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ENCELIN OD/TORGLIP OD

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**1. Generic Name**

Vildagliptin Sustained Release Tablets I.P. 100 mg.

**2. Qualitative and quantitative Composition:**

Each film coated sustained release tablet contains:

Vildagliptin I.P.....100 mg

Excipients .....q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Methocel K 100M, Xanthan Gum, Dibasic Calcium Phosphate, Polyvinyl Pyrrolidone K 30, Isopropyl Alcohol, Colloidal Silicon Dioxide, Carbopol 71G, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide, Talcum and Methylene Chloride.

**3. Dosage form and strength.**

**Dosage form:** Sustained Release Tablet

**Strength:** 100 mg

**4. Clinical particulars**

**4.1. Therapeutic indication**

It is indicated as an adjunct to diet and exercise to improve glycemetic control in patients with Type-II Diabetes mellitus (T2DM).

**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 ( $\geq 65$ years)*

No dose adjustments are necessary in elderly patients.

#### *Renal impairment*

No dose adjustment is required in patients with mild renal impairment (creatinine clearance  $\geq 50$  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.

### **4.5. Drugs interactions**

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

#### Combination with pioglitazone, metformin and glyburide

Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

#### Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

#### Combination with amlodipine, ramipril, valsartan or simvastatin

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

#### Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors.

As with other oral antidiabetic medicinal products the 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. 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. 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 5 451 patients exposed to vildagliptin at daily dose of 100 mg (50 mg twice daily) in randomised double-blind placebo controlled trials of at least 12 weeks duration. Of these patients, 4 622 patients received vildagliptin as monotherapy and 829 patients received placebo.

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. Hypoglycaemia has been reported in patients receiving vildagliptin concomitantly with sulphonylurea and insulin. The risk of acute pancreatitis has been reported with the use of vildagliptin.

#### 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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.

**Table: Adverse reactions reported in patients who received vildagliptin as monotherapy or as add-on therapy in controlled clinical studies and in post-marketing experience**

<b>System organ class - adverse reaction</b>	<b>Frequency</b>
<b>Infections and infestations</b>	
Nasopharyngitis	Very common
Upper respiratory tract infection	Common
<b>Metabolism and nutrition disorders</b>	
Hypoglycaemia	Uncommon
<b>Nervous system disorders</b>	
Dizziness	Common
Headache	Common
Tremor	Common
<b>Eye disorders</b>	
Vision blurred	Common
<b>Gastrointestinal disorders</b>	
Constipation	Common
Nausea	Common
Gastro-oesophageal reflux disease	Common
Diarrhoea	Common
Abdominal pain, including upper	Common
Vomiting	Common
Flatulence	Uncommon
Pancreatitis	Rare
<b>Hepatobiliary disorders</b>	
Hepatitis	Not known*
<b>Skin and subcutaneous tissue disorders</b>	
Hyperhidrosis	Common
Rash	Common
Pruritis	Common
Dermatitis	Common
Urticaria	Uncommon
Exfoliative and bullous skin lesions, including bullous pemphigoid	Not known*
Cutaneous vasculitis	Not known*
<b>Musculoskeletal and connective tissue disorders</b>	
Arthralgia	Common
Myalgia	Common
<b>Reproductive system and breast disorders</b>	
Erectile dysfunction	Uncommon
<b>General disorders and administration site conditions</b>	
Asthenia	Common

<b>System organ class - adverse reaction</b>	<b>Frequency</b>
Oedema peripheral	Common
Fatigue	Uncommon
Chills	Uncommon
<b>Investigations</b>	
Abnormal liver function tests	Uncommon
Weight increase	Uncommon
*Based on post-marketing experience	

### *Description of selected adverse reactions*

#### Hepatic impairment

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.

#### Angioedema

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.

#### Hypoglycaemia

Hypoglycaemia was uncommon when vildagliptin (0.4%) was used as monotherapy in comparative controlled monotherapy studies with an active comparator or placebo (0.2%). No severe or serious events of hypoglycaemia were reported. When used as add-on to metformin, hypoglycaemia occurred in 1% of vildagliptin-treated patients and in 0.4% of placebo-treated patients. When pioglitazone was added, hypoglycaemia occurred in 0.6% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. When sulphonylurea was added, hypoglycaemia occurred in 1.2% of vildagliptin treated patients and in 0.6% of placebo-treated patients. When sulphonylurea and metformin were added, hypoglycaemia occurred in 5.1% of vildagliptin treated patients and in 1.9% of placebo treated patients. In patients taking vildagliptin in combination with insulin, the incidence of hypoglycaemia was 14% for vildagliptin and 16% for placebo.

