Applicant/PHRC: ***Hetero Drugs South Africa (Pty) Ltd***
Product proprietary name: ***DAGFOTIN 50/850; DAGFOTIN 50/1000***
Dosage form and strength: ***Each film coated tablet contains vildagliptin and metformin Hydrochloride 50 mg/ 850 mg and 50 mg/ 1000 mg.***

PROFESSIONAL INFORMATION FOR

DAGFOTIN 50/850
DAGFOTIN 50/1000

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DAGFOTIN 50/850 (film-coated tablet)

DAGFOTIN 50/1000 (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DAGFOTIN 50/850:

Each film-coated tablet contains 50 mg vildagliptin and 850 mg of metformin hydrochloride.

DAGFOTIN 50/1000:

Each film-coated tablet contains 50 mg vildagliptin and 1000 mg of metformin hydrochloride.

DAGFOTIN is sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

DAGFOTIN 50/850:

Light pink to pink oval shaped, bevelled edge biconvex film-coated tablets, debossed with "V16" on one side and "H" on the other side.

DAGFOTIN 50/1000:

White to off-white oval shaped, bevelled edge biconvex film-coated tablets, debossed with "V17" on one side and "H" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For patients with Type 2 diabetes mellitus (T2DM):

DAGFOTIN is indicated as an adjunct to diet and exercise in patients who are already stabilised with the combination of vildagliptin and metformin hydrochloride at the same dosages, as separate tablets.

DAGFOTIN is indicated as add-on to insulin as an adjunct to diet and exercise in patients on a stable dose of insulin plus vildagliptin and metformin hydrochloride.

DAGFOTIN is indicated as an add-on to insulin at the same dosages as the separate tablets of vildagliptin and metformin hydrochloride.

DAGFOTIN is indicated in combination with sulphonylurea (SU) (i.e., triple combination therapy) as an adjunct to diet and exercise in patients stabilised on vildagliptin, metformin hydrochloride and a sulphonylurea.

DAGFOTIN can be used to replace the vildagliptin and metformin hydrochloride at the same dosages as the separate tablets.

4.2 Posology and method of administration

Posology

In using DAGFOTIN do not exceed the maximum daily dose of vildagliptin (100 mg).

The recommended starting dose of DAGFOTIN should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride.

Use in combination with sulphonylurea or with insulin

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

Special populations

Patients with renal impairment

A glomerular filtration rate (GFR) should be assessed before initiation of treatment with metformin-containing medicines, as in DAGFOTIN, 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 to 6 months. The maximum daily dose of metformin should preferably be divided into 2 to 3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin-containing medicines, as in DAGFOTIN, in patients with GFR < 60 ml/min.

DAGFOTIN is contraindicated in patients with GFR < 30 ml/min because of its metformin component (see section 4.3).

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of DAGFOTIN is available, individual components should be used instead of the fixed dose combination.

Dose adjustments in patients with renal impairment

GFR (mL/min)	Metformin	Vildagliptin
60 – 89	Maximum daily dose is 3000 mg*. Dose reduction may be considered if renal function declines.	Maximum daily dose is 100 mg.
45 – 59	Starting dose should not be more than 1000 mg with a maximum daily dose of 2000 mg*.	Maximum daily dose is 50 mg.
30 – 44	Starting dose should not be more than 500 mg with a maximum daily dose of 1000 mg.	

GFR (mL/min)	Metformin	Vildagliptin
< 30	Metformin is contraindicated.	

*If metformin doses higher than those achievable with DAGFOTIN alone are considered necessary.

Patients with hepatic impairment

DAGFOTIN is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST > 2, 5 x the ULN (see section 4.4).

Elderly

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing medicines, as in DAGFOTIN, should have their renal function monitored regularly. The dosage of DAGFOTIN for elderly patients should be adjusted based on renal function (see section 4.3 "renal disease" and section 4.4 "Monitoring of renal function").

Paediatric population

Safety and efficacy of DAGFOTIN in paediatric patients have not been established. Therefore, DAGFOTIN is not recommended for use in children below 18 years of age.

