NovoMix® 50 FlexPen®

100 U/ml

Suspension for injection in a pre-filled pen.

Qualitative and quantitative composition

1 ml of the suspension contains 100 U of soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 50/50 (equivalent to 3.5 mg).
1 pre-filled pen contains 3 ml equivalent to 300 U.
*Insulin aspart produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

Pharmaceutical form

White suspension for injection in a pre-filled pen. FlexPen®.

Therapeutic indications

Treatment of patients with diabetes mellitus requiring insulin.

Posology

NovoMix® 50 is a biphasic suspension of the insulin analogue, insulin aspart. The suspension contains rapid-acting and intermediate-acting insulin aspart in the ratio 50/50.

NovoMix® 50 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.

The individual insulin requirement is usually between 0.5 and 1.0 unit/kg/day in adult patients and this may be fully or partially supplied with NovoMix® 50. The daily insulin requirement may be higher in patients with insulin resistance (e.g. due to obesity), and lower in patients with residual endogenous insulin production. In patients with type 2 diabetes, NovoMix® 50 can be given in monotherapy or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone.

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

Special populations

As with all insulin products, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dosage adjusted on an individual basis.
Renal or hepatic impairment may reduce the patient's insulin requirements.

Transfer from other insulin products

Transfer to NovoMix® 50 from other insulin preparations may require adjustment of dose and timing of administration. As with all insulin products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see *Special warnings and precautions for use*).

Method of administration

NovoMix® 50 is for subcutaneous administration only. NovoMix® 50 must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. NovoMix® 50 is not to be used in insulin infusion pumps.

NovoMix® 50 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. As with all insulin products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

8-9671-00-006-1

The rapid onset of action and early peak of activity of insulin aspart allows NovoMix® 50 to be given immediately before a meal. When necessary, NovoMix® 50 can be given soon after a meal.

Contraindications

Hypersensitivity to insulin aspart or any of the excipients (see *List of excipients*).

Special warnings and precautions for use

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.

Since NovoMix® 50 should be administered in immediate relation to a meal, the rapid onset of action should therefore be considered in patients with concomitant diseases or medication 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 of 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 products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

Transferring: a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (human insulin, insulin analogue) and/or method of manufacture may result in the need for a change in dosage. Patients transferred to NovoMix® 50 from another type of insulin may require an increased number of daily injections or a change in dosage from that used with their usual insulin products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Hyperglycaemia (high blood sugar)

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 (low blood sugar)

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 (see *Undesirable effects* and *Overdose*).

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. Usually warning symptoms may disappear in patients with longstanding diabetes.

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 NovoMix® 50.

Combination of thiazolidinediones and insulin medicinal products

Cases of congestive heart failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of congestive heart failure. This should be kept in mind if treatment with the combination of thiazolidinediones and insulin medicinal products is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema.
Thiazolidinediones 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 hyper- or hypoglycaemia.

Interaction with other medicinal products and other forms of interaction

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 products, monoamine oxidase inhibitors (MAOIs), 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-blocking agents 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.

Pregnancy and lactation

NovoMix® 50 has not been investigated in pregnant women. However, data from two randomised controlled clinical trials (157 and 14 insulin aspart-exposed pregnancies respectively, in basal-bolus regimen) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to soluble human insulin (see *Pharmacodynamic properties*).

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 normally return rapidly to pre-pregnancy values.

There are no restrictions on treatment with NovoMix® 50 during lactation. Insulin treatment of the breast-feeding mother presents no risk to the baby. However, the NovoMix® 50 dosage may need to be adjusted.

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.

Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoMix® are mainly due to the pharmacologic effect of insulin. The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.
At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible.
Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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 conditions	Uncommon – Injection site reactions
	Uncommon – Oedema

* see section c

c. 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 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.

Lipodystrophy

Lipodystrophy is reported as uncommon. Lipodystrophy may occur at the injection site.

Overdose

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.

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting.
ATC code: A10AD05.

NovoMix® 50 is a biphasic suspension of soluble insulin aspart (rapid-acting insulin analogue) and insulin aspart crystallised with protamine (intermediate-acting insulin analogue). Insulin aspart is equipotent to human insulin on a molar basis.

Mechanism of action

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.

NovoMix® 50 is a biphasic insulin, which contains 50% soluble insulin aspart. This has a rapid onset of action, thus allowing it to be given closer to a meal (within zero to 10 minutes of a meal) when compared to soluble human insulin. The crystalline phase (50%) consists of protamine-crystallised insulin aspart, which has an activity profile that is similar to that of human NPH insulin.

