***For the Use of a Registered Medical Practitioner only***

## 1. GENERIC NAME AND BRAND NAME

Vildagliptin and Metformin Hydrochloride Sustained-release Tablets I.P.
**Abvida® - M 50/500**
**Abvida® - M 50/1000**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Abvida® - M 50/500**
Each film coated tablet contains:

| | |
|---|---|
| Vildagliptin I.P. | 50 mg |
| Metformin Hydrochloride I.P. (as sustained release) | 500 mg |
| Excipients | q.s. |

Colour: Brilliant Blue FCF Lake, Indigo Carmine Lake, Yellow Oxide of Iron and Titanium Dioxide I.P.

**Abvida® - M 50/1000**
Each film coated tablet contains:

| | |
|---|---|
| Vildagliptin I.P. | 50 mg |
| Metformin Hydrochloride I.P. (as sustained release) | 1000 mg |
| Excipients | q.s. |

Colour: Brilliant Blue FCF Lake, Indigo Carmine Lake, Yellow Oxide of Iron and Titanium Dioxide I.P.

## 3. DOSAGE FORM AND STRENGTH

Kindly refer to section 1 & 2

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATION

For the treatment of Type 2 diabetes mellitus when single drug therapy along with diet, exercise do not result in adequate glycemic control**.**

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

**Dosage**

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. In using **FDC of Vildagliptin and Metformin** SR do not exceed the maximum daily dose of vildagliptin (100 mg) and Metformin SR 2000mg.

The dosage of FDC of Vildagliptin and Metformin SR should be based on the patient's conditionand/or current regimen of vildagliptin and/or metformin hydrochloride.

The FDC may be initiated at either the 50 mg/500 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.

For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy:

The starting dose of the FDC should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken, or the nearest therapeutically appropriate dose. Following a switch from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made

accordingly.
For patients switching from co-administration of vildagliptin and metformin as separate tablets:
The FDC should be initiated at the dose of vildagliptin and metformin already being taken

**General target population**
Adults 18 years of age and above.

**Special populations Renal impairment**
Factors that may increase the risk of lactic acidosis (see section WARNINGS AND PRECAUTIONS) should be reviewed before considering initiation of metformin-containing products (such as the FDC) in patients with GFR<60 ml/min. The FDC is contraindicated in patients with GFR <30 ml/min because of its metformin component (see section CONTRAINDICATIO

If no adequate strength of FDC is available, individual mono-components should be used insteadof the fixed dose combination.

Dose adjustments in patients with renal impairment :-

| GFR ml/min | Metformin | Vildaglipti n |
|---|---|---|
| 60-89 | Maximum daily dose is 3000 mg*.<br>Dose reduction may be considered if renal functiondeclines | Maximal daily dose is 100 mg. |
| 45-59 | Starting dose should not be more than 1000mg with amaximum daily dose of 2000 mg. | Maximal daily dose is 50 mg. |
| 30-44 | Starting dose should not be more than 500mg with amaximum daily dose of 1000 mg. | |
| <30 | Metformin is contraindicated. | |

*If metformin doses higher than those achievable with the FDC alone are considered necessary

**Hepatic impairment**
FDC of Vildagliptin and Metformin SR is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (see section WARNINGS AND PRECAUTIONS).
**Pediatric patients**
Safety and effectiveness of FDC of Vildagliptin and Metformin SR in pediatric patients have notbeen established. Therefore, FDC of Vildagliptin and Metformin SR is not recommended for usein children below 18 years of age.
**Geriatric patients**
As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking FDC of Vildagliptin and Metformin SR should have their renal function monitored regularly. FDC of Vildagliptin and Metformin SR The dosage of FDC of Vildagliptin and Metformin SR for elderly patients should be adjusted based on renal function (see section CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

**Method of administration**
Oral use
FDC of Vildagliptin and Metformin SR should be given with meals to reduce the

gastrointestinal side effects associated with metformin hydrochloride.

## 4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients (see section DESCRIPTION AND COMPOSITION, sub-section Excipients).
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 ml/min) (see section SPECIAL POPULATIONS, sub-section renal impairment)
- Acute conditions with the potential to alter renal function, such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents (see section WARNINGS AND PRECAUTIONS).
- Acute or chronic disease which may cause tissue hypoxia, such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock.
- Hepatic impairment (see section WARNINGS AND PRECAUTIONS).
- Acute alcohol intoxication, alcoholism
- Breast-feeding

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**FDC of Vildagliptin and Metformin SR**

FDC of Vildagliptin and Metformin SR is not a substitute for insulin in insulin-requiring patients. FDC of Vildagliptin and Metformin SR should not be used in patients with type 1 diabetes or forthe treatment of diabetic ketoacidosis.

