

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

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## **TORGLIP M SR**

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### **1. Generic Name**

Metformin Hydrochloride (As Sustained Release) and Vildagliptin Tablets

### **2. Qualitative and quantitative composition**

#### **TORGLIP M SR 500**

Each uncoated bilayered tablet contains:

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

Colour : Ferric Oxide Yellow USP-NF

The excipients used are HPMC K-200 M CR, Povidone K 30, Dicalcium Hydrogen Phosphate Anhydrous, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Lactose and Microcrystalline Cellulose.

#### **TORGLIP M SR 1000**

Each uncoated bilayered tablet contains:

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

Colour : Ferric Oxide Yellow USP-NF

The excipients used are HPMC K-200 M CR, Povidone K 30, Dicalcium Hydrogen Phosphate Anhydrous, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Lactose and Microcrystalline Cellulose.

### **3. Dosage form and strength**

**Dosage form:** Tablet

**Strength:** Metformin 500 mg / 1000 mg; Vildagliptin 50 mg

### **4. Clinical particulars**

#### **4.1 Therapeutic indication**

It is indicated for the treatment of type-II diabetes mellitus when single drug therapy along with diet, exercise do not result in adequate glycemic control.

#### **4.2 Posology and method of administration**

**Posology**

### Adults with normal renal function (GFR $\geq$ 90 ml/min)

The dose of antihyperglycaemic therapy with TORGLIP M SR should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. TORGLIP M SR may be initiated at 50 mg/500 mg 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 TORGLIP M SR should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

- For patients switching from co-administration of vildagliptin and metformin as separate tablets:

TORGLIP M SR should be initiated at the dose of vildagliptin and metformin already being taken.

- For patients inadequately controlled on dual combination with metformin and a sulphonylurea:

The doses of TORGLIP M SR should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When TORGLIP M SR is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin:

The dose of TORGLIP M SR should provide vildagliptin dose as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established.

### Special populations

#### *Elderly ( $\geq$ 65 years)*

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking TORGLIP M SR should have their renal function monitored regularly.

#### *Renal impairment*

A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.

If no adequate strength of TORGLIP M SR is available, individual monocomponents should be used instead of the fixed dose combination.

<b>GFR ml/min</b>	<b>Metformin</b>	<b>Vildagliptin</b>
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	No dose adjustment.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximal daily dose is 50 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

#### *Hepatic impairment*

TORGLIP M SR should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).

#### *Paediatric population*

TORGLIP M SR is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of TORGLIP M SR in children and adolescents (< 18 years) have not been established. No data are available.

#### **Method of administration**

For oral use.

Taking TORGLIP M SR with or just after food may reduce gastrointestinal symptoms associated with metformin.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

#### General

TORGLIP M SR is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.

#### Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

#### Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

#### Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function.

#### Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with TORGLIP M SR.

#### 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 TORGLIP M SR in order to know the patient's baseline value. Liver function should be monitored during treatment with TORGLIP M SR 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 LFTs until the abnormality (ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of TORGLIP M SR therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue TORGLIP M SR.

Following withdrawal of treatment with TORGLIP M SR and LFT normalization, treatment with TORGLIP M SR should not be re-initiated.

#### Skin disorders

Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in non-clinical toxicology studies. Although skin lesions were not observed at an increased incidence in reported 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.

#### Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

### **4.5 Drugs interactions**

There have been no formal interaction studies for TORGLIP M SR. The following statements reflect the information available on the individual active substances.

#### **Vildagliptin**

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.

Results from reported clinical trials conducted with the oral antidiabetics' pioglitazone, metformin and glyburide in combination with vildagliptin have shown no clinically relevant pharmacokinetic interactions in the target population.

Drug-drug interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin.

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these reported studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin. However, this has not been established in the target population.

#### Combination with ACE inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE inhibitors. As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

## **Metformin**

### Combinations not recommended

#### *Alcohol*

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

#### *Iodinated contrast agents*

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

#### *Cationic active substances*

Cationic active substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems and hence delay the elimination of metformin, which may increase the risk of lactic acidosis. A reported study in healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

### Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of TORGLIP M SR may need to be adjusted during concomitant therapy and on its discontinuation.

Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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

### **Pregnancy**

There are no adequate data from the use of TORGLIP M SR in pregnant women. For vildagliptin reported studies in animals have shown reproductive toxicity at high

doses. For metformin, studies in animals have not shown reproductive toxicity. Reported studies in animals performed with vildagliptin and metformin have not shown evidence of teratogenicity, but foetotoxic effects at maternotoxic doses. The potential risk for humans is unknown. TORGLIP M SR should not be used during pregnancy.

### **Breast-feeding**

Reported studies in animals have shown excretion of both metformin and vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk, but metformin is excreted in human milk in low amounts. Due to both the potential risk of neonate hypoglycaemia related to metformin and the lack of human data with vildagliptin, TORGLIP M SR should not be used during breast-feeding.

### **Fertility**

No studies on the effect on human fertility have been conducted for TORGLIP M SR.

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

The majority of adverse reactions 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 with vildagliptin. 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  $\geq 3x$  ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

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

Adverse reactions reported in patients who received vildagliptin in double-blind studies as monotherapy and add-on therapies are listed below by system organ class and absolute frequency. Frequencies are defined as very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).



Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Adverse reactions reported in patients who received vildagliptin 100 mg daily as add-on therapy to metformin compared to placebo plus metformin in double-blind reported studies (N=208)**

<b>Metabolism and nutrition disorders</b>	
Common	Hypoglycaemia
<b>Nervous system disorders</b>	
Common	Tremor, headache, dizziness
Uncommon	Fatigue
<b>Gastrointestinal disorders</b>	
Common	Nausea

**Description of selected adverse reactions**

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

In reported clinical trials, the incidence of hypoglycaemia was common in patients receiving vildagliptin in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In reported clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

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

**Combination with a sulphonylurea**

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

<b>Metabolism and nutritional disorders</b>	
Common	Hypoglycaemia
<b>Nervous system disorders</b>	

Common	Dizziness, tremor
<b>Skin and subcutaneous tissue disorders</b>	
Common	Hyperhidrosis
<b>General disorders and administration site conditions</b>	
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

**Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin) in reported double-blind studies (N=371)**

<b>Metabolism and nutrition disorders</b>	
Common	Decreased blood glucose
<b>Nervous system disorders</b>	
Common	Headache, chills
<b>Gastrointestinal disorders</b>	
Common	Nausea, gastro-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Description of selected adverse reactions

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

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

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

Additional information on the individual active substances of the fixed combination

**Vildagliptin**

**Adverse reactions reported in patients who received vildagliptin 100 mg daily as monotherapy in reported double-blind studies (N=1855)**

<b>Infections and infestations</b>	
Very rare	Upper respiratory tract infection, Nasopharyngitis
<b>Metabolism and nutrition disorders</b>	
Uncommon	Hypoglycaemia
<b>Nervous system disorders</b>	
Common	Dizziness
Uncommon	Headache
<b>Vascular disorders</b>	
Uncommon	Oedema peripheral
<b>Gastrointestinal disorders</b>	
Uncommon	Constipation
<b>Musculoskeletal and connective tissue disorders</b>	
Uncommon	Arthralgia

Description of selected adverse reactions

The overall incidence of withdrawals from reported controlled monotherapy trials 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 reported 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 reported 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.

## Metformin

### Adverse reactions for metformin component

<b>Metabolism and nutrition disorders</b>	
Very rare	Decrease of vitamin B absorption and lactic acidosis*
<b>Nervous system disorders</b>	
Common	Metallic taste
<b>Gastrointestinal disorders</b>	
Very common	Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite
<b>Hepatobiliary disorders</b>	
Very rare	Liver function test abnormalities or hepatitis**
<b>Skin and subcutaneous tissue disorders</b>	
Very rare	Skin reactions such as erythema, pruritus and urticarial
<p>*A decrease in vitamin B12 absorption with decrease in serum levels has been very rarely observed in patients treated long-term with metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.</p> <p>**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.</p>	

Gastrointestinal adverse reactions occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

### Post-marketing experience

<b>Gastrointestinal disorders</b>	
Not known	Pancreatitis
<b>Hepatobiliary disorders</b>	

Not known	Hepatitis (reversible upon discontinuation of the medicinal product) Abnormal liver function tests (reversible upon discontinuation of the medicinal product)
<b>Musculoskeletal and connective tissue disorders</b>	
Not known	Myalgia
<b>Skin and subcutaneous tissue disorders</b>	
Not known	Urticaria Exfoliative and bullous skin lesions, including bullous pemphigoid

### **Reporting of side effects**

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

[http://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting)

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

## **4.9 Overdose**

No data are available with regard to overdose of TORGLIP M SR.

