120x240mm

Nylomet™

(Glimepiride + Metformin HCl)

Highnoon

COMPOSITION
Nylomet 1mg/500mg Tablet:
Each Film-coated tablet contains:
Glimepiride 1mg
Metformin HCl 500mg
Nylomet 2mg/500mg Tablet:
Each Film-coated tablet contains:
Glimepiride 2mg
Metformin HCl 500mg

DESCRIPTION
Nylomet tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Glimepiride and metformin.
Glimepiride is an oral sulfonylurea and metformin is a member of the biguanide class.

MECHANISM OF ACTION
Glimepiride
Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

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

PHARMACOKINETICS
Glimepiride
Glimepiride is completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 2-3 hours and it is highly protein bound. The drug is extensively metabolised in the liver to two main metabolites. The cytochrome P450 isoenzymes is involved in the formation of hydroxy derivatives, which is further metabolised to a carboxy derivatives by cytosolic enzymes. The half-life after multiple doses is about 9 hours. About 60% of the dose is eliminated in the urine and 40% in the faeces.

Metformin
Metformin is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50% to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS AND USAGE
It is indicated:
- An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Type 2 diabetes mellitus not controlled by metformin or glimepiride alone.

DOSAGE AND ADMINISTRATION
It is recommended to start the treatment with the lowest effective dose which can be increased depending on blood glucose level.
When switching from combination therapy of glimepiride plus metformin as separate tablets, It should be administered on the basis of the dosage currently being taken.
Changes in weight, lifestyle, or stress may require dose adjustment.
The maximum dose of glimepiride is 8mg per day and the maximum dose of metformin is 2000mg per day or as directed by the physician.
It should be taken once daily by mouth immediately before or with the meals. Tablet should be swallowed whole with about half a glass of water.

CONTRAINDICATIONS
Metformin and Glimepiride combination is contraindicated in patients with the following conditions:
- hypersensitivity to metformin or glimepiride, other sulfonylureas or sulfonamides or to any of its constituents
- insulin dependent diabetes
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- diabetic pre-coma or diabetic coma
- severe renal or hepatic function disorders
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock
- disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- hepatic insufficiency, acute alcohol intoxication, alcoholism

In case of severe renal or hepatic function disorders, a change over to insulin is required.

ADVERSE REACTIONS
The reported adverse events are; vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases, thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication, leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock, cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible, vitamin B12 decrease/deficiency, lactic acidosis and hypoglycaemic reactions, visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels, taste disturbance, gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal distension, abdominal pain and loss of appetite, isolated reports of liver function tests abnormalities or hepatitis, and hepatic failure, hypersensitivity reactions of the skin may occur as erythema, pruritus, rash, urticaria and photosensitivity, blood sodium decrease.
Paediatric population: Metformin in published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

DRUG INTERACTIONS
- Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).
- Potentiation of the blood-glucose-lowering effect and, thus in some instances hypoglycaemia may occur when one of the following medicinal products is taken, for example: phenylbutazone, azapropazone and oxyfenbutazone, insulin and oral antidiabetic products, salicylates and p-amino-salicylic acid, anabolic steroids and male sex hormones, chloramphenicol, certain long acting sulfonamides, tetracyclines, quinolone antibiotics and clarithromycin, coumarin anticoagulants, fenfluramine, disopyramide, fibrates, ACE inhibitors, fluoxetine, MAO-inhibitors, allopurinol, probenecid sulfinpyrazone, sympatholytics, cyclophosphamide, trophosphamide and iphosphamides, miconazole, fluconazole, pentoxifylline (high dose parenteral), tritoqualine
- Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken for example: oestrogens and progestogens, saluretics, thiazide diuretics, thyroid stimulating agents, glucocorticoids, phenothiazine derivatives, chlorpromazine, adrenaline and sympathicomimetics, nicotinic acid (high dosages) and nicotinic acid derivatives, laxatives (long term use), phenytoin, diazoxide, glucagon, barbiturates and rifampicin, acetazolamide, calcium channel blockers, and isoniazid.
- H2 antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.
- Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.
- Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
- Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.
- Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.
- Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
- Alcohol is known to potentiate the effect of metformin on lactate metabolism. Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.
- Coadministration with insulin may increase the risk of hypoglycaemia.

WARNINGS AND PRECAUTIONS
Nylomet must be taken shortly before or during a meal. When meals are taken at irregular hours or skipped altogether, treatment with it may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias. The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke. Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect. It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.
Factors favouring hypoglycaemia include: unwillingness or (more commonly in older patients) incapacity of the patient to cooperate, undernutrition, irregular mealtimes or missed meals or periods of fasting, alterations in diet, imbalance between physical exertion and carbohydrate intake, consumption of alcohol, especially in combination with skipped meals, impaired renal function, serious liver dysfunction, overdosage with Glimepiride and combination medicines, certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency), concurrent administration of certain other medicinal products.
Treatment with Nylomet requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended. Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride tablets in stress-situations (e.g. accidents, acute operations, infections with fever etc) a temporary switch to insulin may be indicated. In patients with severe impairment of renal or liver function change over to insulin is indicated.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered. This combination contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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), Nylomet should be temporarily discontinued. Consultation with doctor is immediately advised. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and 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. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Nylomet and seek immediate medical attention.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Nylomet is contraindicated.

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Nylomet should 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.

Surgery
Nylomet 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.

Other precautions
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.
Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Nylomet therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.
Metformin in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides) may cause hypoglycaemia.

USE IN SPECIFIC POPULATIONS
Pregnancy
It should not be used during the whole pregnancy. If the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Lactation
Excretion of glimepiride in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Paediatric Use
The available data on safety and efficacy are insufficient in the paediatric population and because of its adverse effects on body weight and hypoglycaemia it is not recommended for paediatric use.

OVERDOSAGE
After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.
Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.
In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.
Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of the reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Nylomet 1mg/500mg Tablets:
Alu. PVC. Blister Pack of 3 x 10's.
Nylomet 2mg/500mg Tablets:
Alu. PVC. Blister Pack of 3 x 10's.

نائیلومیٹ™

(گلیمیپرائیڈ+میٹ فارمن ہائیڈروکلورائیڈ)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14001976

120x240mm