

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 30 Penfill 100 units/ml suspension for injection in cartridge
NovoMix 30 FlexPen 100 units/ml suspension for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoMix 30 Penfill

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 30/70 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units.

NovoMix 30 FlexPen

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 30/70 (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 units.

*Insulin aspart is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin aspart, is expressed in units, whereas the potency of human insulin is expressed in international units.

NovoMix 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, NovoMix 30 can be given as monotherapy. NovoMix 30 can also be given in combination with oral antidiabetic medicinal products and/or GLP-1 receptor agonists. For patients with type 2 diabetes, the recommended starting dose of NovoMix 30 is 6 units at breakfast and 6 units at dinner (evening meal). NovoMix 30 can also be initiated once daily with 12 units at dinner (evening meal). When using NovoMix 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 NovoMix 30 results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (thrice daily dosing).

The following titration guideline is recommended for dose adjustments:

Pre-meal blood glucose level		NovoMix 30 dose adjustment
<4.4 mmol/l	<80 mg/dl	-2 units
4.4–6.1 mmol/l	80–110 mg/dl	0
6.2–7.8 mmol/l	111–140 mg/dl	+2 units
7.9–10 mmol/l	141–180 mg/dl	+4 units
>10 mmol/l	>180 mg/dl	+6 units

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 HbA_{1c} is reached. Pre-meal blood glucose levels should be used to evaluate the adequacy of the preceding dose.

In patients with type 2 diabetes, a dose reduction of 20% is recommended for patients with an HbA_{1c} less than 8% when a GLP-1 receptor agonist is added to NovoMix 30, to minimise the risk of hypoglycaemia. For patients with an HbA_{1c} higher than 8% a dose reduction should be considered. Subsequently, dosage should be adjusted individually.

In patients with type 1 diabetes, the individual insulin requirement is usually between 0.5 and 1.0 unit/kg/day. NovoMix 30 may fully or partially meet this requirement.

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

Special populations

Elderly (≥65 years old)

NovoMix 30 can be used in elderly patients; however there is limited experience with the use of NovoMix 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

NovoMix 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. There is limited clinical experience with NovoMix 30 in children aged 6–9 years (see section 5.1).

No data are available for NovoMix 30 in children below 6 years of age.

Transfer from other insulin medicinal products

When transferring a patient from biphasic human insulin to NovoMix 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 (see section 4.4).

Method of administration

NovoMix 30 is a biphasic suspension of the insulin analogue, insulin aspart. The suspension contains rapid-acting and intermediate-acting insulin aspart in the ratio 30/70.

NovoMix 30 is for subcutaneous administration **only**.

NovoMix 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 (see sections 4.4 and 4.8). The influence of different injection sites on the absorption of NovoMix 30 has not been investigated. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoMix 30 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix 30 can be given soon after a meal.

For detailed user instructions, please refer to the package leaflet.

NovoMix 30 Penfill

Administration with an insulin delivery system

NovoMix 30 Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. NovoMix 30 Penfill is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

NovoMix 30 FlexPen

Administration with FlexPen

NovoMix 30 FlexPen is a pre-filled pen (colour-coded) designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1–60 units in increments of 1 unit. NovoMix 30 FlexPen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NovoMix 30 must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. NovoMix 30 is not to be used in insulin infusion pumps.

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, NovoMix must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.2, 4.8 and 4.9).

Compared with biphasic human insulin, NovoMix 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 NovoMix 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 NovoMix 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 NovoMix 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 NovoMix 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 NovoMix 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.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix and other insulin products.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 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 medicinal products, GLP-1 receptor agonists, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with NovoMix 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 NovoMix 30 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoMix 30 dose may need to be adjusted.

Fertility

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding fertility.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions observed in patients using NovoMix are mainly due to the pharmacological effect of insulin aspart.

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 Description of selected adverse reactions 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 a 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.

Tabulated list of adverse reactions

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).

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*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Oedema

	Uncommon – Injection site reactions
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* 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 (see section 4.4).

Paediatric population

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 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).

Mechanism of action and pharmacodynamic effects

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 30 is a biphasic insulin, which contains 30% 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 the meal) when compared to soluble human insulin. The crystalline phase (70%) consists of protamine-crystallised insulin aspart, which has an activity profile similar to that of human NPH insulin.

When NovoMix 30 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 up to 24 hours (Figure 1).