Method of administration

DAGFOTIN should be given with meals, to reduce the gastrointestinal side effects associated with metformin hydrochloride.

4.3 Contraindications

DAGFOTIN is contraindicated in patients with:

- known hypersensitivity to vildagliptin, metformin hydrochloride or to any of the excipients of DAGFOTIN (see section 6.1).
- severe renal impairment (GFR < 30 mL/min).

- hepatic impairment, including patients with a pre-treatment ALT or AST > 2,5 x the upper limit of normal (see section 4.4).
- congestive heart failure requiring pharmacological treatment (see section 4.4).
- acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

DAGFOTIN is not a substitute for insulin in patients requiring insulin. DAGFOTIN should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

If metabolic acidosis is suspected, treatment with DAGFOTIN should be discontinued and the patient hospitalised immediately (see section 4.9).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP-4 inhibitors including DAGFOTIN. SCARs are regarded as a class effect of DPP-4 inhibitors such as DAGFOTIN. If a patient develops SCAR, treatment with DPP-4 inhibitors such as DAGFOTIN must immediately be discontinued and appropriate treatment instituted. Patients should continue with an alternative class of anti-diabetic medicines.

Monitoring of renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin, as contained in DAGFOTIN is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Metformin hydrochloride is substantially excreted by the kidneys, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. As elderly people are associated with reduced renal function, metformin-containing medicines such as DAGFOTIN should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly (see section 4.2).

Concomitant medicines that may affect renal function, result in significant haemodynamic change, or inhibit renal transport and increase metformin systemic exposure, should be used with caution (see section 4.5).

DAGFOTIN should be discontinued if evidence of renal impairment is present.

Hepatic impairment

Vildagliptin, as in DAGFOTIN, is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 2, 5 x the ULN (see section 4.3).

Impaired hepatic function has been associated with some cases of lactic acidosis, a risk associated with metformin-containing medicines such as DAGFOTIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Liver enzyme monitoring

Cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Liver function tests (LFTs) should be performed prior to the initiation of treatment with DAGFOTIN. LFTs should be monitored during DAGFOTIN treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 x ULN or

greater persist, withdrawal of therapy with DAGFOTIN is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue DAGFOTIN and contact their medical practitioner immediately. Following withdrawal of treatment with DAGFOTIN and LFT normalisation, DAGFOTIN should not be reinitiated.

Lactic Acidosis

Lactic acidosis is a serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (e.g., due to severe diarrhoea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing medicines such as DAGFOTIN and seek immediate medical attention.

Medicines that can acutely impair renal function, such as antihypertensives, diuretics and NSAIDs, should be initiated with caution in patients treated with metformin-containing medicines such as DAGFOTIN. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicines that may cause lactic acidosis (see section 4.3 and 4.5).

Patients and/or caregivers 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. 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. If metabolic acidosis is suspected, treatment with metformin-containing medicines such as DAGFOTIN should be discontinued and the patient should be immediately hospitalised.

Heart Failure

In a study of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III, showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.

There is no experience of vildagliptin use in clinical studies in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Vildagliptin as in DAGFOTIN may cause arthralgia that can be severe.

Alcohol intake

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin containing medicines such as DAGFOTIN.

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

Administration of intravascular iodinated contrast materials

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

Rhabdomyolysis

Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing medicines such as DAGFOTIN. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (renal failure, hypovolemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing medicines in presence of predisposing risk factors is recommended.

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal uraemia. If such events occur in patients receiving DAGFOTIN therapy, the medicine should be promptly discontinued.

Surgical procedures

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

Vitamin B12 levels

The metformin as in DAGFOTIN has been associated with a decrease in serum vitamin B12 levels without clinical manifestations. Such decrease is associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B12 supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving metformin-containing medicines such as DAGFOTIN and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at minimally two-to-three-year intervals may be useful.

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

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

Hypoglycaemia

Hypoglycaemia does not usually occur in patients receiving DAGFOTIN alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly and in people taking beta-adrenergic blocking medicines.

Hypoglycaemia may occur when DAGFOTIN is used as add-on therapy to other anti-diabetic medicines.

