For PPB use only	
1.17	**Product Information**
1.17.1	**Summary Product Characteristics (SPC)**

1. Name of the medicinal product

Vildagliptin ER 100mg & Metformin Hydrochloride ER 850mg Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Vildagliptin 100mg

(As extended release)

Metformin Hydrochloride BP 850mg

(As extended release)

S. No.	Wt. / tablet (mg)	Ingredient	Spec	Overages	Std. Qty for 100,000 tablets (in kg)
1.	850.00	Metformin Hydrochloride	BP	Nil	85.000
2.	42.50	Cetostearyl Alcohol	BP	Nil	4.250
3.	58.65	Hypromellose K4	BP	Nil	5.865
4.	58.65	Hypromellose K100	BP	Nil	5.865
5.	17.00	Ethylcellulose N50	BP	Nil	1.700
6.	17.00	Povidone K30	BP	Nil	1.700
7.	--	*Dichloromethane	BP	Nil	q.s
	Lubrication				
8.	15.73	Hypromellose K4	BP	Nil	1.573
9.	15.73	Hypromellose K100	BP	Nil	1.573
10.	100.00	Vildagliptin	IHS	Nil	10.000
11.	2.74	Purified Talc	BP	Nil	0.274
12.	8.50	Colloidal Anhydrous Silica	BP	Nil	0.850
13.	8.50	Magnesium Stearate	BP	Nil	0.850
Coating					
14.	24.00	Hypromellose E15	BP	Nil	2.400
15.	5.00	Titanium Dioxide	BP	Nil	0.500
16.	5.00	Purified Talc	BP	Nil	0.500
17.	1.00	Ponceau 4R Lake	IHS	Nil	0.100
18.	---	* Isopropyl Alcohol	BP	Nil	q.s
19.	---	* Dichloromethane	BP	Nil	q.s

* Represents solvents, will not be present in the finished Product.

BP – British Pharmacopoeia & IHS – In-House Specification.

3. Pharmaceutical form

Tablet: A pink color oblong shape biconvexed film coated tablet, scored in the middle on one side and plain on other side of the tablet.

4. Clinical particulars

4.1 Therapeutic indications

Vildamet XR is indicated in the treatment of type 2 diabetes mellitus. Vildamet XR is indicated in the treatment of adult patients who are unable to achieve sufficient glycemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Vildamet XR is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Vildamet XR is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycemic control.

4.2 Posology and method of administration

The dose of antihyperglycemic therapy with Vildamet XR should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Vildamet XR may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening or as directed by physician. Not recommended for children below 18 years of age.
Mode of Administration: Oral.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed. 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 and intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia, such as, cardiac or respiratory failure, recent myocardial infarction & shock, Hepatic impairment, Acute alcohol intoxication, alcoholism & Breast-feeding.

4.4 Special warnings and precautions for use

Vildamet XR is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, Pregnancy and lactation

Vildamet XR should not be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Hypoglycaemia, Tremor, Headache, Dizziness, Fatigue, Nausea & Asthenia.

4.9 Overdose

A large overdose of Vildagliptin and Metformin (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital.
Treatment: The most effective method of removing metformin is haemodialysis. However, vildagliptin cannot be removed by haemodialysis, although the major hydrolysis metabolite (LAY 151) can. Supportive management is recommended.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Vildamet XR combines two Antidiabetic agents with complimentary mechanisms of action to improve glycemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer class, and metformin hydrochloride, a member of the biguanide class. Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor. Metformin acts primarily by decreasing endogenous hepatic glucose production.

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 glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels. By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia. The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Metformin: Metformin is a biguanide with antihyperglycemic effects, lowering both basal and

postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain. Metformin may exert its glucose-lowering effect via three mechanisms: By reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis; in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation; - by delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

5.2 Pharmacokinetic properties

Vildamet XR

Absorption: Bioequivalence has been demonstrated between Vildamet XR at three dose strengths (100 mg/500 mg, 100 mg/850 mg and 100 mg/1000 mg) versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses. Food does not affect the extent and rate of absorption of vildagliptin from Vildamet XR. The rate and extent of absorption of metformin from Vildamet XR 100 mg/1000 mg were decreased when given with food as reflected by the decrease in Cmax by 26%, AUC by 7% and delayed Tmax (2.0 to 4.0 h).

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 Cmax (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 (Vss) 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). 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.

Elimination: Following oral administration of 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.

Metformin

Absorption: After an oral dose of metformin, the maximum plasma concentration (Cmax) 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 (Cmax) 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 (Vd) 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

There are no pre-clinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Cetostearyl Alcohol

Hypromellose K4M

Hypromellose K100M
Ethylcellulose N50
Povidone K30
Purified Talc
Colloidal Anhydrous Silica
Magnesium Stearate
Hypromellose E15
Titanium Dioxide
Ponceau 4R Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

Commercial Presentation: 4's, 7's, 10's, 14's, 20's, 30's & 100's
3 x 10's (10 tablets are packed in one PVC blister and 3 such PVC blisters are kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder and Manufacturing Site Address

Marketing authorisation holder:

Company name: INNOCIA LIFESCIENCES PVT. LTD.,
Address: Block A, No.12, Balaji Nagar, Ambattur, Chennai-600 053
Country: INDIA.

Manufacturing Site:

ATOZ Pharmaceutials Pvt.Ltd.,
No.12, Balaji Nagar, Ambattur, Chennai-600053,
India.

8. Marketing authorisation number(s)

Telephone: 044 26585811, 26585855

Telefax: -

E-Mail: ah@innocialife.com

9. Date of first registration / Renewal of the registration

Date of first Authorization: 18.01.2021

Date of Latest Renewal: Not Applicable

10. Date of revision of the text: Not Applicable

11. Dosimetry (If Applicable): Not Applicable

12. Instructions for preparation of radiopharmaceuticals (If Applicable): Not Applicable