### **Vildagliptin**

Information regarding overdose with vildagliptin is limited.

#### *Symptoms*

Information on the likely symptoms of overdose with vildagliptin was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), 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.

### **Metformin**

A large overdose of metformin (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital.

## Management

The most effective method of removing metformin is haemodialysis. However, vildagliptin cannot be removed by haemodialysis, although the major hydrolysis metabolite (LAY 151) can. Supportive management is recommended.

## **5. Pharmacological properties**

### **5.1 Mechanism of Action**

TORGLIP M SR combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer 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. Metformin acts primarily by decreasing endogenous hepatic glucose production.

### **5.2 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08

#### *Vildagliptin*

Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide).

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 and GIP.

By increasing, the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA- $\beta$  (Homeostasis Model Assessment- $\beta$ ), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose appropriate glucagon secretion.

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

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

### *Metformin*

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain.

Metformin may exert its glucose-lowering effect via three mechanisms:

- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

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

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces serum levels of total cholesterol, LDL cholesterol and triglycerides.

The prospective randomised UKPDS (UK Prospective Diabetes Study) reported study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction in the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years),  $p=0.0023$ , and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years),  $p=0.0034$ ;
- a significant reduction in the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years,  $p=0.017$ ;
- a significant reduction in the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years ( $p=0.011$ ), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient years ( $p=0.021$ );
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years ( $p=0.01$ ).

### **Clinical efficacy and safety**

In reported study, vildagliptin added to patients whose glycaemic control was not satisfactory despite treatment with metformin monotherapy resulted after 6-month treatment in additional statistically significant mean reductions in HbA compared to placebo (between group differences of -0.7% to -1.1% for vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a decrease in HbA

of  $\geq 0.7\%$  from baseline was statistically significantly higher in both vildagliptin plus metformin groups (46% and 60%, respectively) versus the metformin plus placebo group (20%).

In a reported 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 of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.

In a reported clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA 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 was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

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

A reported 24-week randomised, double-blind, placebo-controlled trial conducted in 318 patients evaluated the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin ( $\geq 1500$  mg daily) and glimepiride ( $\geq 4$  mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA of 8.8% was -0.76%.

A reported 24-week randomised, double-blind, placebo-controlled trial conducted in 449 patients evaluated 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 compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).

In another 24-week reported study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA 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%).

#### 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).

### **5.3 Pharmacokinetic properties**

#### **Vildagliptin**

##### 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 (19%) compared to dosing in the fasting state. However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85%.

### Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vd) 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 amide hydrolysis product (4% of dose). 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, and 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 comedications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

### Elimination

Following oral administration of [<sup>14</sup>C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose was 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 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 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.

**Age:** In healthy elderly subjects ( $\geq 70$  years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). These changes are not considered to be clinically relevant, however. DPP-4 inhibition by vildagliptin is not affected by age.

**Hepatic impairment:** In subjects with mild, moderate or severe hepatic impairment (Child-Pugh A-C) there were no clinically significant changes (maximum ~30%) in exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (C<sub>8</sub>- 66%; AUC 32-134%) and total body clearance was reduced compared to subjects with normal renal function.

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

## **Metformin**

### Absorption

After an oral dose of metformin, the maximum plasma concentration (C<sub>max</sub>) is achieved after about 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C<sub>max</sub>) did not exceed 4 µg/ml, even at maximum doses. Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was 40% lower, AUC was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes. The clinical relevance of this decrease is unknown.

### Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (V<sub>d</sub>) ranged between 63-276 litres.

### Biotransformation

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

### Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

## **6. Nonclinical properties**

### **6.1 Animal Toxicology or Pharmacology**

Animal studies of up to 13-week duration have been conducted with the combined substances in TORGLIP M SR. No new toxicities associated with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

## Vildagliptin

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.