Loss of control of blood glucose

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

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of the vildagliptin and metformin hydrochloride in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

Vildagliptin

Vildagliptin, as contained in DAGFOTIN, has a low potential for medicine interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co-medicines that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medicines metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. According to medicine-medicine interaction studies conducted with frequently co-prescribed medicines for patients with type 2 diabetes or medicines with a narrow therapeutic area, no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, and metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin hydrochloride

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

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

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

Cationic medicines (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport

systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60 % and 40 % respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin-containing medicines such as DAGFOTIN and such medicines are recommended.

Some medicines 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 medicines in combination with metformin-containing medicines such as DAGFOTIN, close monitoring of renal function is necessary. Certain medicines tend to cause hyperglycaemia and may lead to loss of glycaemic control. These medicines include the hydrochlorothiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such medicines are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Avoid consumption of alcohol and medicines containing alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in lactation has not been established.

DAGFOTIN should not be administered to breastfeeding women.

4.7 Effects on ability to drive and use machines

DAGFOTIN may cause dizziness. Patients who experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions are angioedema, hepatic dysfunction, and a less frequent adverse reaction is hypoglycaemia.

b. Tabulated list of adverse reactions

Vildagliptin and metformin:

System organ class	Frequency	Adverse event
Infections and infestations	Frequent	Upper respiratory tract infection, nasopharyngitis
Metabolism and nutrition disorders	Frequent	Hypoglycaemia
Nervous system disorders	Frequent	Tremor, dizziness, headache.
Gastrointestinal disorders	Frequent	Nausea, gastroesophageal reflux disease
	Less frequent	Diarrhoea, flatulence
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis
General disorders and administration site conditions	Frequent	Chills

Vildagliptin

System organ class	Frequency	Adverse event
Nervous system	Frequent	Dizziness.

System organ class	Frequency	Adverse event
disorders	Less frequent	Headache
Gastrointestinal disorders	Less frequent	Constipation.
	Less frequent	Diarrhoea, flatulence
General disorders and administration site conditions	Less frequent	Oedema peripheral

Metformin

System organ class	Frequency	Adverse event
Metabolism and nutrition disorders	Frequent	Decreased appetite
	Less frequent	Lactic acidosis
Nervous system disorders	Frequent	Metallic taste
Gastrointestinal disorders	Frequent	Flatulence, nausea, vomiting, diarrhoea, abdominal pain
Hepatobiliary disorders	Less frequent	Liver function test abnormalities, hepatitis**
Skin and subcutaneous tissue disorders	Less frequent	Skin reactions such as erythema, pruritus, urticaria
General disorders and administration site conditions	Frequent	Chills
Investigations	Less frequent	Decrease of vitamin B12 absorption*

*A decrease of vitamin B12 absorption with decrease of serum levels has been occasionally observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

**Cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

c. Description of selected adverse reactions

Vildagliptin

The following additional adverse drug reactions have been reported:

- •Cases of hepatitis reversible upon discontinuation of treatment
- •Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid
- •Pancreatitis
- •Arthralgia, sometimes severe

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP -4 inhibitors including DAGFOTIN.

Metformin

Gastrointestinal adverse effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP-4 inhibitors including DAGFOTIN.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit–risk balance of the medicine. Healthcare professionals are asked to report all suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via:

- Med Safety App (Medsafety X SAHPRA)
- SAHPRA's eReporting platform: https://who-umc.org (accessible via the SAHPRA website)

In addition, suspected adverse reactions may also be reported to the Holder of the Certificate of Registration at: pvg.cdma@heterogroups.com. By reporting suspected adverse reactions, you help improve the safety information for DAGFOTIN.]

4.9 Overdose

Signs and symptoms

Vildagliptin

Reports include muscle pain, paraesthesia, fever and oedema. Increases in lipase levels (2 x ULN), creatine phosphokinase (CPK) levels, aspartate aminotransferase (AST), C-reactive protein, and myoglobin may occur. Vildagliptin is not dialysable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Metformin Hydrochloride

Hypoglycaemia may develop and should be monitored for. Lactic acidosis has been reported in approximately 32 % of metformin hydrochloride overdose cases. Metformin hydrochloride is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated medicine from patients in whom metformin hydrochloride overdosage is suspected.