When NovoMix® 50 is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is 14 to 24 hours.

Pregnancy: NovoMix® 50 has not been investigated in pregnant women. However, a clinical trial comparing safety and efficacy of insulin aspart vs. soluble human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; soluble human insulin: 165)) 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. soluble human insulin (insulin aspart: 14; soluble human insulin: 13) showed similar safety profiles between treatments.

Pharmacokinetic properties

In insulin aspart substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with human insulin. The insulin aspart in the soluble phase of NovoMix® 50 comprises 50% of the total insulin; this is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 50% is in crystalline form as protamine-crystallised insulin aspart; this has a prolonged absorption profile similar to human NPH insulin.

In healthy volunteers a mean maximum serum concentration of 445 ± 135 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.30 U/kg body weight. In type 2 patients with diabetes, the maximum concentration was reached about 95 minutes after dosing.

Special populations: The pharmacokinetics of NovoMix® 50 has not been investigated in paediatrics, elderly or patients with renal or hepatic impairment.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

In *in vitro* tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

List of excipients

Glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections.

Special precautions for storage

Storage when not in use: Store in a refrigerator (2°C – 8°C). Keep away from the cooling element. Do not freeze.
The expiry date is printed on the label and carton. After removing NovoMix® 50 FlexPen® from the refrigerator, it is recommended to allow NovoMix® 50 FlexPen® to reach room temperature before resuspending the insulin as instructed for the first time use.

Storage during use or when carried as a spare:

NovoMix® 50 FlexPen® that is being used or carried as a spare is not to be kept in the refrigerator. It can be kept at room temperature (below 30°C) for up to 4 weeks. Keep the pen cap on FlexPen® in order to protect from light.
NovoMix® 50 must be protected from excessive heat and light.

Nature and contents of container

3 ml suspension cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene in a carton. The cartridge contains a glass ball to facilitate resuspension.
Pack sizes of 1, 5 or 10 pre-filled pens. Not all pack sizes may be marketed.

Special precautions for disposal and other handling

Needles and NovoMix® 50 FlexPen® must not be shared. The cartridge must not be refilled.
NovoMix® 50 must not be used if the resuspended liquid does not appear uniformly white and cloudy. The necessity of resuspending the NovoMix® 50 FlexPen® suspension immediately before use is to be stressed to the patient.
NovoMix® 50 which has been frozen must not be used. The patient should be advised to discard the needle after each injection.

Produced by

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

INSTRUCTIONS FOR USE FOR THE PATIENT

Do not use NovoMix® 50

- **If you are allergic (hypersensitive)** to insulin aspart or any of the other ingredients in NovoMix® 50 (see *List of excipients*).
- **If you suspect hypoglycaemia** (low blood sugar) is starting (see *Hypoglycaemia*).
- **In insulin infusion pumps.**
- **If FlexPen® 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 and cloudy.**
- **If, after re-suspension clumps** of material are present or if solid white particles stick to the bottom or the wall of the cartridge.

Before using NovoMix® 50

- **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 NovoMix® 50 FlexPen® must not be shared.**

NovoMix® 50 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 reduces 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 handle NovoMix® 50 FlexPen®

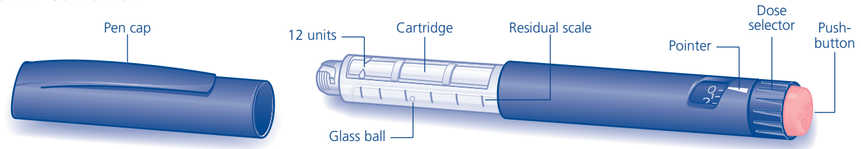
Read and follow the included NovoMix® 50 FlexPen® instructions for use carefully.

NovoMix® 50 suspension for injection in a pre-filled pen. FlexPen® INSTRUCTIONS FOR USE FOR THE PATIENT

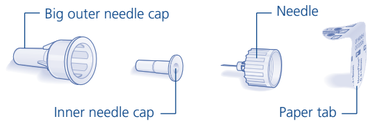
Please read the following instructions carefully before using your NovoMix® 50 FlexPen®.

Your FlexPen® is a unique dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. FlexPen® is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm. As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen® is lost or damaged.