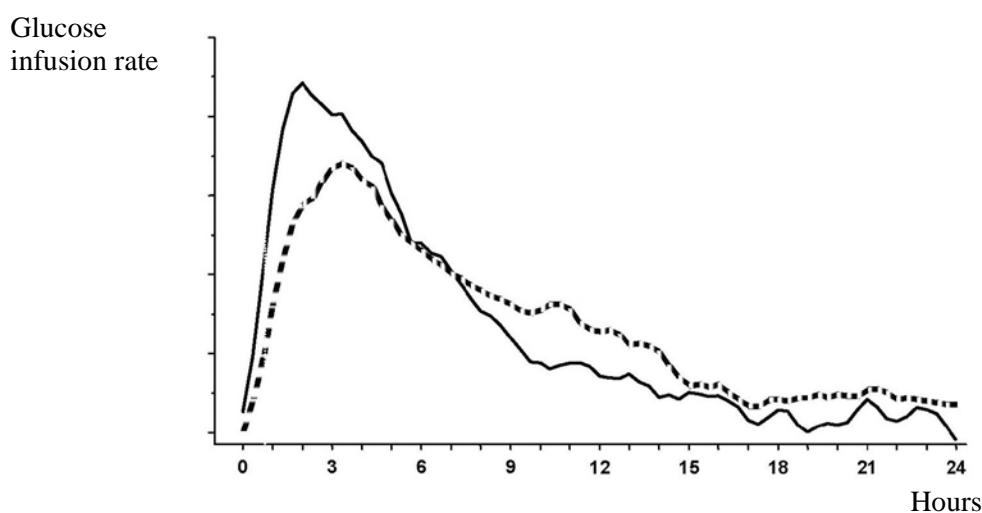


Figure 1: Activity profile of NovoMix 30 (—) and biphasic human insulin 30 (---) in healthy subjects.

Clinical efficacy and safety

In a 3 month trial in patients with type 1 and type 2 diabetes, NovoMix 30 showed equal control of glycosylated haemoglobin compared to treatment with biphasic human insulin 30. Insulin aspart is equipotent to human insulin on a molar basis. Compared to biphasic human insulin 30, administration

of NovoMix 30 before breakfast and dinner resulted in lower postprandial blood glucose after both meals (breakfast and dinner).

A meta-analysis including nine trials in patients with type 1 and type 2 diabetes showed that fasting blood glucose was higher in patients treated with NovoMix 30, than in patients treated with biphasic human insulin 30.

In one study, 341 patients with type 2 diabetes were randomised to treatment with NovoMix 30 either alone or in combination with metformin, or to metformin together with sulfonylurea. The primary efficacy variable - HbA_{1c} after 16 weeks of treatment - did not differ between patients with NovoMix 30 combined with metformin and patients with metformin plus sulfonylurea. In this trial, 57% of the patients had baseline HbA_{1c} above 9%; in these patients, treatment with NovoMix 30 in combination with metformin resulted in significantly lower HbA_{1c} than metformin in combination with sulfonylurea.

In one study, patients with type 2 diabetes, insufficiently controlled on oral hypoglycaemic agents alone, were randomised to treatment with twice daily NovoMix 30 (117 patients) or once daily insulin glargine (116 patients). After 28 weeks of treatment following the dosing guideline outlined in section 4.2, the mean reduction in HbA_{1c} was 2.8% with NovoMix 30 (mean at baseline = 9.7%). With NovoMix 30, 66% and 42% of the patients reached HbA_{1c} levels below 7% and 6.5%, respectively, and mean FPG was reduced by about 7 mmol/l (from 14.0 mmol/l at baseline to 7.1 mmol/l).

In patients with type 2 diabetes, a meta-analysis showed a reduced risk of overall nocturnal hypoglycaemic episodes and major hypoglycaemia with NovoMix 30 compared to biphasic human insulin 30. The risk of overall daytime hypoglycaemic episodes was increased in patients treated with NovoMix 30.

Paediatric population

A 16-week clinical trial comparing postprandial glycaemic control of meal-related NovoMix 30 with meal-related human insulin/biphasic human insulin 30 and bedtime NPH insulin was performed in 167 patients aged 10 to 18 years. Mean HbA_{1c} remained similar to baseline throughout the trial in both treatment groups, and there was no difference in hypoglycaemia rate with NovoMix 30 or biphasic human insulin 30.

