Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Glucanix-Met 50/1000 **(**Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg Tablets)

1.1 Strength

Each Film Coated Tablet Contains:

Vildagliptin 50 mg

Metformin Hydrochloride USP 1000 mg

Excipients Q.S.

Colour: Titanium Dioxid BP, Yellow Oxide of Iron

1.2 Pharmaceutical form

Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Name of raw material	Specification	Label Claim (mg)	Qty./Tab (mg)	Purpose
Dry Mixing					
1.	Metformin Hydrochloride$	USP	1000.00	1000.00	Active
2.	Sodium Starch Glycolate	BP	-	36.60	Disintegrant
Binding					
3.	P.V.P.K-30	BP	-	25.28	Binder
4.	Purified water**	BP	-	Q.S.	Vehicle
Lubrication					
5.	Vildagliptin	In-house	50.00	50.00	Active
6.	Microcrystalline cellulose pH 102#	BP	-	66.30	Anticaking agent
7.	Magnesium Stearate	BP	-	6.10	Lubricant
8.	Sodium Starch Glycolate	BP	-	23.52	Disintegrant
9.	Colloidal Silicon Dioxide	BP		12.20	Glidant
Total Weight of Uncoated Tablets				**1220.0 mg**	
Coating					

Sr. No.	Name of raw material	Specification	Label Claim (mg)	Qty./Tab (mg)	Purpose
10.	Ready mix film coat color Titanium Dioxide and Yellow oxide of Iron @	In-House	-	25.0	Coating Material
11.	Isopropyl Alcohol**	BP	-	Q.S	Solvent
12.	Methylene Dichloride**	BP	-	Q.S	Solvent
Total Weight of coated Tablets				**1245.000 mg**	

BP: British Pharmacopeia

1) $: Quantity to be calculated on the basis of it's potency (Assay).
2) # : Quantity to be compensates against active material base on potency
3) @ : Overages taken to compensate loss during process.
4) ** : Quantity to be evaporate during process.

3. PHARMACEUTICAL FORM

Yellow color Oblong shape biconvex film coated tablet having one side break line and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Type II Diabetes Mellitus.

4.2 Posology and method of administration

Dose The use of antihyperglycaemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. When using This Tablet do not exceed the maximum daily dose of vildagliptin (100 mg). The recommended starting dose of This Tablet should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. Starting dose for patients inadequately controlled on vildagliptin monotherapy Based on the usual starting doses of metformin hydrochloride (850 mg once daily), This Tablet may be initiated at the 50 mg/1000mg tablet strength once daily and gradually titrated after assessing the adequacy of therapeutic response. Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy Based on the patient's current dose of metformin hydrochloride, This Tablet may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily. Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets This Tablet may be initiated with either the 50 mg/850 mg or 50 mg/1000 mg tablet strength based on the dose of vildagliptin or metformin already being taken. Use in combination with a sulphonylurea (SU) or with insulin The dose of This Tablet 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 GFR should be assessed before initiation of treatment with metformin-containing products (such as This Tablet) 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 should be reviewed before considering initiation of metformin-containing products (such as This Tablet) in patients with GFR<60 ml/min. This Tablet is contraindicated in patients with GFR<30 ml/min because of its metformin component.

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

Table 1: Dose adjustments in patients with renal impairment

GFR ml/min	Metformin	Vildagliptin
> 120	Maximum daily dose is 3000 mg*.	Maximal daily dose is 100 mg.
60-120	Maximum daily dose is 2000 mg*.	Maximal daily dose is 100 mg.
30-60	Maximum daily dose is 1000 mg.	Maximal daily dose is 50 mg.
<30	Metformin is contraindicated.	

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

Patients with hepatic impairment

This Tablet is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the upper limit of normal (ULN).

Elderly patients

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products (such as This Tablet) should have their renal function monitored regularly. The use or dosage of This Tablet should be based on renal function.

Paediatric patients

The safety and effectiveness of This Tablet in paediatric patients have not been established. Therefore, This Tablet is not recommended for use in children below 18 years of age.

Method of administration

For oral use only. This Tablet should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. If a dose of This Tablet is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

4.4 Contraindications

Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients.

- Severe renal impairment (GFR <30 ml/min)

- Congestive heart failure requiring pharmacological treatment.
- Metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma.
- Radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

4.5 Special warnings and precautions for use

Pregnancy

Due to a lack of sufficient safety and efficacy data, This 1000/50 Tablet is not recommended for use in pregnancy. Consult your doctor if you are pregnant or planning a pregnancy.

Breast-feeding

This 1000/50 Tablet may passes into breastmilk. This medicine is not recommended while breastfeeding due to the increased risk of hypoglycaemia in your baby. Consult your doctor if you are breastfeeding.

General warnings

Skin disorders

This 1000/50 Tablet may increase the risk of skin lesions (abnormal changes on the skin). Therefore, monitoring for skin disorders such as blistering or ulceration (open sores) is recommended while taking this medicine.

Use in children

This 1000/50 Tablet is not recommended for use in children below 18 years of age due to a lack of safety and efficacy data.

