



Please bring Rapilin to room temperature before use and follow the injection steps described below:

1. Check the insulin to make sure it is clear and colorless. Do not use Rapilin if particulate matter or coloration is seen.
2. Please refer to the relevant reusable pen package insert, when using Rapilin in conjunction with a reusable pen.
3. Rapilin is injected under the skin (subcutaneously) of the upper arm, thigh, or stomach area (abdomen). Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before injection. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localised cutaneous amyloidosis.
4. Pinch the skin of the injection site with fingers and puncture the needle. After the pusher is pushed to the end, keep the needle under the skin for a few seconds to ensure that the correct dose is injected, then pull out the needle, and gently press the injection site with the sterile cotton ball for a few seconds, but do not rub the injection site to avoid damage to the subcutaneous tissue or cause the exudation of Rapilin.

**Dosage:**

1. Individualise and adjust the dosage of Rapilin based on route of administration, the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal.
2. Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness.
3. Rapilin can be used in combination with intermediate-acting or long-acting insulin under the doctor’s guidance for specific usage and dose.
4. Dosage adjustment may be needed when switching from another insulin to Rapilin.

**ADVERSE REACTIONS**

**Tabulated list of adverse reactions:**

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

Immune system disorders	Uncommon – Urticaria, rash, eruptions
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site	Uncommon – Injection site reactions

conditions	Uncommon – Oedema
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\* see below for descriptions of selected adverse reactions.

### **Hypoglycaemia:**

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

### **Anaphylactic reactions:**

Severe, life-threatening, generalised allergy, including anaphylaxis, can occur with insulin products, including Rapilin. If hypersensitivity reactions occur, discontinue Rapilin; treat per standard of care and monitor until symptoms and signs resolve. Rapilin is contraindicated in patients who have had hypersensitivity reactions to insulin aspart or one of the excipients.

### **Lipodystrophy:**

Lipodystrophy (including lipohypertrophy, lipodystrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area reduces the risk of developing these reactions.

## **CONTRAINDICATIONS**

Hypersensitivity to insulin aspart or to any of the excipients listed in COMPOSITION

## **PRECAUTIONS**

Before travelling between different time zones, the patients should seek the doctor's advice since this may mean that the patient has to take the insulin and meals at different times.

### **Hyperglycaemia**

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis.

### **Hypoglycaemia**

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since Rapilin should be administered in immediate relation to a meal, the rapid onset of action

should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

### **Transfer from other insulin medicinal products**

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to Rapilin from another type of insulin may require a change in the number of daily injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

### **Injection site reactions**

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Rapilin.

### **Combination of Insulin with pioglitazone**

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Rapilin is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

### **Insulin antibodies**

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

### **Effect on ability to drive and use machines**

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

## **USE FOR PREGNANT WOMEN AND NURSING MOTHERS**

### **Pregnancy**

Rapilin can be used in pregnancy. Data from two randomised controlled clinical trials do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

Intensified blood glucose control and monitoring of pregnant women with diabetes (type 1 diabetes, type 2 diabetes or gestational diabetes) are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

### **Breast-feeding**

There are no restrictions on treatment with Rapilin during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, Rapilin dose may need to be adjusted.

### **PEDIATRIC USE**

According to literatures:

Pediatric patients can maintain long-term glycemetic control when using insulin aspart for treatment. A clinical trial for children and adolescents among 2 to 17 years old showed that, the pharmacodynamics of insulin aspart is similar between children and adults.

A clinical trial for type 1 diabetic patients showed that, when compared to soluble human insulin, insulin aspart can lower the risk of nocturnal hypoglycaemia, and the risk of having day-time hypoglycaemia did not increase significantly.

A study about pharmacodynamics and pharmacokinetics among type 1 diabetic children and adolescents showed that, insulin aspart can be quickly absorbed by two groups, and the time to peak is similar to that of adults. However, for maximum serum drug concentration, differences among age groups exists. As a result, individualized treatment should be emphasised.

Rapilin can be used in children in preference to soluble human insulin when a rapid onset of action might be beneficial, for example, in the timing of the injections in relation to meals.

### **GERIATRIC USE**

According to literatures:

A study comparing PK/PD of insulin aspart and soluble human insulin on elderly type 2 diabetic patients showed that, the relative difference between insulin aspart and soluble human insulin on elderly patients is similar to that on young diabetic patients.

In elderly patients, the time to peak (82 minutes) delays due to the decrease of absorption rate, and the maximum serum drug concentration in elderly patients is similar to that in young type 2 diabetic patients, which is slightly lower than the results obtained from type 1 diabetic patients.

### **DRUG INTERACTIONS**

A number of substances are known to interact with the glucose metabolism.

The following substances may reduce the patient's insulin requirements:

Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.

The following substances may increase the patient's insulin requirements:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

## OVERDOSAGE

A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:

1. Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
2. Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by physicians or other healthcare staff. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

## PHARMACOLOGY

The blood glucose lowering effect of insulin aspart is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Rapilin produces a more rapid onset of action compared to soluble human insulin, together with a lower glucose concentration, as assessed within the first four hours after a meal. Rapilin has a shorter duration of action compared to soluble human insulin after subcutaneous injection.

When Rapilin is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after injection. The duration of action is 3 to 5 hours.

When compared with soluble human insulin, clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose using Rapilin. According to literature, in two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, insulin aspart reduced glycated haemoglobin by 0.12% and by 0.15% compared to human insulin; a difference of limited clinical significance.

Clinical trials in patients with type 1 diabetes have demonstrated a reduced risk of nocturnal hypoglycaemia with insulin aspart compared with soluble human insulin. The risk of daytime hypoglycaemia was not significantly increased.

### *Pregnancy*

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn. In addition, the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

## PHARMACOKINETICS

Insulin aspart is a rapid-acting insulin analogue that is modified by altering the B28 proline

residue to aspartic acid residue from human insulin. As a result, Rapilin has a lower tendency to form hexamers than soluble human insulin.

Like other insulins, insulin aspart's primary function is the regulation of glucose metabolism. Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

The faster absorption characteristic of insulin aspart depends on its fast release after subcutaneous injection and subsequent fast absorption into the blood.

In healthy subjects and diabetic patients, insulin serum concentrations indicated a faster absorption after subcutaneous injection of insulin aspart in comparison to human insulin.

The relative bioavailability of insulin aspart compared to regular human insulin indicates that two insulins are absorbed to a similar extent.

According to literature, diabetic patients were administered subcutaneously both insulin aspart and regular human insulin, and mean  $C_{max}$  is much larger than that of regular human insulin.

The mean insulin clearance was similar for both insulin aspart and regular human insulin.

In clinical studies, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy in insulin aspart-treated patients compared to the entire study population.

## **STORAGE**

### Unopened cartridges

Store in a refrigerator (2°C -8°C)

Do not freeze or place next to freezer compartment or a freezer pack.

Keep the cartridge in the outer carton in order to protect from light.

### In-use cartridges

The medicinal product may be stored for maximum of 4 weeks not above 25 °C and away from direct heat or direct light.

## **PACKAGE**

Cartridge, compound aluminum cap, brominated butyl rubber stopper, 1 cartridge/box.

## **SHELF LIFE**

Rapilin 100 units/mL solution for injection in a cartridge.

24 months.

## **MANUFACTURER**

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