placebo (difference of 0.6%) from a mean baseline of 7.8% at week 16. In the subgroup with NYHA class III, the decrease in HbA_{1c} compared to placebo was lower (difference 0.3%) but this conclusion is limited by the small number of patients (n=44). The incidence of hypoglycaemia in the overall population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.

Cardiovascular risk

A reported meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and IV monotherapy and combination therapy clinical studies of up to more than 2 years duration (mean exposure 50 weeks for vildagliptin and 49 weeks for comparators) was performed and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute myocardial infarction, stroke or cardiovascular death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95% CI 0.61-1.11)]. A MACE occurred in 83 out of 9,599 (0.86%) vildagliptin-treated patients and in 85 out of 7,102 (1.20%) comparator-treated patients. Assessment of each individual MACE component showed no increased risk (similar M-H RR). Confirmed heart failure (HF) events defined as HF requiring hospitalisation or new onset of HF were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients with M-H RR 1.08 (95% CI 0.68-1.70).

Table 8 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

Monotherapy placebo controlled studies	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%) at week 24**	**Placebo-corrected mean change in HbA_{1c} (%) at week 24 (95% CI)**
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)

Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
		* p< 0.05 for comparison versus placebo	
Add-on / Combination studies			
Vildagliptin 50 mg twice daily + metformin (N=143)	8.4	-0.9	-1.1* (-1.4, -0.8)
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + metformin + glimepiride (N=152)	8.8	-1.0	-0.8* (-1.0, -0.5)
		* p< 0.05 for comparison versus placebo + comparator	

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus.

5.3 Pharmacokinetic 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 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 (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. Vildagliptin 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.

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.

Characteristics in specific groups of patients

Gender

No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Elderly

In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 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 was studied 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 was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of the hepatic disease and changes in the exposure to vildagliptin.

Renal impairment

A multiple-dose, open-label trial was conducted to evaluate the pharmacokinetics of the lower therapeutic dose of vildagliptin (50 mg once daily) in patients with varying degrees of chronic renal impairment defined by creatinine clearance (mild: 50 to <80 ml/min, moderate: 30 to <50 ml/min and severe: <30 ml/min) compared to normal healthy control subjects.

Vildagliptin AUC increased 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 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. Limited 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 was removed by haemodialysis to a limited extent (3% over a 3-4 hour haemodialysis session starting 4 hours post dose).

Ethnic group

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

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

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

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

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

In reported study 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.

In a reported 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 reported 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.

7. Description

Light yellow to yellow colored, round, uncoated, debossed with “N1” on one side and plain on the other side with occasionally black specks.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Available in 10 BLISTER STRIPS OF 10 TABLETS EACH.

8.4 Storage and handing instructions

STORE AT A TEMPERATURE

NOT EXCEEDING 30°C,

PROTECT FROM MOISTURE.

9. Patient Counselling Information

ENCELIN 50

VILDAGLIPTIN TABLETS

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, 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 is and what it is used for

9.2. What you need to know before you use ENCELIN

9.3. How to use ENCELIN

9.4. Possible side effects

9.5. How to store ENCELIN

9.6. Contents of the pack and other information

9.1 What ENCELIN is and what it is used for

The active substance of ENCELIN, vildagliptin, belongs to a group of medicines called “oral antidiabetics”.

ENCELIN is used to treat adult patients with type 2 diabetes. It is used when diabetes cannot be controlled by diet and exercise alone. It helps to control the level of sugar in the blood. Your doctor will prescribe ENCELIN either alone or together with certain other antidiabetic medicines which you will already be taking, if these have not proved sufficiently effective to control diabetes.

Type 2 diabetes develops if the body does not make enough insulin or if the insulin that the body makes does not work as well as it should. It can also develop if the body produces too much glucagon.

Insulin is a substance which helps to lower the level of sugar in the blood, especially after meals.

Glucagon is a substance which triggers the production of sugar by the liver, causing the blood sugar level to rise. The pancreas makes both of these substances.

How ENCELIN works

ENCELIN works by making the pancreas produce more insulin and less glucagon. This helps to control the blood sugar level. This medicine has been shown to reduce blood sugar, which may help to prevent complications from your diabetes. Even though you are now starting a medicine for your diabetes, it is important that you continue to follow the diet and/or exercise which has been recommended for you.

9.2 What you need to know before you use ENCELIN

Do not take ENCELIN:

if you are allergic to vildagliptin or any of the other ingredients of this medicine. If you think you may be allergic to vildagliptin or any of the other ingredients of ENCELIN, do not take this medicine and talk to your doctor.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking ENCELIN

- if you have type 1 diabetes (i.e. your body does not produce insulin) or if you have acondition called diabetic ketoacidosis.
- 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 in order to avoid low blood glucose [hypoglycaemia]).
- if you have moderate or severe kidney disease (you will need to take a lower dose of ENCELIN).
- if you are on dialysis.
- if you have liver disease.
- if you suffer from heart failure.
- if you have or have had a disease of the pancreas.