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

A two-year carcinogenicity reported study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1000 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 reported study in cynomolgus monkeys, skin lesions have been recorded at doses  $\geq 5$  mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses  $\geq 20$  mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at  $\geq 80$  mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

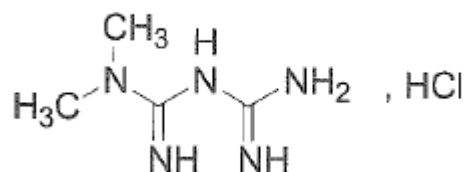
## **Metformin**

Non-clinical data on metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

### **7. Description**

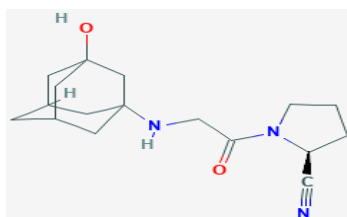
#### **Metformin Hydrochloride**

Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula is  $C_4H_{11}N_5$ , HCl and its molecular weight is 165.6 g/mol. The chemical structure of Metformin Hydrochloride is:



#### **Vildagliptin**

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



#### **TORGLIP M SR 500/1000**

Metformin Hydrochloride (As Sustained Release) and Vildagliptin Tablets are white to off white / yellow coloured, capsule shaped, biconvex, uncoated bilayer tablets plain on both side. The excipients used are HPMC K-200 M CR, Povidone K 30, Dicalcium Hydrogen Phosphate Anhydrous, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Lactose and Microcrystalline Cellulose.

### **8. Pharmaceutical particulars**

#### **8.1 Incompatibilities**

Not applicable.

#### **8.2 Shelf-life**

Do not use later than the date of expiry.

### 8.3 Packaging information

TORGLIP M SR are packed in Blister pack of 10 tablets.

### 8.4 Storage and handing instructions

Store between 8°C to 25°C, protect from moisture.

Keep out of reach of children.

## 9. Patient Counselling Information

### TORGLIP M SR

#### (Metformin Hydrochloride (As Sustained Release) and Vildagliptin Tablets)

- Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet

9.1. What TORGLIP M SR is and what it is used for

9.2. What you need to know before you take TORGLIP M SR

9.3. How to take TORGLIP M SR

9.4. Possible side effects

9.5. How to store TORGLIP M SR

9.6. Contents of the pack and other information

#### 9.1 What TORGLIP M SR is and what it is used for

The active substances of TORGLIP M SR, vildagliptin and metformin, belong to a group of medicines called “oral antidiabetics”.

TORGLIP M SR is used to treat adult patients with type 2 diabetes. This type of diabetes is also known as noninsulin-dependent diabetes mellitus.

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.

Both insulin and glucagon are made in the pancreas. Insulin helps to lower the level of sugar in the blood, especially after meals. Glucagon triggers the liver to make sugar, causing the blood sugar level to rise.

### **How TORGLIP M SR works**

Both active substances, vildagliptin and metformin, help to control the level of sugar in the blood. The substance vildagliptin works by making the pancreas produce more insulin and less glucagon. The substance metformin works by helping the body to make better use of insulin. This medicine has been shown to reduce blood sugar, which may help to prevent complications from your diabetes.

## **9.2 What you need to know before you take TORGLIP M SR**

### **Do not use TORGLIP M SR:**

- if you are allergic to vildagliptin, metformin or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic to any of these, talk to your doctor before taking TORGLIP M SR.
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see “Risk of lactic acidosis” below) or ketoacidosis. Ketoacidosis is a condition in which substances called ketone bodies accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems.
- if you have severely reduced kidney function.
- if you have a severe infection or are seriously dehydrated (have lost a lot of water from your body).
- if you are going to have a contrast x-ray (a specific type of x-ray involving an injectable dye).

Please also see information about this in section “Warnings and precautions”.

- if you have liver problems.
- if you drink alcohol excessively (whether every day or only from time to time).
- if you are breast-feeding (see also “Pregnancy and breast-feeding”).

### **Warnings and precautions**

#### Risk of lactic acidosis

TORGLIP M 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 TORGLIP M 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 TORGLIP M 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.

TORGLIP M SR is not a substitute for insulin. Therefore, you should not receive TORGLIP M SR for the treatment of type 1 diabetes.

Talk to your doctor, pharmacist or nurse before taking TORGLIP M SR if you have or have had a disease of the pancreas.

Talk to your doctor, pharmacist or nurse before taking TORGLIP M SR 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 TORGLIP M SR in order to avoid low blood glucose (hypoglycaemia).