**Vildagliptin Hepatic impairment**

Vildagliptin is not recommended in patients with hepatic impairment, including patients with apre-treatment ALT or AST >2.5X the upper limit of normal.

**Liver enzyme monitoring**

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with FDC of Vildagliptin and Metformin SR. LFTs should bemonitored during FDC of Vildagliptin and Metformin SR treatment 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 to normal. Should an increase in AST or ALT of 3X upper limit of normal or greater persist, withdrawal oftherapy with FDC of Vildagliptin and Metformin SR is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue FDC of Vildagliptin and Metformin SR and contact their physician immediately. Following withdrawal of treatment with FDC of Vildagliptin and Metformin SR and LFT normalization, FDC of Vildagliptin and Metformin SR should not be reinitiated.

FDC of Vildagliptin and Metformin SR is not recommended in patients with hepatic impairment.

**Heart 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 CLINICAL STUDIES).

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 patient

Metformin Hydrochloride Lactic acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia (see also sections CONTRADINDICATIONS and INTERACTIONS).

**Diagnosis of lactic acidosis**

Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalized immediately (see section OVERDOSAGE).

**Monitoring of renal function**

Metformin hydrochloride is known to be substantially excreted by the kidneys, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Since advancing age is associated with reduced renal function, FDC of Vildagliptin and Metformin SR should be carefully titrated in the elderly to establish the minimum dose for adequate glycemic effect, and renal function should be monitored regularly. Also, special caution should be exercised where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID. Renal function should be assessed before the initiation of FDC of Vildagliptin and Metformin SR, then at least once a year in patients with normal renal function and at least two tofour times a year in patients with creatinine clearance at the lower limit of normal clearance and in elderly subjects. Additionally, patients in whom renal dysfunction is anticipated, should have their renal function assessed more frequently. (see section DOSAGE AND ADMINISTRATION and section CONTRAINDICATIONS)

**Concomitant medications that may affect renal function or metformin hydrochloride disposition**

Concomitant medications that may affect renal function, result in significant hemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that

are eliminated by renal tubular secretion should be used with caution (see section INTERACTIONS).

**Administration of intravascular iodinated contrast materials**

FDC of Vildagliptin and Metformin SR should be temporarily discontinued in patients

undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function and increase the risk of lactic acidosis. In patients undergoing such studies, FDC of Vildagliptin andMetformin SR should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

**Hypoxic states**

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotmeia. If such events occur in patients receiving FDC of Vildagliptin andMetformin SR therapy, the medication should be promptly discontinued.

**Surgical procedures**

Use of FDC of Vildagliptin and Metformin SR should be temporarily suspended for any surgicalprocedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

**Alcohol intake**

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving FDC of Vildagliptinand Metformin SR.

**Impaired hepatic function**

Since impaired hepatic function has been associated with some cases of lactic acidosis, a risk associated with metformin hydrochloride, FDC of Vildagliptin and Metformin SR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

**Vitamin B12 levels**

The metformin component of FDC of Vildagliptin and Metformin SR has been associated with adecrease in serum vitamin B12 levels without clinical manifestations, in approximately 7% of patients. Such decrease is very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B12 supplementation. Measurement of hematological parameters on at least an annual basis is advised for patients receiving FDC of Vildagliptin and Metformin SR and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitaminB12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at minimally two-to- three-year intervals may be useful.

**Change in clinical status of patients with previously controlled type 2 diabetes**

A patient with type 2 diabetes previously well-controlled on FDC of Vildagliptin and MetforminSR who develops laboratory abnormalities or clinical illness (especially vague and poorly definedillness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, FDC of Vildagliptin and Metformin SR must be stopped immediately and appropriate measures initiated.

**Hypoglycemia**

Hypoglycemia does not usually occur in patients receiving FDC of Vildagliptin and Metformin SR alone, but could occur when caloric intake is deficient, when strenuous

exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs.

**Loss of control of blood glucose**

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold FDC of Vildagliptin and Metformin SR and temporarily administer insulin. FDC of Vildagliptin and Metformin SR may be reinstituted after the acute episode is resolved.

## 4.5 DRUGS INTERACTIONS

**Vildagliptin**

Vildagliptin has a low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely tointeract with co-medications that are substrates, inhibitors or inducers of these enzymes. Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin wereobserved after co-administration with vildagliptin.

**Metformin Hydrochloride**

The following is known for metformin component:

**Furosemide**

Furosemide increased $C_{max}$ and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased $C_{max}$, blood AUC of furosemide, with no change in renal clearance of furosemide.

**Nifedipine**

Nifedipine increased absorption, $C_{max}$ and AUC of metformin, and increased excretion ofmetformin in urine. Metformin had minimal effects on nifedipine.

**Glyburide**

Glyburide produced no changes in metformin PK/PD parameters. Decreases in $C_{max}$, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance ofthis finding was unclear.

