BIPHASIC ISOPHANE INSULIN
(rDNA Origin)

GLYSOLIN® 30/70

100 IU / mL
Suspension for Injection (S.C.)
Intermediate Acting Insulin

℞

FORMULATION
Each mL contains:
Insulin Human USP.....100 IU
(30% Regular insulin human neutral & 70% Isophane insulin)
m-Cresol (as preservative) .....0.16% w/v
Phenol (as preservative).....0.065% w/v
Water for Injection.....q.s.

DIABETES
Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs. To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or your urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly and take your insulin injections as prescribed. Always keep an extra supply of insulin as well as spare syringe and needle handy.

PRODUCT DESCRIPTION
Recombinant Biphasic Isophane Insulin (Glysolin® 30/70) is a recombinant human insulin, synthesized in a laboratory strain of Hansenula polymorpha (a yeast), in which the gene for human insulin has been inserted by the recombinant DNA technique. It is a mixture of insulin human regular injection 30% with isophane insulin human suspension 70% and providing an intermediate-acting insulin with an onset of action similar to regular insulin (0.5 hours). The onset of action of Biphasic Isophane Insulin (Glysolin® 30/70) is dependent on dose, site of injection. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. It is a sterile solution and is for subcutaneous injection only. It should not be used intravenously o intramuscularly.

PHARMACODYNAMICS
Mechanism of Action
Like all other insulins, the glucose lowering effect of Biphasic Isophane Insulin (Glysolin® 30/70) is due to the facilitated uptake of glucose in the body tissues. This uptake occurs following the binding of insulin to its receptors present in the muscle and adipose tissue. The blood glucose lowering effect of insulin also occurs due to the simultaneous inhibition of glucose output from the liver.

PHARMACOKINETICS
Insulin has a half-life of a few minutes in the blood stream. Consequently, the time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with insulin preparations, the intensity and duration of action of Biphasic Isophane Insulin (Glysolin® 30/70) is dependent on the dose, site of injection, blood supply, temperature, and physical activity.
An average action profile after subcutaneous injection indicates:
- Onset within 0.5 minutes
- Peak levels attained between 2-12 hours
- Duration of action approximately 18-24 hours

INDICATIONS
Biphasic Isophane Insulin (Glysolin® 30/70) is indicated for the following:
- Management of all patients with type 1 diabetes
- Management of patients with type 2 diabetes who are not adequately controlled by diet and/or oral hypoglycemic agent.
- For the initial stabilization of diabetes in patients with diabetic ketoacidosis, hyperosmolar non-ketotic syndrome and during periods of stress such as severe infections and major surgery in diabetic patients.
- Management of gestational diabetes

DOSAGE AND ADMINISTRATION
The dosage of Biphasic Isophane Insulin (Glysolin® 30/70) is determined by the physician, as per the needs of the patient. With Biphasic Isophane Insulin (Glysolin® 30/70), it is important to use a syringe that is marked for the desired strength (i.e. U-100 insulin preparations). Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems such as severe hypoglycemia or hyperglycemia.

The average range of total daily insulin requirement for maintenance in type 1 diabetic patient ranges between 0.5 and 1.0 IU/kg. Further, in insulin resistance, the daily requirement of insulin may be substantially higher. In patients with type 2 diabetes, the requirements are lower i.e. approximately 0.3-0.6 IU/kg/day.

- Biphasic Isophane Insulin (Glysolin® 30/70) is usually administered subcutaneously in the abdominal wall, thigh, gluteal region or the deltoid region. Intramuscular injections are possible under guidance by a physician. Intravenous administration are suitable only for vial products and should be carried out under the guidance of a physician.

- To avoid lipodystrophy, the site of injection should be frequently changed and any injection of insulin should be followed by a meal or snack containing carbohydrates within 30 minutes.
  Adjustment of dosage may be necessary if you undertake increased physical activity or change your usual diet.

USE ALONG WITH OTHER TYPES OF INSULIN
Biphasic Isophane Insulin (Glysolin® 30/70) injection can be used in combination with human insulin regular.

CONTRAINDICATIONS
Biphasic Isophane Insulin (Glysolin® 30/70) is contraindicated on the following conditions:
- Hypoglycemia
- Hypersensitivity to insulin or any other component of the formulation

WARNINGS AND PRECAUTIONS
Never share a Biphasic Isophane Insulin(rDNA Origin) (Glysolin® 30/70) or syringe between patients, even if the needle is changed.
• Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen: Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring.
• Hypoglycemia: May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness.
• Hypersensitivity Reactions: May be life-threatening. Discontinue Biphasic Isophane Insulin(rDNA Origin) (Glysolin® 30/70), monitor and treat if indicated.
• Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated.
• Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.
Renal Impairment: The requirements for insulin may be reduced in patients with renal impairment.
Hepatic Impairment: Although impaired hepatic function does not affect the absorption or disposition of Biphasic Isophane Insulin, careful glucose monitoring and dose adjustments of insulin may be necessary.

