

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

AZAGLIN VM 10/100/1000 (Dapagliflozin 10 mg, Vildagliptin SR 100 mg & Metformin Hydrochloride SR 1000 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated bilayered tablet contains:

Dapagliflozin Propanediol monohydrate

Equivalent to Dapagliflozin 10 mg

Vildagliptin 100 mg

(as sustained release)

Metformin Hydrochloride BP 1000 mg

(as sustained release)

Excipients.....q.s.

Colour: Approved colour used.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Bilayer Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

AZAGLIN VM is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM) whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of Vildagliptin, Dapagliflozin and metformin hydrochloride, as separate tablets.

AZAGLIN VM is also indicated as initial therapy in patients with T2DM whose diabetes is not adequately controlled by diet and exercise alone.

4.2 Posology and method of administration

Posology

The recommended dose is 1 tablet once daily orally based on the individual dosage of each ingredient.

Dapagliflozin

The recommended dose is 5 or 10 mg dapagliflozin once daily orally.

Special populations

Treatment of diabetes mellitus in patients with renal impairment

As glycaemic efficacy is dependent on renal function, Dapagliflozin should not be initiated to improve glycaemic control in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. No dose adjustment is required based on renal function.

Treatment of heart failure in patients with renal impairment

No dose adjustment is required based on renal function. There is limited experience with dapagliflozin for the treatment of heart failure in patients with severe renal impairment (GFR < 30 mL/min).

Dosage in patients with renal impairment

GFR mL/min	Metformin	Dapagliflozin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 10 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Dapagliflozin should not be initiated. Maximum total daily dose is 10 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Dapagliflozin is not recommended.
< 30	Metformin is contraindicated.	Dapagliflozin is not recommended.

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg when indicated.

Patients with type 1 diabetes mellitus

Dapagliflozin 10 mg is not recommended for the treatment of heart failure in patients with type 1 diabetes mellitus.

Elderly (≥ 65 years)

No dose adjustment is recommended based on age.

Paediatric population

The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Vildagliptin

Adults

When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Doses higher than 100 mg are not recommended.

If a dose of Vildagliptin is missed, it should be taken as soon as the patient remembers.

A double dose should not be taken on the same day.

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

Additional information on special populations

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients.

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Vildagliptin is 50 mg once daily.

Hepatic impairment

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN)

Paediatric population

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets in children and adolescents (< 18 years) have not been established. No data are available

Method of administration

Oral use

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets can be administered with or without a meal.

Method of administration

FDC of Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- 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;
- 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.

4.4 Special warnings and precautions for use

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), Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets 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 non-steroidal anti-inflammatory drugs [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 on the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps,

asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Renal function

The glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment. Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets should not be initiated in patients with GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min.

Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis.

Monitoring of renal function:

Renal function should be assessed:

- Before initiation of treatment and regularly thereafter.
- For renal function with GFR levels < 60 mL/min and in elderly patients, at least 2 to 4 times per year.
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
- If renal function falls persistently below GFR 45 mL/min, treatment should be discontinued.
- Metformin is contraindicated in patients with GFR of < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a NSAID.

Use in patients at risk for volume depletion and/or hypotension

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment

with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets in patients with type 1 diabetes have not been established and Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies, DKA was reported with common frequency.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary Tract Infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.

Lower Limb Amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Urine Laboratory Assessments

Due to its mechanism of action, patients taking this medicinal product will test positive for glucose in their urine.

Surgery

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets must be discontinued at the time of surgery with 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 Interaction with other medicinal products and other forms of interaction

Coadministration of multiple doses of Dapagliflozin, vildagliptin and metformin does not meaningfully alter the pharmacokinetics of either Dapagliflozin, vildagliptin or metformin in healthy subjects.

No interaction studies have been performed for Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets. 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 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 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.(see section 4.8).

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

This medicinal product may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP-glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4.

Therefore, this medicinal product is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anti-coagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Paediatric population

Interaction studies have only been performed in adults.

Metformin

Concomitant use not recommended

Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. 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 coadministered.

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product. Consumption of alcohol and medicinal products containing alcohol should be avoided.

