Tablets

Insutol-M

(Vildagliptin + Metformin Hydrochloride USP)

انسوٹول۔ایم گولیاں

(ولڈاگلپٹن + میٹفارمن ہائیڈروکلورائیڈ یو ایس پی)

COMPOSITION:
Insutol-M 50mg/500mg:
Each film coated tablet contains:
Vildagliptin 50mg
Metformin Hydrochloride USP ... 500mg [Innovator's Specs.]

Insutol-M 50mg/850mg:
Vildagliptin 50mg
Metformin Hydrochloride USP ... 850mg [Innovator's Specs.]

Insutol-M 50mg/1000mg:
Vildagliptin 50mg
Metformin Hydrochloride USP ... 1000mg [Innovator's Specs.]

INDICATIONS: Insutol-M is indicated in the treatment of type 2 diabetes mellitus in adults.
- In the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral Metformin alone or who are already treated with the combination of Vildagliptin and Metformin Hydrochloride as separate tablets.
- In combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with Metformin Hydrochloride and a sulphonylurea.
- In triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and Metformin Hydrochloride alone do not provide adequate glycaemic control.

PHARMACODYNAMICS: Mechanism of Action: Insutol-M combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes. 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). 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.

PHARMACOKINETICS: Absorption: Bioequivalence has been demonstrated between **Insutol-M** at three dose strengths (50mg/500mg, 50mg/850mg and 50mg/1000mg) 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 **Insutol-M**. The rate and extent of absorption of Metformin Hydrochloride from **Insutol-M** were decreased when given with food as reflected by the decrease in C_{max} by 26%, AUC by 7% and delayed T_{max} (2.0 to 4.0 h).
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. Plasma protein binding is negligible. Metformin Hydrochloride partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63-276 litres.
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 glucuronide (BQS867) and the amide hydrolysis products (4% of dose). Accordingly, the metabolic clearance of Vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. 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. Metformin Hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination: Following oral administration of [14C] Vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged Vildagliptin accounted for 23% of the dose after oral administration. The elimination half-life after oral administration is approximately 3 hours. Metformin Hydrochloride is eliminated by renal excretion. Renal clearance of metformin is > 400ml/min, indicating that Metformin Hydrochloride 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 Hydrochloride in plasma.

DOSAGE AND ADMINISTRATION: Insutol-M can be administered orally with or without a meal. **Insutol-M** may be initiated at either the 50mg/850mg or 50mg/1000mg tablet strength twice daily, one tablet in the morning and the other in the evening.
- For patients inadequately controlled at their maximal tolerated dose of Metformin Hydrochloride monotherapy: The starting dose of **Insutol-M** should provide Vildagliptin as 50mg twice daily (100mg total daily dose) plus the dose of Metformin Hydrochloride already being taken.
- For patients switching from co-administration of Vildagliptin and Metformin Hydrochloride as separate tablets: **Insutol-M** should be initiated at the dose of Vildagliptin and Metformin Hydrochloride already being taken.
- For patients inadequately controlled on dual combination with Metformin Hydrochloride and a sulphonylurea: The doses of **Insutol-M** should provide Vildagliptin as 50mg twice daily (100mg total daily dose) and a dose of Metformin Hydrochloride similar to the dose already being taken. When **Insutol-M** is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.
- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of Metformin Hydrochloride: The dose of **Insutol-M** should provide Vildagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of Metformin Hydrochloride similar to the dose already being taken.

SPECIAL POPULATIONS: Elderly (> 65 years): As Metformin Hydrochloride is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking **Insutol-M** should have their renal function monitored regularly.

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Renal impairment: A GFR should be assessed before initiation of treatment with Metformin Hydrochloride-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
Hepatic impairment: Insutol-M should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).
Pediatric population: Insutol-M is not recommended for use in children and adolescents (< 18 years).

OVERDOSAGE: Information regarding overdose with Vildagliptin is limited. At 400mg, 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 600mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), AST, C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. Information regarding overdose with Vildagliptin is limited. A large overdose of Metformin Hydrochloride (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients.

WARNING & PRECAUTION: General: Insutol-M is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.
Renal impairment: GFR should be assessed before treatment initiation and regularly thereafter. Metformin Hydrochloride is contraindicated in patients with GFR < 30ml/min and should be temporarily discontinued in the presence of conditions that alter renal function.
Hepatic impairment: Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with **Insutol-M.**
Liver enzyme monitoring: Liver Function Tests should be performed prior to the initiation of treatment with **Insutol-M** in order to know the patient's baseline value. Liver function should be monitored during treatment with **Insutol-M** at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent LFTs until the abnormality (ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of **Insutol-M** therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue **Insutol-M.**
Skin disorders: There have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.
Acute pancreatitis: Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.
Hypoglycemia: Sulphonylureas are known to cause hypoglycemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycemia.
Surgery: Metformin Hydrochloride must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

INTERACTIONS: 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. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. As with other oral antidiabetic medicinal products the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

FERTILITY, PREGNANCY AND LACTATION: Pregnancy: There are no adequate data from the use of Vildagliptin & Metformin Hydrochloride in pregnant women.
Breast-feeding: Vildagliptin & Metformin Hydrochloride should not be used during breast-feeding.
Fertility: No studies on the effect on human fertility have been conducted for Vildagliptin & Metformin Hydrochloride.

SIDE EFFECTS: Metabolism and nutrition disorders: Common: Hypoglycaemia and decrease of vitamin B_{12} absorption and lactic acidosis.
Nervous system disorders: Common: Tremor, headache, chills, dizziness, fatigue and metallic taste.
Gastrointestinal disorders: Common: Nausea and gastro-oesophageal reflux disease. **Uncommon:** Diarrhoea, constipation and flatulence.
Skin and subcutaneous tissue disorders: Common: Hyperhidrosis and skin reactions such as erythema, pruritus and urticaria.
General disorders and administration site conditions: Common: Asthenia.
Infections and infestations: Very rare: Upper respiratory tract infection and nasopharyngitis.
Vascular disorders: Uncommon: Oedema peripheral.
Musculoskeletal and connective tissue disorders: Uncommon: Arthralgia.
Hepatobiliary disorders: Very rare: Liver function test abnormalities or hepatitis

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION: Insutol-M 50mg/500mg tablets are available in the pack size of 28's.
Insutol-M 50mg/850mg tablets are available in the pack size of 28's.
Insutol-M 50mg/1000mg tablets are available in the pack size of 28's.

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
NABIQASIM INDUSTRIES (PVT.) LTD.
PHARMA 17/24, Korangi Industrial Area, Karachi-Pakistan.

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