NovoMix® 50 FlexPen®



Needle (example)



Maintenance

Your FlexPen® is designed to work accurately and safely. It must be handled with care. If it is dropped, damaged or crushed, there is a risk of insulin leakage.

You can clean the exterior of your FlexPen® by wiping it with a medicinal swab. Do not soak, wash or lubricate it as it may damage the pen.

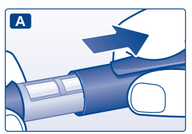
Do not refill your FlexPen®.

Preparing your NovoMix® 50 FlexPen®

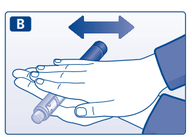
Check the label to make sure that your FlexPen® contains the correct type of insulin. Before your first injection with a new FlexPen®, you must resuspend the insulin:

A Let the insulin reach room temperature before you use it. This makes it easier to resuspend.

Pull off the pen cap.



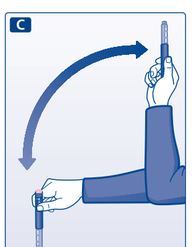
B Roll the pen between your palms 10 times – it is important that the pen is kept horizontal.



C Then move the pen up and down 10 times between the two positions as shown, so the glass ball moves from one end of the cartridge to the other.

Repeat rolling and moving the pen until the liquid does appear uniformly white and cloudy.

For every following injection move the pen up and down between the two positions at least 10 times until the liquid does appear uniformly white and cloudy. If the moving procedure alone is not enough to give a uniformly white and cloudy liquid, repeat the rolling and moving procedures (see **B** and **C**) until the liquid does appear uniformly white and cloudy.



After you have resuspended the insulin, complete all the following steps of injection without delay.

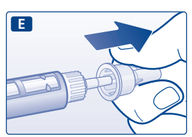
⚠ Always check there are at least 12 units of insulin left in the cartridge to allow resuspension. If there are less than 12 units left, use a new FlexPen®.

Attaching a needle

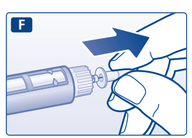
D Remove the paper tab from a new disposable needle.

Screw the needle straight and tightly onto your FlexPen®.

E Pull off the big outer needle cap and keep it for later.



F Pull off the inner needle cap and dispose of it.

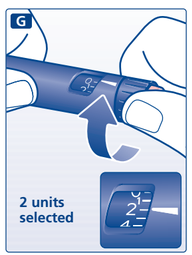


⚠ Always use a new needle for each injection to prevent contamination.
⚠ Be careful not to bend or damage the needle before use.
⚠ To reduce the risk of unexpected needle sticks, never put the inner needle cap back on when you have removed it from the needle.

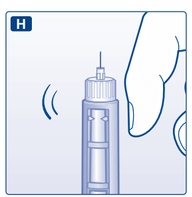
Checking the insulin flow

Prior to each injection, small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:

G Turn the dose selector to select 2 units.



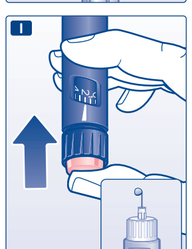
H Hold your FlexPen® with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.



I Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If a drop of insulin still does not appear, the pen is defective, and you must use a new one.



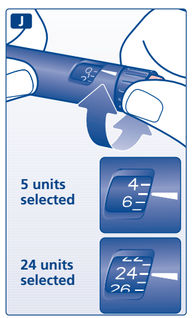
Selecting your dose

Check that the dose selector is set at 0.

J Turn the dose selector to select the number of units you need to inject.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.



⚠ Do not use the residual scale to measure your dose of insulin.

Making the injection

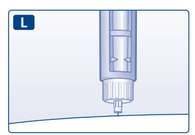
Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.

K Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.

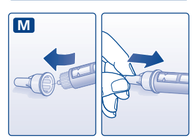
L Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose.

Withdraw the needle from the skin, then release the pressure on the push-button.



M Lead the needle into the big outer needle cap without touching it. When the needle is covered, carefully push the big outer needle cap completely on and then unscrew the needle.

Dispose of it carefully and put the pen cap back on.



⚠ Always remove the needle after each injection and store your FlexPen® without the needle attached. Otherwise the liquid may leak out which can cause inaccurate dosing.
⚠ Caregivers should be most careful when handling used needles to avoid needle sticks.
⚠ Dispose of the used FlexPen® carefully without the needle attached.
⚠ Needles and NovoMix® 50 FlexPen® must not be shared.