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. Dapagliflozin and Metformin HCl (Extended Release) Tablets 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.

Combination requiring precautions for use

Glucocorticoids (given by systemic and local routes), 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 with such medicinal products. If necessary, the dose of the glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin.

4.6 Pregnancy and Lactation

Pregnancy

There are no data from the use of Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

For vildagliptin studies in animals have shown reproductive toxicity at high doses. For metformin, studies in animals have not shown reproductive toxicity. 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.

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Breast-feeding

It is unknown whether this medicinal product or Dapagliflozin, Metformin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/ toxicological data in animals have shown excretion of Dapagliflozin, Metformin/ metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used while breast-feeding.

Fertility

The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity.

4.7 Effects on ability to drive and use machines

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8 Undesirable effects

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin. There have been no therapeutic clinical trials conducted with Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets

Dapagliflozin plus metformin

Summary of the safety profile

In an analysis of 5 placebo-controlled dapagliflozin add-on to metformin studies, the safety results were similar to that of the pre-specified pooled analysis of 13 placebo-

controlled dapagliflozin studies (see Dapagliflozin, *Summary of the safety profile* below). No additional adverse reactions were identified for the dapagliflozin plus metformin group compared with those reported for the individual components. In the separate dapagliflozin add-on to metformin pooled analysis, 623 subjects were treated with dapagliflozin 10 mg as add-on to metformin and 523 were treated with placebo plus metformin.

Dapagliflozin

Summary of the safety profile

In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled dapagliflozin plus metformin clinical studies, dapagliflozin clinical studies and metformin clinical studies and post-marketing experience. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: 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 ($< 1/10,000$), and not known (cannot be estimated from the available data). **Table 2. Adverse reactions in dapagliflozin and metformin immediate-release clinical trial and post-marketing data^a**

System organ class	Very common	Common	Uncommon	Rare	Very rare
<i>Infections and infestations</i>		Vulvovaginitis, balanitis and related genital	Fungal Infection**		Necrotising fasciitis of the perineum

		infections ^{*,b,c} Urinary tract infection ^{*,b,d}			(Fournier's gangrene) ^{b,k}
<i>Metabolism and nutrition disorders</i>	Hypoglycaemia (when used with SU or insulin) ^b		Volume depletion ^{b,e} Thirst ^{**}	Diabetic ketoacidosis ^{b,k,l}	Lactic acidosis Vitamin B12 deficiency ^{h,§}
<i>Nervous system disorders</i>		Taste disturbance [§] Dizziness			
System organ class	Very common	Common	Uncommon	Rare	Very rare
<i>Gastrointestinal disorders</i>	Gastrointestinal Symptoms ^{i,§}		Constipation ^{**} Dry mouth ^{**}		
<i>Hepatobiliary disorders</i>					Liver function disorders [§] Hepatitis [§]
<i>Skin and subcutaneous tissue disorders</i>		Rash ^m			Urticaria [§] Erythema [§] Pruritus [§]
<i>Musculoskeletal And connective Tissue disorders</i>		Back pain [*]			
<i>Renal and Urinary disorders</i>		Dysuria Polyuria ^{*,f}	Nocturia ^{**}		
<i>Reproductive system and breast disorders</i>			Vulvovaginal pruritus ^{**} Pruritus Genital ^{**}		
<i>Investigations</i>		Haematocrit increased ^g Creatinine renal clearance decreased during initial treatment ^b Dyslipidaemia ^j	Blood creatinine increased during initial treatment ^{**} Blood urea increased ^{**} Weight decreased ^{**}		

^aThe table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with §, for which adverse reaction and frequency categories are based on information from the metformin Summary of Product Characteristics available in the European Union.

^bSee corresponding subsection below for additional information.

^cVulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms:

vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

^dUrinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

^eVolume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

^fPolyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

^gMean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

^hLong-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

ⁱGastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

^jMean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

^kSee section 4.4

^lReported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

^mAdverse reaction was identified through post-marketing surveillance with the use of dapagliflozin. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

^{*}Reported in $\geq 2\%$ of subjects and $\geq 1\%$ more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

^{**}Reported by the investigator as possibly related, probably related or related to study treatment and reported in $\geq 0.2\%$ of subjects and $\geq 0.1\%$ more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Dapagliflozin plus metformin

Hypoglycaemia

In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycaemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events of hypoglycaemia were reported. Similar observations were made for the combination of dapagliflozin with metformin in drug-naïve patients.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea. No major events of hypoglycaemia were reported.