#### **Reporting of 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. Report suspected adverse reactions via any point of contact available at [www.torrentpharma.com](http://www.torrentpharma.com).

## 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 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

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- $\beta$  (Homeostasis Model Assessment- $\beta$ ), 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  $\geq 65$  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 HbA1c from baseline at study endpoint.

In reported clinical trials, the magnitude of HbA1c reductions with vildagliptin was greater in patients with higher baseline HbA1c.

In a 52-week double-blind controlled trial, vildagliptin (50 mg twice daily) reduced baseline HbA1c 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 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 HbA1c 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 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 HbA1c was -0.5% for vildagliptin and -0.6% for gliclazide, from a mean baseline HbA1c 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 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 HbA1c 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 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 HbA1c were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA1c 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 HbA1c was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 52-week 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 HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 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 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 HbA1c 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 HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline  $\geq 10.0\%$  was greater.

A 24-week, multi-centre, randomised, double-blind, placebo-controlled 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 HbA1c compared with placebo (difference of -0.53%) from a mean baseline of 7.9%. In patients with severe renal impairment, vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.56%) from a mean baseline of 7.7%.

A 24-week 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 ( $\geq 1500$  mg daily) and glimepiride ( $\geq 4$  mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA1c compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA1c of 8.8% was -0.76%.

A 24-week 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 HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA1c 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c 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 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 HbA1c 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 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 HbA1c 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 HbA1c 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.

A five-year multi-centre, randomised, double-blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the effect of an early combination therapy with vildagliptin and metformin (N = 998) against standard-of-care initial metformin monotherapy followed by combination with vildagliptin (sequential treatment group) (N = 1 003) in newly diagnosed patients with type 2 diabetes. The combination regimen of vildagliptin 50 mg twice daily plus metformin resulted in a statistically and clinically significant relative reduction in hazard for “time to confirmed initial treatment failure” (HbA1c value  $\geq 7\%$ ) vs metformin monotherapy in treatment-naïve patients with type 2 diabetes over the 5-year study duration (HR [95% CI]: 0.51 [0.45, 0.58];  $p < 0.001$ ). The incidence of initial treatment failure (HbA1c value  $\geq 7\%$ ) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group.

### Cardiovascular risk

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

<b>Monotherapy placebo controlled studies</b>	<b>Mean baseline HbA1c (%)</b>	<b>Mean change from baseline in HbA1c (%) at week 24</b>	<b>Placebo-corrected mean change in HbA1c (%) at week 24 (95% CI)</b>
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)
<b>Add-on / Combination studies</b>		* $p < 0.05$ for comparison	versus placebo
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	8.8	-1.0	-0.8* (-1.0, -0.5)

(N=152)			
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\*  $p < 0.05$  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 ( $\geq 70$  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  $\sim 30\%$ , 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**

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

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

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, 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.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at  $\geq 150$  mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

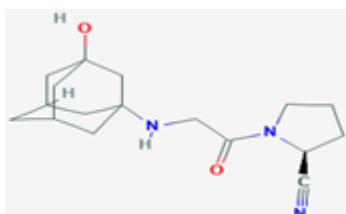
A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses  $\geq 5$  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  $\geq 20$  mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at  $\geq 80$  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

### 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 303.4 g/mol. The chemical structure is:



Vildagliptin Sustained Release Tablets 100mg are white to off white coloured, round, biconvex, plain on both side film coated tablet. The excipients used are Methocel K 100M, Xanthan Gum, Dibasic Calcium Phosphate, Polyvinyl Pyrrolidone K 30, Isopropyl Alcohol, Colloidal Silicon Dioxide, Carbopol 71G, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide, Talcum and Methylene Chloride.

## **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 OD 100/ TORGLIP OD 100** are packed in Blister strip of 10 tablets.

### **8.4. Storage and handing instructions**

Store below 30°C & Protect from light and moisture.

Keep out of reach of children.

## **9. Patient Counselling Information**

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

## **10. Details of manufacturer**

Synokem Pharmaceuticals Ltd

Plot No. 35-36, Sector - 6A,

I.I.E.(SIDCUL),Ranipur (BHEL),

Haridwar – 249403

## **11. Details of permission or licence number with date**

Mfg Lic No 19/UA/2005 issued on 06.10.2021

## **12. Date of revision**

Jan 2026

**MARKETED BY**



**TORRENT PHARMACEUTICALS LTD.**

**IN/ENCELIN OD /TORGLIP OD 100 mg/ Jan 2026/03/PI**