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Insulin Aspart 30 Injection

DRUG NAME

Generic name: Insulin Aspart 30 Injection

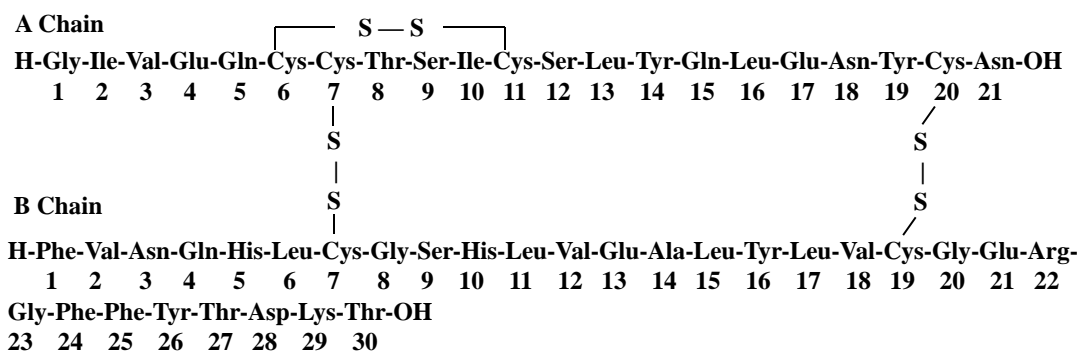
Trade name: Rapilin 30

COMPOSITION

Active ingredient: Insulin Aspart

Chemical name: B28-Asp insulin (human)

Chemical structural formula:



Molecular formula: C₂₅₆H₃₈₁N₆₅O₇₉S₆

Molecular weight: 5825.8 Da

Excipient: glycerol, phenol, m-cresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

DESCRIPTION

Rapilin 30 is a uniform, white, sterile suspension that contains insulin aspart 100 units/mL.

INDICATION

Rapilin 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

STRENGTHS

100 units/mL in 3 mL cartridge

DOSAGE AND ADMINISTRATION

Dosage

Always use your insulin and adjust your dose exactly as your doctor has told you. Rapilin 30 dosing

is individual and determined in accordance with the needs of the patient. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

In patients with type 2 diabetes, Rapilin 30 can be given as monotherapy. Rapilin 30 can also be given in combination with oral antidiabetic medicinal products.

How to start treatment

For patients with type 2 diabetes, the recommended starting dose of Rapilin 30 is 6 units at breakfast and 6 units at dinner (evening meal).

Transfer from other insulin medicinal products

When transferring a patient from biphasic human insulin to Rapilin 30, start with the same dose and regimen. Then titrate according to individual needs (see the titration guideline in the table above). Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter.

How to intensify treatment

Rapilin 30 can also be initiated once daily with 12 units at dinner (evening meal). When using Rapilin 30 once daily, it is generally recommended to move to twice daily when reaching 30 units by splitting the dose into equal breakfast and dinner doses. If twice daily dosing with Rapilin 30 results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (thrice daily dosing).

How to adjust the dose

See the titration guideline in the table below

Pre-meal blood glucose level		Rapilin 30 dose adjustment
<4.4 mmol/L	<80 mg/dL	<4.4 mmol/L
4.4–6.1 mmol/L	80–110 mg/dL	4.4–6.1 mmol/L
6.2–7.8 mmol/L	111–140 mg/dL	6.2–7.8 mmol/L
7.9–10 mmol/L	141–180 mg/dL	7.9–10 mmol/L
>10 mmol/L	>180 mg/dL	>10 mmol/L

The lowest of the three previous days' pre-meal blood glucose levels should be used. The dose should not be increased if hypoglycaemia occurred within these days. Dose adjustments can be made once a week until target HbA1c is reached. Pre-meal blood glucose levels should be used to evaluate the adequacy of the preceding dose.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Elderly (≥65 years old)

Rapilin 30 can be used in elderly patients; however there is limited experience with the use of Rapilin 30 in combination with oral antidiabetic medicinal products in patients older than 75 years.

In elderly patients, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Renal and hepatic impairment

Renal or hepatic impairment may reduce the patient's insulin requirements.

In patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

Rapilin 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. There is limited clinical experience with Rapilin 30 in children aged 6–9 years. No data are available for Rapilin 30 in children below 6 years of age.

Usage

Important Administration Information

- Rapilin 30 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). Rapilin 30 is only suitable for injecting under the skin using a reusable pen.
- Rapilin 30 is not to be used in insulin infusion pumps
- Rapilin 30 is administered subcutaneously by injection in the thigh or in the abdominal wall. If convenient, the gluteal or deltoid region may be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Like other insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
- Rapilin 30 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, Rapilin 30 can be given soon after a meal.
- Do not refill the cartridge, never Share Rapilin 30 between Patients, and suggest to remove and discard the needle after each injection.
- Inspect Rapilin 30 visually before use. It should appear uniformly white and cloudy.
- Rapilin 30 must be resuspended immediately before use.
- Do not freeze Rapilin 30.

Do not use Rapilin 30

- If you are allergic to insulin aspart or any of the other ingredients in this medicine (see *Composition*).
- If you suspect hypoglycemia (low blood sugar) is starting.
- In insulin infusion pumps.
- If Rapilin 30 is dropped, damaged or crushed.
- If it has not been stored correctly or if it has been frozen.
- If the resuspended insulin does not appear uniformly white, cloudy and aqueous.
- If after resuspension, clumps of material are present or if solid white particles stick to the bottom or the wall of the cartridge.

Before using Rapilin 30

- Check the label to make sure it is the right type of insulin.
- Always use a new needle for each injection to prevent contamination.
- Needles and Rapilin 30 must not be shared.