**Cationic drugs**

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended.

**Other**

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and metformin doseadjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of FDC of Vildagliptin and Metformin SR. Avoid consumption of alcohol and medicinal products containing alcohol (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

**WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY**

**Pregnancy**

Embryo-fetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio and produced no evidence of teratogenicity in either species. There is insufficient experience with FDC of Vildagliptin and Metformin SR in pregnant women. Therefore, FDC of Vildagliptin and Metformin SR should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Animal studies are not always predictive of human response.

**Breast-feeding**

No studies have been conducted with the combined components of FDC of Vildagliptin and Metformin SR. Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. FDC of Vildagliptin and Metformin SR should notbe administered to breast-feeding women.

**Fertility**

Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 200 times the human dose and have revealed no evidence of impaired fertility or early embryonic development due to vildagliptin. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons. No studies on the effect on human fertility have been conducted for FDC of Vildagliptin and Metformin SR.

## 4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Elderly (≥ 65 years)

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based onrenal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75years and older and metformin initiation is therefore not recommended in these patients.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and

at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g., every 3-6 months.

| GFR (mL/min) | Total maximum daily dose | Additional considerations |
|---|---|---|
| 60-89 | 2000 mg | Dose reduction may be considered in relation to declining renal function. |
| 45-59 | 2000 mg | Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose. |
| 30-44 | 1000 mg | |
| <30 | - | Metformin is contraindicated |

Pediatric population
In the absence of available data, Metformin SR should not be used in children

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
No studies on the effects of Vildagliptin 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.

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglinitides).

**4.8 UNDESIRABLE EFFECTs**

**Summary of the safety profile**

FDC of Vildagliptin and Metformin SR

The safety profile has been demonstrated in bioequivalence study conducted on FDC and co-administered vildagliptin and metformin in normal, healthy, adult, human subjects under fed conditions. Data from this study demonstrated that the test and the reference products were well tolerated. Most adverse reactions were mild and transient, not requiring treatment discontinuations.There were no deaths or serious AEs during the conduct of the study.

The data presented here relate to the administration of vildagliptin and metformin as a free or fixed dose combination.

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.

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials 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 finalon-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg 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.
In clinical trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.
Vildagliptin is weight neutral when administered in combination with metformin.
Gastrointestinal adverse reactions including diarrhea and nausea are known to occur very commonly during the introduction of metformin hydrochloride. In the vildagliptin monotherapy clinical program (n =2,264) where vildagliptin was administered 50 mg once daily, 50 mg twicedaily, or 100 mg once daily, the rate of diarrhea was 1.2%, 3.5% and 0.8 % respectively and therate of nausea was 1.7%, 3.7% and 1.7% respectively as compared to 2.9% for both in the placebogroup (n = 347) and 26.2% and 10.3%, respectively, in the metformin hydrochloride group (n =252).
Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.

**Tabulated summary of adverse drug reactions from clinical trials**
Adverse reactions reported in patients who received vildagliptin in double-blind studies as add- on to metformin and as monotherapy, are listed below, for each indication, by MedDRA systemorgan class and absolute frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

**Table 1: Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double- blind studies**

| | |
|---|---|
| **Nervous system disorders** | |
| Common | Tremor, dizziness, headache |

Long term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.
When vildagliptin was studied as initial combination therapy with metformin, no additional

safetysignal or unforeseen risk was observed.

**Combination with insulin**

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 hypoglycemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4 % in the placebo group). Two patients reported severe hypoglycemic events in thevildagliptin 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 inthe vildagliptin group and no weight change in the placebo group).

**Table 2 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with insulin (with or without metformin (n= 371)**

| | |
|---|---|
| **Nervous system disorders** | |
| Common | Headache |
| **Gastrointestinal disorders** | |
| Common | Nausea, gastrooesophageal reflux disease |
| Uncommon | Diarrhoea, flatulence |

| | |
|---|---|
| **General disorders and administration site conditions** | |
| Common | Chills |
| **Investigations** | |
| Common | Blood glucose decreased |

**Combination with SU**

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

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride vs. 1.9 % for the placebo + metformin + glimepiride). One severehypoglycemic 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 vildagliptingroup and -0.1 kg in the placebo group).

**Table 3 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and SU (n=157)**

| | |
|---|---|
| **Nervous system disorders** | |
| Common | Dizziness, tremor |
| **General disorders and administration site condition** | |
| Common | Asthenia |
| **Metabolism and nutritional disorders** | |
| Common | Hypoglycemia |
| **Skin and subcutaneous tissue disorders** | |
| Common | Hyperhidrosis |

**Vildagliptin**

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 4.

**Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) as monotherapy in double-blind studies**

| | |
|---|---|
| **Nervous system disorders** | |
| Common | Dizziness |
| Uncommon | Headache |
| **Gastrointestinal disorders** | |
| Uncommon | Constipation |
| **General disorders and administration site conditions** | |
| Uncommon | Oedema peripheral |

None of the adverse reactions reported for the vildagliptin monotherapy were observed at clinically significant higher rates when vildagliptin was administered concomitantly with metformin.
The overall incidence of withdrawals from monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).
In monotherapy studies, hypoglycemia was uncommon, reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with vildagliptin 50 mg twice 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. Vildagliptin is weight neutral when administered as monotherapy.
Long term clinical trials of up to 2 years did not show any additional safety signals or unforeseenrisks with vildagliptin monotherapy.

**Adverse drug reactions from spontaneous reports and literature cases - Post-marketing Experience (frequency not known)**
The following adverse drug reactions have been derived from post-marketing experience with FDC of Vildagliptin and Metformin SR via spontaneous case reports and literature cases. Becausethese reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.
Hepatitis, reversible upon drug discontinuation (see also section WARNINGS AND PRECAUTIONS).
Urticaria, pancreatitis, bullous and exfoliative skin lesions.
Arthralgia, sometimes severe.
**Metformin Hydrochloride**
Known adverse reactions for metformin component are summarized in Table 5.

**Table 5: Known adverse reactions for metformin**

| **Metabolism and Nutrition disorders** | |
|---|---|
| Very common | Decreased appetite |
| Very Rare | Lactic acidosis |
| **Nervous system disorders** | |
| Common | Dysgeusia |
| **Gastrointestinal disorders** | |
| Very Common | Flatulence, nausea, vomiting, diarrhea, abdominal pain |
| **Hepatobiliary disorders** | |
| Very Rare | Hepatitis** |
| **Skin and subcutaneous tissue disorders** | |
| Very rare | Skin reactions such as erythema, pruritus, urticaria |
| **Investigations** | |
| Very rare | Decrease of vitamin B12 absorption*, Liver function test abnormal |

*A decrease of vitamin B12 absorption with decrease of serum levels has been very rarely observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.
**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.
Gastrointestinal undesirable effects occur most frequently during initiation of therapy and resolvespontaneously in most cases.

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

**4.9 OVERDOSAGE**
**Signs and symptoms**
**Vildagliptin**
In healthy subjects (seven to fourteen subjects per treatment group), vildagliptin was administeredin once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses upto 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paresthesia, fever, edema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced edema of the feet and hands, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with edema of both feet, accompanied by paresthesia in two cases. All symptoms and laboratoryabnormalities resolved after study drug discontinuation.
Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by hemodialysis.

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

## 5. CLINICAL PHARMACOLOGY

### 5.1 MECHANISM OF ACTION

**FDC of Vildagliptin and Metformin SR combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.**

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase- 4(DPP-4) inhibitor that improves glycemic control. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

Metformin hydrochloride decreases hepatic glucose production, decrease intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

### 5.2 PHARMACODYNAMICS PROPERTICE

FDC of Vildagliptin and Metformin SR The efficacy and safety of the separate components have been previously established and the co-administration of the separate components have been evaluated for efficacy and safety in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled type 2 diabetes while on metforminhydrochloride therapy (see section 12 Clinical studies).

**Vildagliptin**

The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period.

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 50 to 100 mg daily in patients with type 2 diabetes significantly improved markersof beta cell function. The degree of improvement in beta-cell function is dependenton the initial degree of impairment; in non-diabetic (normal glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriateglucagon during meals in turn attenuates insulin resistance.

The enhanced increase in the insulin/glucagon ratio during hyperglycemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipemia that is not associated withvildagliptin's incretin mediated effect to improve islet function, has been observed.

**Metformin Hydrochloride**

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike sulfonylureas, metformin hydrochloride does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances and does not cause hyperinsulinemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In humans, independently of its action on glycemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc andtriglyceride levels.

## 5.3 PHARMACOKINETICS PROPERTIES

FDC of Vildagliptin and Metformin SR

Bioequivalence, in regard to the rate and extent of absorption, has been demonstrated between FDC of Vildagliptin IR and Metformin SR at 50 mg/1000 mg strength (test arm) versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses (reference arm) in normal, healthy, adult, human subjects under fed conditions.

Following oral administration, similar peak plasma concentrations of vildagliptin were attained inapproximately 6 hours and 5.5 hours in test and reference arms, respectively. Also, similar peak plasma concentrations of metformin were attained in approximately 9 hours and 8.5 hours in test and reference arms, respectively.

The following statements reflect the pharmacokinetic properties of the individual active substancesof the FDC as available in the literature:

**Vildagliptin**

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

**Metformin Hydrochloride**

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration ($C_{max}$), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35minute prolongation of time to peak plasma concentration ($T_{max}$) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered under fasting conditions. The clinical relevance of these decrease is unknown.