Dapagliflozin

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin.

In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study.

For studies of dapagliflozin as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. In a study with add-on insulin therapy, higher rates of hypoglycaemia were observed.

In an add-on to insulin study up to 104 weeks, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects in dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In the dapagliflozin cardiovascular outcomes study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

Volume depletion

In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo.

In the dapagliflozin cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and

placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACE-I/ARB use.

In patients with eGFR < 60 mL/min/1.73 m at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis

In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event.

Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population.

Urinary tract infections

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.7% versus 3.5%, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR = 60 mL/min/1.73 m) this grouping of reactions were reported in 1.3% and 0.8% of

patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR = 30 and < 60 mL/min/1.73 m² (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of $\leq$ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the dapagliflozin cardiovascular outcomes study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m²), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Description of selected adverse reactions

Vildagliptin

Hepatic impairment

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.

Angioedema

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

Hypoglycaemia

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

4.9 Overdose

Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis.

Dapagliflozin

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin

High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Vildagliptin

Information regarding overdose with vildagliptin is limited.

Symptoms

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, **ATC code:** A10BK01

Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a highly potent (K_i : 0.55 nM), selective and reversible inhibitor of SGLT2.

The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

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- β (Homeostasis Model Assessment- β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

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

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

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.

Clinical efficacy and safety

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 HbA1c 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 HbA1c 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 24-week trial, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2020 mg). Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. A

mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.

In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA1c were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA1c of 7.3%. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA1c was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 52-week trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1928 mg/day). After 1 year, mean reductions in HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 8.5%); statistical non-inferiority was achieved (95% CI -0.11 – 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.

In a 24-week trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA1c by -1.82%, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline $\geq 10.0\%$ was greater.

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥ 1500 mg daily) and glimepiride (≥ 4 mg daily).

Vildagliptin in combination with metformin and glimepiride significantly decreased HbA1c compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA1c of 8.8% was -0.76%.

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

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA1c 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).

In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA1c when vildagliptin (50 mg twice daily) was

added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).

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).

Paediatric Population

The European Medicines Agency has waived the obligation to submit the results of studies with vildagliptin in combination with metformin in all subsets of the paediatric population with type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

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) 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 ($p=0.01$).

5.2 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 $C_{\max}$ (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 (V_{ss}) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the 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 co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [^{14}C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose 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 $C_{\max}$ for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in 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 (≥ 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 $\sim 30\%$) in exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased ($C_{\max}$ 8-66%; 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 ($C_{\max}$) 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_{max}) 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_d) 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.

5.3 Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Dapagliflozin, Vildagliptin (SR) and Metformin (SR) Tablets. No new toxicities associated with the combination were identified. The following data are findings from studies performed with Vildagliptin, dapagliflozin and 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. 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. Embryofoetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

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

Dapagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies. Reproductive and developmental toxicity Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period. In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal

pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose. In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

Metformin

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Lactose, Crospovidone, Ferric oxide yellow, Povidone, Polysorbate 80 Isopropyl Alcohol, Colloidal anhydrous silica, Crospovidone, Magnesium Stearate, Hypromellose (HPMC K200M), Hypromellose (HPMC K4M), Purified water, Opadry clear 03K19229, Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

03 x 10 Capsules Alu- Alu Blister pack

Primary Container: Alu- Alu Blister

Secondary Container: Unit carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufactured By

Ravenbhel Healthcare Pvt. Ltd.

16-17, EPIP, SIDCO, Kartholi,

Bari Brahmana- 181133, Jammu, India

Manufacturing Authorisation Holder:

Emcure Pharmaceuticals Limited.

Plot No. P-1 & P-2, IT-BT Park, Phase-II, M.I.D.C.,

Hinjawadi, Pune – 411057 Maharashtra, INDIA.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of preparation of the text

28/03/2023

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

**12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
(IF APPLICABLE)**

Not Applicable