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. Should these occur, you should promptly consult your doctor.

A test to determine your liver function will be performed before the start of ENCELIN 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.

Children and adolescents

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

Other medicines and ENCELIN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may wish to alter your dose of ENCELIN if you are taking other medicines such as:

- thiazides or other diuretics (also called water tablets)
- corticosteroids (generally used to treat inflammation)
- thyroid medicines
- certain medicines affecting the nervous system

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.

You should not use ENCELIN during pregnancy. It is not known if ENCELIN passes into breast milk. You should not use ENCELIN if you are breast-feeding or plan to breast-feed.

Driving and using machines

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

ENCELIN contains lactose

ENCELIN contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

9.3 How to take ENCELIN

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

How much to take and when

The amount of ENCELIN people have to take varies depending on their condition. Your doctor will tell you exactly how many tablets of ENCELIN to take. The maximum daily dose is 100 mg.

The usual dose of ENCELIN is either:

- 50 mg daily taken as one dose in the morning if you are taking ENCELIN with another medicine called a sulphonylurea.
- 100 mg daily taken as 50 mg in the morning and 50 mg in the evening if you are taking ENCELIN alone, with another medicine called metformin or a glitazone, with a combination of metformin and a sulphonylurea, or with insulin.
- 50 mg daily in the morning if you have moderate or severe kidney disease or if you are on dialysis.

How to take ENCELIN

Swallow the tablets whole with some water.

How long to take ENCELIN

- Take ENCELIN every day for as long as your doctor tells you. You may have to take this treatment over a long period of time.
- Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you take more ENCELIN than you should
- If you take too many ENCELIN tablets, or if someone else has taken your medicine, talk to your doctor straight away. Medical attention may be needed. If you need to see a doctor or go to the hospital, take the pack with you.

If you forget to take ENCELIN

If you forget to take a dose of this medicine, take it as soon as you remember. Then take your next dose at the usual time. If it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking ENCELIN

Do not stop taking ENCELIN unless your doctor tells you to. If you have 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.

Some symptoms need immediate medical attention:

You should stop taking ENCELIN and see your doctor immediately if you experience the following side effects:

- Angioedema (rare: may affect up to 1 in 1,000 people): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulties breathing, sudden onset 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.

Some patients have had the following side effects while taking ENCELIN and metformin:

- Common (may affect up to 1 in 10 people): Trembling, headache, dizziness, nausea, low blood glucose
- Uncommon (may affect up to 1 in 100 people): Tiredness

Some patients have had the following side effects while taking ENCELIN and a sulphonylurea:

- Common: Trembling, headache, dizziness, weakness, low blood glucose
- Uncommon: Constipation
- Very rare (may affect up to 1 in 10,000 people): Sore throat, runny nose

Some patients have had the following side effects while taking ENCELIN and a glitazone:

- Common: Weight increase, swollen hands, ankle or feet (oedema)
- Uncommon: Headache, weakness, low blood glucose

Some patients have had the following side effects while taking ENCELIN alone:

- Common: Dizziness
- Uncommon: Headache, constipation, swollen hands, ankle or feet (oedema), joint pain, low blood glucose
- Very rare: Sore throat, runny nose, fever

Some patients have had the following side effects while taking ENCELIN, metformin and a sulphonylurea:

- Common: Dizziness, tremor, weakness, low blood glucose, excessive sweating

Some patients have had the following side effects while taking ENCELIN and insulin (with or without metformin):

- Common: Headache, chills, nausea (feeling sick), low blood glucose, heartburn
- Uncommon: Diarrhoea, flatulence

Since this product has been marketed, the following side effects have also been reported:

- 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 side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

How to store ENCELIN

- Keep this medicine out of the sight and reach of children
- Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last date of that month.
- Store in the original package in order to protect from moisture.
- Do not use any ENCELIN pack that is damaged or shows signs of tampering.

9.5 Contents of the pack and other information

What ENCELIN contain:

The active substance is vildagliptin.

Each tablet contains 50 mg vildagliptin.

The other ingredients are microcrystalline cellulose, lactose, sodium starch glycollate, ferric oxide yellow, polyvinyl pyrrolidone, isopropyl alcohol, magnesium stearate

10 Details of manufacturer

Torrent Pharmaceuticals Ltd.

32 No, Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135.

OR

Ravenbhel Biotech

EPIP, SIDCO, Kartholi,

Bari-Brahmana, Jammu – 181133.

11 Details of permission or licence number with date

M/563/2010 dated 20.01.2020

OR

Mfg Licence No.: JK/01/11-12/192 issued on 10.10.2020

12 Date of revision

Aug-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ENCELIN 50 mg/Aug-22/02/PI