**Distribution Vildagliptin**

The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin is distributed equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration ($V_{SS}$) is 71 L, suggesting extravascular distribution.

**Metformin Hydrochloride**

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

**Biotransformation/metabolism Vildagliptin**

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an *in-vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. *In-vitro* studies demonstrated that vildagliptin does not inhibitor induce cytochrome P450 enzymes.

**Metformin Hydrochloride**

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

**Elimination Vildagliptin**

Following oral administration of [$^{14}$C]- vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the feces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After an intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 L/hour and 13 L/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

**Metformin Hydrochloride**

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

**Linearity**

Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

**Special populations**

**Gender Vildagliptin**

No differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by vildagliptinwas unaffected by gender.

**Metformin Hydrochloride**
Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride was comparable in males and females.

**Obesity Vildagliptin**
BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

**Hepatic impairment Vildagliptin**
The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function.The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptinfor subjects 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 hepatic function impairment and changes in exposure to vildagliptin.
The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.

**Metformin Hydrochloride**
No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects withhepatic insufficiency.

**Renal impairment Vildagliptin**
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 increased 1.6, 3.2 and 7.3-fold and that of BQS867 increased on average about 1.4, 2.7 and 7.3-fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. 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 in ESRD patients 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).

**Metformin Hydrochloride**
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased inproportion to the decrease in creatinine clearance.

**Geriatric patients Vildagliptin**

In otherwise healthy elderly subjects (≥70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32% with an 18% increase in peak plasma concentration compared toyounger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.

**Metformin Hydrochloride**
Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, thehalf-life is prolonged, and $C_{max}$ is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.
FDC of Vildagliptin and Metformin SR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

**Pediatric patients**
No pharmacokinetic data available.

**Ethnic Group Vildagliptin**
There was no evidence that ethnicity affects the pharmacokinetics of vildagliptin.

**Metformin Hydrochloride**
No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

## 6. NONCLINICAL PROPERTIES

### 6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Vildagliptin

- Single dose toxicity
  Vildagliptin exhibits low acute toxicity. In mice and rats no toxicological signs were observed after a single oral dose of 2000 mg/kg.
- Repeat dose toxicity (with toxicokinetics)
  Repeat dose toxicity studies were performed in rats (up to 26 weeks) and dogs (up to 52 weeks). These models are considered relevant, based on the lack of species specificity for the pharmacological activity of vildagliptin, and the similarities in metabolism to humans.

  The main toxicological effect noted in rats was the accumulation of clusters of foamy alveolar macrophages in the lung. Similar observations were made in mice. This finding was proposed to be due to an exaggerated pharmacological effect of DPP-4 inhibition in the rat. The clinical relevance of the lung findings in rats cannot be fully excluded. There is a considerable safety margin (5 x human AUC at NOAEL) and the findings are considered of limited importance.

  The most consistent toxicological finding in the dog was the appearance of gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhea and at higher doses, faecal blood. These signs were observed at relatively low systemic exposures (observed already at lowest dose representing 2 x human AUC). GI findings were not observed in any other species and

according to the applicant no GI disorders have been observed in clinical trials. The CHMP was of the opinion, that these findings are unlikely to be of clinical importance.

- Genotoxicity
  The data from genotoxicity studies conducted with vildagliptin in several standard genotoxicity tests do not indicate a genotoxic potential.

- Carcinogenicity
  Life-time carcinogenicity studies were performed in mice and rats. No evidence for a carcinogenic potential was observed in the rat. An increased incidence of hemangiosarcomas was observed at the highest dose in female rats while in male rats, the incidence was slightly decreased. Given the mouse findings discussed below, a relation to treatment cannot be fully excluded. In the mouse there was an increased incidence of hemangiosarcomas and mammary carcinoma. The increased incidence of hemangiosarcoma in mice occurred only in organs where this tumour occurs as a relatively common spontaneous finding in the mouse (liver, spleen, uterus etc.). It is suggested that a predisposition to spontaneous hemangiosarcoma at the affected site is needed for vildagliptin to promote an increased incidence. A study in the mouse demonstrated that vildagliptin inhibits VEGF-induced angiogenesis. Based on these mechanistic data the applicant proposes a mechanism whereby inhibition of VEGF-induced angiogenesis over a long period exerts selection pressure in favour of endothelium that proliferates independently of VEGF and hence increases the likelihood of endothelial neoplasia. There was a disproportionate increase in hemangiosarcoma involving the liver in treated male mice at ≥ 250 mg/kg/day. At the same time there was a decreased incidence of hepatocellular carcinoma in male mice. The applicant hypothesizes that hemangiosarcomas may originate within early hepatocellular tumours or preneoplastic lesions followed by obliteration of the hepatocellular tumour and its replacement with the more aggressive hemangiosarcoma. There is a substantial safety margin (exposure margin at NOAEL = 16). It was considered that vildagliptin is likely to act by promoting development of a tumour form that appears commonly mice, and that the data do not suggest an increased risk for hemangiosarcoma development in humans where this tumour form is uncommon. The fact that the incidences of other common spontaneous tumours were not increased by vildagliptin treatment supports the view that a more general tumour promoting effect of vildaglitin is unlikely. The applicant will further study the mechanism for tumour development in the liver of mice, and the findings were considered by the CHMP not to represent a significant risk to humans.