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.21.2 Oral Hypoglycaemics

Pharmacotherapeutic group: Medicines used in diabetes, Combinations of oral blood glucose lowering medicines, ATC code: A10BD08.

Mechanism of action

DAGFOTIN combines two antihyperglycaemic medicines with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (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 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta-cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

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

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 to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function, has been observed.

Metformin hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

5.2 Pharmacokinetic properties

Absorption

DAGFOTIN

Studies of fixed-dose combination of metformin and vildagliptin at two dose strengths (50 mg/850 mg and 50 mg/1000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the fixed-dose combination of metformin and vildagliptin tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of vildagliptin from fixed-dose combination of metformin and vildagliptin. The C_{max} and AUC of the metformin hydrochloride component from fixed-dose combination of vildagliptin and metformin hydrochloride were decreased by 26 % and 7 % respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2.0 to 4.0 hours) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride was given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of fixed-dose combination of vildagliptin and metformin hydrochloride were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

Vildagliptin

Following oral administration in the fasting state, vildagliptin is well absorbed with peak plasma concentrations observed at 1,75 hours. Coadministration with food slightly decreases the rate of absorption of vildagliptin, as characterised by a 19 % decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2,5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60 %. Studies using single oral doses of metformin hydrochloride tablets 500

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

Distribution

Vildagliptin

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 L, suggesting extravascular distribution.

Metformin hydrochloride

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

Biotransformation

Vildagliptin

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

Metformin Hydrochloride

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

Elimination

Vildagliptin

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

Metformin hydrochloride

Studies in normal subjects demonstrated that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90 % of the absorbed medicine is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood, the elimination half-life

is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Linearity

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

Special Populations

Hepatic impairment

Vildagliptin

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20 % and 8 %, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22 %. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30 %, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2,5 x the ULN (upper limit of normal).

Metformin Hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment.

Renal impairment

Vildagliptin

Vildagliptin AUC increased on average 1.4, 1.7 and 2 -fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3 -fold and that of BQS867 increased 1.4, 2.7 and 7.3 -fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment.

Vildagliptin was removed by haemodialysis to a limited extent (3 % over a 3-4 - hour haemodialysis session starting 4 hours post dose).

Metformin hydrochloride

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

Elderly

Vildagliptin

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

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears

that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

DAGFOTIN treatment should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Obesity Vildagliptin

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

Paediatric

No pharmacokinetic data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose; Hydroxypropyl cellulose; Magnesium stearate.

Film-coating;

Opadry II white/ pink; Polyvinyl alcohol-part hydrolysed; Titanium dioxide; Macrogol/PEG; Talc; Iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

In-use shelf life

Shelf life after first opening of the 100's HDPE bottle container is 4 months.

6.4 Special precautions for storage

Store at or below 25°C.

Keep in outer carton until required for use.

Keep bottles tightly closed to protect from moisture.

After first opening of the 100's HDPE bottle, the product should be used within 4 months.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10's Blister pack Alu-Alu

10 tablets packed in aluminium foil blister, form-pack film with desiccant.

50's count HDPE container

High density polyethylene container 120 cc with 38 mm child resistant cap with pulp liner, with 2g of silica gel sachet.

50's count HDPE container with molecular sieve canister

High density polyethylene container 120 cc with 38 mm child resistant cap with pulp liner, with 2g of molecular sieve canister.

100's count HDPE container

High density polyethylene container 250 cc with 53 mm child resistant cap with pulp liner, with 2g of silica gel sachet.

100's count HDPE container with molecular sieve canister

High density polyethylene container 250 cc with 53 mm child resistant cap with pulp liner, with 2g of molecular sieve canister.

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

DAGFOTIN 50/850: 59/21.2/0343.341

DAGFOTIN 50/1000: 59/21.2/0344.342

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

27 January 2026

10 DATE OF REVISION OF THE TEXT

TBA