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

Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking TORGLIP M SR. Should these occur, you should promptly consult your doctor.

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

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



During treatment with TORGLIP M SR, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or have worsening renal function. Your doctor will test your blood and urine for sugar regularly.

### **Children and adolescents**

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

### **Other medicines and TORGLIP M 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 TORGLIP M SR before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with TORGLIP M 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 TORGLIP M SR. It is especially important to mention the following:

- glucocorticoids generally used to treat inflammation
- beta-2 agonists generally used to treat respiratory disorders
- other medicines used to treat diabetes
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as
- ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- certain medicines affecting the thyroid, or
- certain medicines affecting the nervous system.

### **TORGLIP M SR with alcohol**

Avoid excessive alcohol intake while taking TORGLIP M SR since this may increase the risk of lactic acidosis (please see section “Warnings and precautions”).

### **Pregnancy and breast-feeding**

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risk of taking TORGLIP M SR during pregnancy.
- Do not use TORGLIP M SR if you are pregnant or breast-feeding (see also “Do not take TORGLIP M SR”).

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

If you feel dizzy while taking TORGLIP M SR, do not drive or use any tools or machines.

### **9.3 How to take TORGLIP M SR**

The amount of TORGLIP M SR that people have to take varies depending on their condition. Your doctor will tell you exactly the dose of TORGLIP M SR to take.

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

The recommended dose is one film-coated tablet (50 mg/500 mg) twice a day.

If you have reduced kidney function, your doctor may prescribe a lower dose. Also, if you are taking an anti-diabetic medicine known as a sulphonylurea your doctor may prescribe a lower dose.

Your doctor may prescribe this medicine alone or with certain other medicines that lower the level of sugar in your blood.

### **When and how to take TORGLIP M SR**

- Swallow the tablets whole with a glass of water,
- Take one tablet in the morning and the other in the evening with or just after food. Taking the tablet just after food will lower the risk of an upset stomach.

Continue to follow any advice about diet that your doctor has given you. In particular, if you are following a diabetic weight control diet, continue with this while you are taking TORGLIP M SR.

### **If you take more TORGLIP M SR than you should**

If you take too many TORGLIP M SR tablets, or if someone else takes your tablets, talk to a doctor or pharmacist immediately. Medical attention may be necessary. If you have to go to a doctor or hospital, take the pack and this leaflet with you.

### **If you forget to take TORGLIP M SR**

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

### **If you stop taking TORGLIP M SR**

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

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

#### 9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. You should stop taking TORGLIP M SR and see your doctor immediately if you experience the following side effects:

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

##### Other side effects

Some patients have experienced the following side effects while taking TORGLIP M SR:

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

Some patients have experienced the following side effects while taking TORGLIP M SR and a sulphonylurea:

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

Some patients have had the following side effects while taking TORGLIP M SR and insulin:

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

- Uncommon: diarrhoea, flatulence.

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

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

### **Reporting of side effects**

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

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

### **9.5 How to store TORGLIP M SR.**

Store between 8°C to 25°C, protect from moisture.

### **9.6 Contents of the pack and other information**

#### **What TORGLIP M SR contains**

TORGLIP M SR consists of Metformin Hydrochloride (As Sustained Release) and Vildagliptin as active substance and comes in the strengths containing 500/1000 mg of Metformin Hydrochloride and Vildagliptin 50 mg.

TORGLIP M SR are white to off white / yellow coloured, capsule shaped, biconvex, uncoated bilayer tablets plain on both side.

The excipients used are HPMC K-200 M CR, Povidone K 30, Dicalcium Hydrogen Phosphate Anhydrous, Isopropyl Alcohol, Magnesium Stearate, Ferric Oxide Yellow, Lactose and Microcrystalline Cellulose.

TORGLIP M SR are packed in Blister pack of 10 tablets.

### **10 Details of manufacturer**

Manufactured by:

Exemed Pharmaceuticals

Plot No. 133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi – 396195, Gujarat (India).

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

Mfg Lic No G/25/2011 issued on 24.12.2021

### **12 Date of revision**

Not Applicable

MARKETED BY



Torrent Pharmaceuticals Ltd.

**IN/TORGLIP M SR 500/1000 mg and 50 mg/Apr-22/01/PI**