  In the case of mammary adenocarcioma, the applicant suggested that tumours noted in the mouse carcinogenicity study are likely the result of an effect on the pituitary-gonadal axis that is unlikely to be of relevance to humans. In mammary tissue from mice treated with vildagliptin for 53 weeks there was a dramatic upregulation of genes related to milk production, such as casein-beta, casein-gamma and lactalbumin, suggesting that hormonally-driven changes are occurring in the mammary gland of mice treated with vildagliptin. The CHMP was of the opinion that these effects are unlikely to be of relevance to humans.

- Reproduction Toxicity
  Vildagliptin showed no effects on fertility, reproductive performance or early embryonic development in the rat. Embryo-foetal toxicity was evaluated in rats and rabbits. In the rat, an increased incidence of wavy ribs was observed at ≥ 225 mg/kg/day, in association with reduced maternal body weight parameters. Although classified as a malformation, literature data suggest that wavy ribs in the rat may be reversible. In rabbits, decreased foetal weight

and skeletal variations indicative of developmental delays were noted in rabbits at 150 mg/kg/day, in the presence of severe maternal toxicity (including mortality). It is concluded that vildagliptin is not selectively embryotoxic and does not exhibit a teratogenic potential. In the peri- and postnatal toxicity study in rats, maternal toxicity was observed at all doses. Transient decrease in F1 generation body weight and a decreased number of central beam breaks in open-field motor activity tests were observed at ≥ 150 mg/kg/day.

- Local tolerance
  Local tolerance of vildagliptin was investigated as part of the intravenous toxicity. No local effects due to vildagliptin were observed in either species. A skin irritation study conducted in rabbits did not indicate any dermal irritant properties.

- Other toxicity studies
  Vildagliptin showed no effect on the immune response in KLH-immunised rats. As discussed in the section on Pharmacology, the lack of immunotoxicity supports the view that the immune function of DPP-4/CD26 is independent of its enzymatic activity.
  No toxicity studies with metabolites were performed. The main human metabolites were present at similar amounts in the toxicology species. In patients with renal impairment, the exposure to the pharmacologically inactive metabolite LAY151 may be increased up to 6 times. There are no indications for any toxicity related to the metabolite and no further studies are warranted.

  Drug impurities requiring toxicological qualification were tested in repeat-dose toxicity and genotoxicity studies with a vildagliptin preparation spiked with the impurities at levels of 2-3%. There were no findings suggesting a change in toxicity profile.

  Available data indicate that the administration of DPP-4 inhibitors to monkeys results in dose and duration-dependent increases in necrotic lesions of the tail, digits, ears, nose and scrotum. The mechanism is unknown and such lesions have not been described in humans, rats or dogs. Data from the safety pharmacology study in monkeys suggest that vildagliptin may cause skin lesions in the monkey. A 13-week toxicology in cynomolgus monkeys shows occurrence of necrotic lesions with a lack of safety margin and lack of reversibility at higher doses. The skin lesions are proposed to result from peripheral vasoconstriction. The skin lesions were observed at doses that produced a tachycardic and a prohypertensive action indicating a sympathomimetic effect of vildagliptin at these doses in monkeys. The applicant argues that these findings were related to DPP4 inhibition, and that monkeys are much more sensitive to DPP4 inhibition than humans. The lack of skin lesions with sitagliptin in rhesus monkeys speaks against this proposal suggesting that other factors may be involved in causing the skin lesions result, such as inhibition of DPP8 and or DPP9, the occurrence of which in vivo is not known.

  <u>Metformin SR</u>
  Preclinical data of Metformin reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

## 7. DESCRIPTION

Abvida® - M 50/500 – Light blue colored, oval shaped film coated tablets debossed Abbott logo on one side and other side plain, with two layer visible lateral view.

Abvida® - M 50/1000 - Blue colored oval shaped film coated tablets film coated tablets debossed Abbott logo on one side other side plain.

