# VIGLITA 50 TABLET

## 1. NAME OF THE MEDICINAL PRODUCT

Viglita 50 Tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Vildagliptin INN 50 mg.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

A white to off-white color round shaped uncoated tablet, engraved “SPL” on one side and break line on other side. Free from any visible defects.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Viglita is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

- As monotherapy
- In dual combination with Metformin, a Sulphonylurea, a Thiazolidinedione, or Insulin when diet, exercise and a single antidiabetic agent do not result in adequate glycemic control.

### 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 Viglita 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 (see also sections 5.1 and 5.2).

*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 Viglita is 50 mg once daily (see also sections 4.4, 5.1 and 5.2).

*Hepatic impairment*

Viglita 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) (see also sections 4.4 and 5.2).

*Paediatric population*

Viglita is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Viglita in children and adolescents (< 18 years) have not been established. No data are available (see also section 5.1).

Method of administration

Oral use

Viglita can be administered with or without a meal (see also section 5.2).

## 4.3 Contraindications

Vildagliptin is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with type 1 diabetes or for the treatment of diabetic ketoacidosis

## 4.4 Special warnings and precautions for use

General
Viglita is not a substitute for insulin in insulin-requiring patients. Viglita 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 Viglita should be used with caution in these patients (see also sections 4.2, 5.1 and 5.2).
Hepatic impairment
Viglita should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN (see also sections 4.2 and 5.2).
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 Viglita in order to know the patient's baseline value. Liver function should be monitored during treatment with Viglita 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 Viglita therapy is recommended.
Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Viglita.
Following withdrawal of treatment with Viglita and LFT normalisation, treatment with Viglita 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 (see section 5.1).
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 (see section 5.3). 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 Interaction with other medicinal products and other forms of interaction

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 ACEinhibitors.(see section 4.8).

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 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Viglita 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. Viglita should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for Viglita (see section 5.3).

## 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 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, nonprogressive in nature and not associated with cholestasis or jaundice.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Tabulated list of adverse reactions

Adverse reactions reported in patients who received Viglita in 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 Viglita 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 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 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 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). 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 Viglita 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 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 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 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 Viglita 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 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 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, the absolute weight increases with placebo, Viglita 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 Viglita 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 Viglita 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 Viglita 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 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).

Reporting suspected adverse reactions after Authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national pharmacovigilance reporting system.

*Post-marketing experience*

**Table 7 post-marketing adverse reactions**

| | |
|---|---|
| **Gastrointestinal disorders** | |
| Not known | Pancreatitis |
| **Hepatobiliary disorders** | |
| Not known | Hepatitis (reversible upon dis continuation of the medicinal product)<br>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<br>Exfoliative and bullous skin lesions, including bullous pemphigoid |

## 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 Viglita 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 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.

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).

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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 leftventricular 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 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 (see section 4.2 for information on paediatric use).

## 5.2 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 Viglita 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.

## 5.3 Preclinical safety data

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 ≥ 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 twoyear 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 ≥ 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline Cellulose (Avicel PH 102)
Lactose (Spray Dried)
Sodium Starch Glycolate (Primojel)
Magnesium Stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 Years.

### 6.4 Special precautions for storage

Store below 30° C. Protect from light and moisture. Keep away from reach of children.

### 6.5 Nature and contents of container

Each box contains 10 / 20 / 30 / 50 / 100 tablets in blister pack.
(Pack size may be different as per customer requirement)

## 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORIZATION HOLDER

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## 8. MARKETING AUTHORIZATION NUMBER:

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## 10. DATE OF REVISION OF THE TEXT

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