Kidney diseases

This 1000/50 Tablet should be used with caution if you have kidney problems as it may increase the risk of lactic acidosis (high levels of lactic acid in the blood). Your doctor may recommend dose adjustment based on your clinical condition.

Driving or operating machines

This 1000/50 Tablet may cause low blood sugar levels and dizziness which may affect your mental alertness. Avoid driving or operating machines if you experience these symptoms after taking this medicine.

Surgery

This 1000/50 Tablet is not recommended to be used during surgery due to the increased risk of lactic acidosis (high levels of lactic acid in the blood). If you are taking this medicine, inform your doctor before undergoing any surgery. Your doctor may suggest you to discontinue the treatment before surgery.

Liver Diseases

This 1000/50 Tablet may increase your risk of liver damage. If you have any liver problems, your doctor may suggest test to monitor your liver functions.

4.6 Interaction with other medicinal products and other forms of interaction

All drugs interact differently for person to person. You should check all the possible interactions with your doctor before starting any medicine.

Interaction with Alcohol

Description

N/A

Instructions

Consumption of alcohol is not recommended during treatment with This 1000/50 Tablet as it may increase the risk of lactic acidosis (increased blood lactic acid levels). It may also affect the ability of this medicine to control your blood sugar levels.

Interaction with Medicine

Clozapine
Estradiol
Gatifloxacin
Corticosteroids
Iodinated Contrast Media
Acetazolamide
ACE inhibitors
Cimetidine

Disease interactions

Pancreatitis

Pancreatitis is the swelling of the pancreas. This 1000/50 Tablet may increase the risk of pancreatitis and should be used with caution if you have a history of acute pancreatitis. Consult your doctor before taking this medicine.

Vitamin B12 deficiency

This 1000/50 Tablet should be used with caution if you have vitamin B12 deficiency. This medicine interferes with the absorption of Vitamin B12 in your body. Consult your doctor if you are taking these medications together.

Food interactions

Information not available.

Lab interactions

Information not available.

This is not an exhaustive list of possible drug interactions. You should consult your doctor about all the possible interactions of the drugs you're taking.

4.7 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

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

Lactation

No studies have been conducted with the combined components of This Tablet. Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. This Tablet should not be administered to breast-feeding women.

4.8 Effects on ability to drive and use machines

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

4.9 Undesirable effects

Major & minor side effects for This1000/50 Tablet

Headache
Low blood sugar levels (hypoglycaemia)
Change in taste
Nausea and Vomiting
Diarrhoea
Abdominal pain
Loss of appetite
Dizziness
Fatigue

4.10 Overdose

Signs and symptoms

Vildagliptin

In healthy subjects (seven to fourteen subjects per treatment group), vildagliptin was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced oedema of the hands and feet, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with oedema of both feet, accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of the accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

This Tablet combines two antihyperglycaemic agents with different 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, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase4 (DPP-4) inhibitor that improves glycaemic control. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagonlike peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacodynamic effects

Vildagliptin

The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improved 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. Unlike sulphonylureas, metformin

hydrochloride does not cause hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances), and does not cause hyperinsulinaemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. In humans metformin hydrochloride has favourable effects on lipid metabolism, independent of its action on glycaemia,. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

Clinical experience and safety

There have been no clinical efficacy studies conducted with This Tablet. However, the efficacy and safety of the separate components have been previously established and the co administration of the separate components have been evaluated for efficacy and safety in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled type 2 diabetes while on metformin hydrochloride therapy.

5.2 Pharmacokinetic properties

Absorption

This Tablet In the bioequivalence studies of This Tablet at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1,000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (Cmax) of both the vildagliptin component and the metformin hydrochloride component of the This Tablet 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 This Tablet. The Cmax and AUC of the metformin hydrochloride component from This Tablet were decreased by 26% and 7% respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the Tmax (2.0 to 4.0 hrs) when given with food. These changes in Cmax 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 This Tablet 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 rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized 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 the time to peak plasma concentration (Tmax) 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 (Vss) 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 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally <1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Biotranformation

Vildagliptin

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

5.3 Preclinical safety data

No data found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Starch Glycolate	BP
P.V.P.K-30	BP
Purified water	BP
Microcrystalline cellulose pH 102#	BP
Magnesium Stearate	BP
Sodium Starch Glycolate	BP
Colloidal Silicon Dioxide	BP
Ready mix film coat colour Titanium Dioxide and Yellow oxide of Iron	In-House
Isopropyl Alcohol	BP
Methylene Dichloride	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place below 30°C, Protect from light

6.5 Nature and contents of container

6 X 10 Tablets in Alu-Alu Blister Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

7. APPLICANT/MANUFACTURER

APPLICANT
Eliora Chemicals and Pharmaceuticals Limited

No 4, Moferere Street, Ado-Ekiti, Ekiti State, Nigeria

MANUFACTURER
SHUKRA PHARMACEUTICALS LTD Plot No. 795, Rakanpur Sola-Santej Road, Ta. Kalol, Dist. Gandhinagar Gujarat, India