## 8. PHARMACEUTICAL PARTICULARS

### 8.1 INCOMPATIBILITIES

Not Applicable

### 8.2 SHELF-LIFE

Refer Pack

### 8.3 PACKAGING INFORMATION

15 tablets

### 8.4 STORAGE AND HANDING INSTRUCTIONS

**Store protected from moisture, at a temperature not exceeding 30°C.**
**Important: Do not crush or chew the tablet. Take whole tablet with water.**

## 9. PATIENT COUNSELLING INFORMATION

- **Vildagliptin**

The active substance, vildagliptin, belongs to a group of medicines called "oral antidiabetics".

Vildagliptin 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 Vildagliptin 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 Vildagliptin works**
Vildagliptin 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.

**What you need to know before you take Vildagliptin**
**Do not take Vildagliptin:**
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 Vildagliptin, do not take this medicine and talk to your doctor.

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before taking Vildagliptin

• if you have type 1 diabetes (i.e. your body does not produce insulin) or if you have a condition 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 Vildagliptin 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 Vildagliptin).
• 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 Vildagliptin. Should these occur, you should promptly consult your doctor.
A test to determine your liver function will be performed before the start of Vildagliptin 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 Vildagliptin in children and adolescents up to 18 years of age is not recommended.

**Other medicines and Vildagliptin**
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 Vildagliptin 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 Vildagliptin during pregnancy. It is not known if Vildagliptin passes into breast milk. You should not use Vildagliptin if you are breast-feeding or plan to breast-feed.

**Driving and using machines**
If you feel dizzy while taking Vildagliptin, do not drive or use machines.
**How to take Vildagliptin**
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 Vildagliptin people have to take varies depending on their condition. Your doctor will tell you exactly how many tablets of Vildagliptin to take. The maximum daily dose is 100 mg.

The usual dose of Vildagliptin is either:
• 50 mg daily taken as one dose in the morning if you are taking Vildagliptin 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 Vildagliptin 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 Vildagliptin**
• Swallow the tablets whole with some water.

**How long to take Vildagliptin**
• Take Vildagliptin 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 Vildagliptin than you should**
If you take too many Vildagliptin 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 Vildagliptin**
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 Vildagliptin**
Do not stop taking Vildagliptin unless your doctor tells you to. If you have questions about how long to take this medicine, talk to your doctor.

**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 Vildagliptin 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 Vildagliptin 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 Vildagliptin 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 Vildagliptin 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 Vildagliptin 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 Vildagliptin, metformin and a sulphonylurea:
• Common: Dizziness, tremor, weakness, low blood glucose, excessive sweating

Some patients have had the following side effects while taking Vildagliptin 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

- **Metformin 500/1000 SR**

**What Metformin 500/1000 SR is and what it is used for**
Metformin 500/1000 SR prolonged release tablets contain the active ingredient metformin hydrochloride and belong to a group of medicines called biguanides, used in the treatment of Type 2 (non-insulin dependent) diabetes mellitus.

Metformin 500/1000 SR is used together with diet and exercise to lower the risk of developing Type 2 diabetes in overweight adults, when diet and exercise alone for 3 to 6 months have not been enough to control blood glucose (sugar). You are at high risk of developing Type 2 diabetes if you have additional conditions like high blood pressure, age above 40 years, an abnormal amount of lipids (fat) in the blood or a history of diabetes during pregnancy.

The medicine is particularly effective if you are aged below 45 years, are very overweight, have high blood glucose levels after a meal or developed diabetes during pregnancy.

Metformin 500/1000 SR is used for the treatment of Type 2 diabetes when diet and exercise changes alone have not been enough to control blood glucose (sugar). Insulin is a hormone that enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that you continue to take your medicine, even though you may not have any obvious symptoms. Metformin 500/1000 SR makes the body more sensitive to insulin and helps return to normal the way your body uses glucose.

Metformin 500/1000 SR is associated with either a stable body weight or modest weight loss.

Metformin 500/1000 SR Prolonged Release Tablets are specially made to release the drug slowly in your body and therefore are different to many other types of tablet containing metformin.

**What you need to know before you take Metformin 500/1000 SR**
Do not take Metformin 500/1000 SR if:
• you are allergic to metformin or to any of the other ingredients of this medicine. An allergic reaction may cause a rash, itching or shortness of breath.
• you have liver problems
• you have severely reduced kidney function
• you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual, fruity smell.
• you have lost too much water from your body (dehydration). Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis.
• you have a severe infection, such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis.
• you have been treated for acute heart problems or have recently had a heart attack or have severe circulatory problems or breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis.
• you are a heavy drinker of alcohol.
• you are under 18 years of age.

**Warnings and precautions**
**Risk of lactic acidosis.**
Metformin 500/1000 SR may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above apply to you, talk to your doctor for further instructions.