Where to inject

- Rapilin 30 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly).
- With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. The insulin will work more quickly if you inject around the waist. You should always measure your blood sugar regularly.

How to inject

- Let the insulin reach room temperature before you use it. This makes it easier to resuspend.
- Roll the cartridge between your palms 10 times – it is important that the cartridge is kept horizontal (level with the ground).
- Move the cartridge up and down 10 times so that the glass ball moves from one end of the cartridge to the other.
- Repeat the rolling and moving procedures until the liquid does appear uniformly white, cloudy and aqueous.
- Wash your hands with soap and water.
- Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose.
- Take a new needle and tear off the paper tab. Screw the needle straight and tightly onto your Xiu Lin pen.
- Pull off the needle cap. Give the airshot before each injection and set the dose.
- Pinch the skin of injection site and insert the needle into the skin. Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose.
- Press the injection site lightly with an alcohol swab. Do not rub the area.
- After each injection, be sure to remove and discard the needle and store Rapilin 30 without the needle attached.

ADVERSE REACTIONS

According to literatures

The 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).

Nervous system disorders	Rare – Peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Oedema
	Uncommon – Injection site reactions
Immune system disorders	Uncommon – Urticaria, rash, eruptions
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*

* see Description of selected adverse reactions.

† ADR from postmarketing sources.

Description of selected adverse reactions

Anaphylactic reactions

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life-threatening.

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 concentrating, 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.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at

the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

CONTRAINDICATIONS

Hypersensitivity to insulin aspart 30 or to any of the excipients listed in *Composition*.

PRECAUTIONS

Before travelling between different time zones, the patient 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. Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

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. In case of hypoglycaemia or if hypoglycaemia is suspected, Rapilin 30 must not be injected. After stabilization of the patient's blood glucose, adjustment of the dose should be considered.

Compared with biphasic human insulin, Rapilin 30 may have a more pronounced glucose lowering effect up to 6 hours after injection. This may have to be compensated for in the individual patient through adjustment of insulin dose and/or food intake.

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.

Tighter control of glucose levels can increase the potential for hypoglycaemic episodes and therefore require special attention during dose intensification as outlined in section 4.2.

Since Rapilin 30 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 insulin, human insulin or 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 30 from another type of insulin may require an increased 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 30.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Combination of Rapilin 30 with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factor for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Rapilin 30 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.

Effects 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 or operating a machine. 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 or operating a machine should be considered in these circumstances.

USE FOR PREGNANT WOMEN AND NURSING MOTHERS

Pregnancy

Ask your doctor or pharmacist for advice taking any medicine.

There is limited clinical experience with Rapilin 30 in pregnancy.

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding embryotoxicity or teratogenicity.

In general, intensified blood glucose control and monitoring of pregnant women with 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 trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Breast-feeding

There are no restrictions on treatment with Rapilin 30 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the Rapilin 30 dose may need to be adjusted.

PEDIATRIC USE

Rapilin 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. There is limited clinical experience with Rapilin 30 in children aged 6–9 years. No data are available for Rapilin 30 in children below 6 years of age, please ask your doctor or pharmacist for advice taking any medicine.

GERIATRIC USE

Rapilin 30 can be used in elderly patients; however there is limited experience with the use of Rapilin 30 in combination with oral antidiabetic medicinal products in patients older than 75 years, please ask your doctor or pharmacist for advice taking any medicine.

DRUG INTERACTIONS

A number of medicinal products 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 sulfonamides.

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:

- 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.
- 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 a healthcare professional. 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

Rapilin 30 is a biphasic suspension of 30% soluble insulin aspart (rapid-acting human insulin analogue) and 70% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue).

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 simultaneous inhibition of glucose output from the liver.

PHARMACOKINETICS

According to literatures

In insulin aspart, substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. The insulin aspart in the soluble phase of Rapilin 30 comprises 30% of the total insulin; this is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 70% is in crystalline form as protamine-crystallised insulin aspart; this has a prolonged absorption profile similar to human NPH insulin.

The maximum serum insulin concentration is, on average, 50% higher with Rapilin 30 than with biphasic human insulin 30. The time to maximum concentration is, on average, half of that for biphasic human insulin 30. In healthy volunteers, a mean maximum serum concentration of 140 ± 32 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.20 unit/kg body weight. The mean half life ($t_{1/2}$) of Rapilin 30, reflecting the absorption rate of the protamine bound fraction, was about 8-9 hours. Serum insulin levels returned to baseline 15-18 hours after a subcutaneous dose. In type 2 diabetic patients, the maximum concentration was reached about 95 minutes after dosing, and concentrations well above zero for not less than 14 hours post-dosing were measured.

Special populations

The pharmacokinetics of Rapilin 30 have not been investigated in elderly patients or in patients with renal or hepatic impairment.

Paediatric population

The pharmacokinetics of Rapilin 30 have not been investigated in children or adolescents. However, the pharmacokinetic and pharmacodynamic properties of soluble insulin aspart have been investigated in children (6-12 years) and adolescents (13-17 years) with type 1 diabetes. Insulin

aspart was rapidly absorbed in both age groups, with similar t_{\max} as in adults. However, C_{\max} differed between the age groups, stressing the importance of the individual titration of insulin aspart.

STORAGE

Before opening: Store in a refrigerator (2°C - 8°C). Keep away from the cooling element. Do not freeze.

During use of when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze. Keep the cartridge in the outer carton in order to protect it from light.

PACKAGE

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

SHELF LIFE

Before opening: 24 months.

During use of when carried as a spare: The product can be stored for a maximum of 4 weeks.

MANUFACTURER

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