PREGNANCY AND LACTATION
Pregnancy: There are no restrictions on the use of insulin during pregnancy since insulin does not cross the placental barrier. Published studies with human insulin suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.
Nursing mothers: There are no restrictions on the use of insulin in lactating mothers as insulin treatment of nursing mothers does not involve any risk to the baby. However, caution should be exercised when administered to nursing mothers and the dosage of insulin may be reduced.
Effects on the ability to drive and use machine: The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where those abilities are of special importance (e.g. driving a car or operating machinery). You are therefore advised to avoid driving during hypoglycemia. This is particularly significant in patients who have reduced awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

SWITCHING TO DIFFERENT TYPE OF INSULIN
If you are switching to another type of insulin, it should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (rapid acting insulin, intermediate acting insulin, long acting insulin, etc.), species (animal, insulin human analog) and/or method of manufacture (recombinant versus animal source insulin) may result in the need for a change in dose. Patients switching to regular insulin human suspension may require a change in dosage from that used with their usual insulin.

LABORATORY TESTS
As with all insulins, the therapeutic response to human insulin should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

DRUG INTERACTIONS
Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, Isoniazid, certain lipid-lowering drugs (e.g. Niacin), estrogens, oral contraceptives, phenothiazines and thyroid replacement therapy. Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors, beta adrenergic blockers, inhibitors of pancreatic function (e.g. Octreotide), and alcohol. Beta adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

ADVERSE DRUG REACTIONS
The most commonly seen adverse reaction with Biphasic Isophane Insulin (Glysolin® 30/70) are:
1. Hypoglycemia:
Hypoglycemia is one of the most common adverse effects seen with the use of any type of insulin including human insulin. This can occur because of the following:
- Use of too much insulin
- Missed meal/delayed meal
- Intercurrent infection or illness
- Strenuous exercise

Disease of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease may also lead to hypoglycemia.

Concomitant administration with other drugs that lower blood glucose such as oral hypoglycemics, salicylates (i.e. Aspirin), sulfa antibiotics, and certain antidepressants may lead to hypoglycemia.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include: sweating, dizziness, palpitation, tremor, hunger, restlessness, tingling of the hands, feet, lips, or tongue, lightheadedness, inability to concentrate, headache, drowsiness, sleep disturbances, anxiety, blurred vision, slurred speech, depressive mood, irritability, abnormal behavior, unsteady movement, personality changes.

Signs of severe hypoglycemia can include: disorientation, unconsciousness, seizures, death.

Therefore it is important that assistance be obtained immediately. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, co-administration of medications such as beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes. The use of preparations of Biphasic Isophane Insulin ((Glysolin® 30/70)) should minimize the incidence of adverse effects associated with the use of animal insulins.

2. Edema
Edema and refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

3. Allergy to insulin
3.a Systemic Allergy: Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening.
3.b Local Allergy: Patients occasionally experience redness, swelling and itching at the site of injection of insulin. This condition called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent.

4. Lipoatrophy and lipodystrophy
Lipodystrophy occurs at the site of injection after long usage. However, this is less common with the newer preparations of insulin.

5. Insulin resistance
When insulin requirement is increased (>200 IU/day), insulin resistance is said to have developed. The following are the different grades of insulin resistance:
Acute: Acute insulin resistance develops rapidly and is usually a short term problem. It usually occurs due to an underlying infection, trauma, surgery and emotional stress. Treatment is to overcome the precipitating factor and to give high doses of regular insulin.
Chronic: This type of insulin resistance is generally seen in patients treated for years with conventional preparations of beef or pork insulin and it is more common in patients with type 2 diabetes. Development of such type of insulin resistance is an indication for switching patients to the newer preparations of insulin. After instituting the newer preparations, insulin requirement gradually declines over weeks and months. Majority of patients stabilize at approximately 60 IU/day.

OVERDOSE AND TREATMENT
Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. It is therefore recommended that the diabetic patient constantly carry some sugar lump, sweets, biscuits, or sugary fruit juice. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagons or concentrated intravenous glucose. Glucose must also be given intravenously. If the patient does not respond to glucagons within 10 to 15 minutes, sustained carbohydrates intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

STORAGE CONDITION
Store between 2-8°C but not allowed to freeze. When in use, vial may be kept at room temperature (15°C to 25°C) for up to six weeks. Do not expose to excessive heat or direct sunlight. It must be kept out of reach of children. Insulin preparations which have been frozen must not be used. Once opened (when the stopper or seal has been punctured with a needle), insulin is kept at room temperature. Cold insulin can be irritating to inject. Thus, patients should be asked to roll the vial in their hands 10 times prior to drawing it up in the syringe (after allowing the vial to sit for 30 minutes at room temperature if the vial is stored in a refrigerator).

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY
10 mL glass vial with rubber stopper brown flip-off seal (Box of 1's)

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