**Stop taking Metformin 500/1000 SR for a short time if you have a condition that may be associated with dehydration** (significant loss of body fluids) such as severe vomiting,

diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

**Stop taking Metformin 500/1000 SR and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis**, as this condition may lead to coma.

Symptoms of lactic acidosis include:
• vomiting
• stomach ache (abdominal pain)
• muscle cramps
• a general feeling of not being well with severe tiredness
• difficulty in breathing
• reduced body temperature and heartbeat

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

If you need to have major surgery you must stop taking Metformin 500/1000 SR during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Metformin 500/1000 SR.

During treatment with Metformin 500/1000 SR, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

If you are older than 75 years, treatment with Metformin 500/1000 SR should not be started to lower the risk of developing type 2 diabetes.

You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet.

You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.

Do not stop taking this medicine without speaking to your doctor.

**Other medicines and Metformin 500/1000 SR**
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Metformin 500/1000 SR before or at the time of injection. Your doctor will decide when you must stop and when to restart your treatment with Metformin 500/1000 SR.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Metformin 500/1000 SR. It is especially important to mention the following:
• Medicines which increase urine production (diuretics (water tablets) such as furosemide).
• Medicines used to treat pain and inflammation (NSAID and COX-2 inhibitors, such as ibuprofen and celecoxib)
• Certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)

• Steroids such as prednisolone, mometasone, beclometasone. • Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.
• Medicines that may change the amount of Metformin 500/1000 SR in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

**Metformin 500/1000 SR with alcohol**
Avoid excessive alcohol intake while taking Metformin 500/1000 SR since this may increase the risk of lactic acidosis.

**Pregnancy and breast-feeding**
Do not take Metformin 500/1000 SR if you are pregnant or breast feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Metformin 500/1000 SR taken on its own does not cause 'hypos' (symptoms of low blood sugar or hypoglycaemia, such as faintness, confusion and increased sweating) and therefore should not affect your ability to drive or use machinery.
You should be aware, however, that Metformin 500/1000 SR taken with other antidiabetic medicines can cause hypos, so in this case you should take extra care when driving or operating machinery.

**How to take Metformin 500/1000 SR**
Your doctor may prescribe Metformin 500/1000 SR for you to take on its own, or in combination with other oral antidiabetic medicines or insulin.
Always take Metformin 500/1000 SR exactly as your doctor has told you.
You should check with your doctor or pharmacist if you are not sure.
Swallow the tablets whole with a glass of water, do not chew.

<u>Recommended dose</u>
Usually you will start treatment with 500 milligrams Metformin 500/1000 SR daily. After you have been taking Metformin 500/1000 SR for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Metformin 500/1000 SR.

If you have reduced kidney function, your doctor may prescribe a lower dose.
Normally, you should take the tablets once a day, with your evening meal.
In some cases, your doctor may recommend that you take the tablets twice a day. Always take the tablets with food.

**If you take more Metformin 500/1000 SR than you should**
If you take extra tablets by mistake you need not worry, but if you have unusual symptoms, contact your doctor. If the overdose is large, lactic acidosis is more likely. Symptoms of lactic acidosis are non-specific, such as vomiting, bellyache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heart beat. If you experience some of these symptoms, you should immediately seek medical attention, as lactic acidosis may lead to coma. Stop taking Metformin 500/1000 SR immediately and contact a doctor or the nearest hospital straightaway.

**If you forget to take Metformin 500/1000 SR**
Take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.

**Possible side effects**
Like all medicines, Metformin 500/1000 SR can cause side effects, although not everybody gets them. The following side effects may occur:

Metformin 500/1000 SR may cause a very rare (may affect up to 1 user in 10,000) but very serious side effect called lactic acidosis. If this happens, you must **stop taking the Metformin 500/1000 SR and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.
Metformin 500/1000 SR may cause abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice (may affect up to 1 user in 10,000). If you develop yellowing of the eyes and/or skin contact your doctor immediately.

Other possible side effects are listed by frequency as follows:

Very common (affects more than 1 person in 10):
• Diarrhoea, nausea, vomiting, stomach ache or loss of appetite. If you get these, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks. It helps if you take the tablets with or immediately after a meal.

Common (affects less than 1 person in 10, but more than 1 person in 100):
• Taste disturbance

Very rare (affects less than 1 person in 10,000):
• Decreased vitamin B12 levels
• Skin rashes including redness, itching and hives.

**10. DETAILS OF MANUFACTURER**
**MANUFACTURED BY:**
Abbott Healthcare Pvt. Ltd.
Village Bhatauli Khurd, PO: Baddi-173205,
Dist: Solan, Himachal Pradesh, India.

**11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**
MNB/06/295 dated 01-Jul-26

**12. DATE OF REVISION**
Version 2.0, dated 26-Aug-26

For Product Complaints/Adverse events or Queries please write to
**webmasterindia@abbott.com**

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