In a smaller (54 patients) and younger (age range 6 to 12 years) population, treated in a double-blind, cross-over trial (12 weeks on each treatment), the rate of hypoglycaemic episodes and the postprandial glucose increase were significantly lower with NovoMix 30 compared to biphasic human insulin 30. Final HbA_{1c} was significantly lower in the biphasic human insulin 30 treated group compared with NovoMix 30.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

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 NovoMix 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 NovoMix 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 NovoMix 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 NovoMix 30 have not been investigated in elderly patients or in patients with renal or hepatic impairment.

Paediatric population

The pharmacokinetics of NovoMix 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.

5.3 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 and development.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Protamine sulfate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening: 2 years.

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

6.4 Special precautions for storage

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

NovoMix 30 Penfill

During use or 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.

NovoMix 30 FlexPen

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze. Keep the cap on FlexPen in order to protect it from light.

6.5 Nature and contents of container

NovoMix 30 Penfill

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene). The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 5 and 10 cartridges. Not all pack sizes may be marketed.

NovoMix 30 FlexPen

3 ml suspension in 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. The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 1 (with or without needles), 5 (without needles) and 10 (without needles) pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After removing NovoMix 30 Penfill or NovoMix 30 FlexPen from the refrigerator, it is recommended to allow NovoMix 30 Penfill or NovoMix 30 FlexPen to reach room temperature before resuspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the resuspended liquid is not uniformly white, cloudy and aqueous.

The necessity of resuspending the NovoMix 30 suspension immediately before use is to be stressed to the patient.

NovoMix 30 which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Needles, cartridges and pre-filled pens must not be shared.

The cartridge must not be refilled.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

NovoMix 30 Penfill

EU/1/00/142/004
EU/1/00/142/005

NovoMix 30 FlexPen

EU/1/00/142/009
EU/1/00/142/010
EU/1/00/142/023
EU/1/00/142/024
EU/1/00/142/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 August 2000

Date of last renewal: 2 July 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 50 Penfill 100 units/ml suspension for injection in cartridge
NovoMix 50 FlexPen 100 units/ml suspension for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoMix 50 Penfill

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 50/50 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units.

NovoMix 50 FlexPen

1 ml of the suspension contains 100 units 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 units.

*Insulin aspart is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NovoMix 50 is indicated for treatment of diabetes mellitus in adults.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin aspart, is expressed in units, whereas the potency of human insulin is expressed in international units.

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. NovoMix 50 may fully or partially meet this requirement.

In patients with type 2 diabetes, NovoMix 50 can be given as monotherapy or in combination with metformin when the blood glucose is inadequately controlled with metformin alone.

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

Special populations

In elderly patients (≥ 65 years old) and in patients with hepatic or renal impairment, glucose

monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

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

Paediatric population

The safety and efficacy of NovoMix 50 in children below 18 years of age have not been established. No data are available.

Transfer from other insulin medicinal products

Transfer to NovoMix 50 from other insulin preparations may require adjustment of dose and timing of administration. Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

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 is for subcutaneous administration **only**.

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 and cutaneous amyloidosis (see sections 4.4 and 4.8). The influence of different injection sites on the absorption of NovoMix 50 has not been investigated. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoMix 50 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix 50 can be given soon after a meal.

For detailed user instructions, please refer to the package leaflet.

NovoMix 50 Penfill

Administration with an insulin delivery system

NovoMix 50 Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. NovoMix 50 Penfill is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

NovoMix 50 FlexPen

Administration with FlexPen

NovoMix 50 FlexPen is a pre-filled pen (colour-coded) designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1–60 units in increments of 1 unit. NovoMix 50 FlexPen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

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, NovoMix must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.2, 4.8 and 4.9).

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.

Since NovoMix 50 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 NovoMix 50 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 NovoMix 50.

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 NovoMix 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 NovoMix 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.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix and other insulin products.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with NovoMix 50 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 NovoMix 50 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoMix 50 dose may need to be adjusted.

Fertility

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding fertility.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions observed in patients using NovoMix are mainly due to the pharmacological effect of insulin aspart.

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 Description of selected adverse reactions 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 a 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.

Tabulated list of adverse reactions

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).

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*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Oedema
	Uncommon – Injection site reactions

* 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 (see section 4.4).

Paediatric population

The safety and efficacy of NovoMix 50 in children below 18 years of age have not been established. No data are available.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 50% soluble insulin aspart (rapid-acting human insulin analogue) and 50% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue).

Mechanism of action and pharmacodynamic effects

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 the meal) when compared to soluble human insulin. The crystalline phase (50%) consists of protamine-crystallised insulin aspart, which has an activity profile 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 (Figure 1).

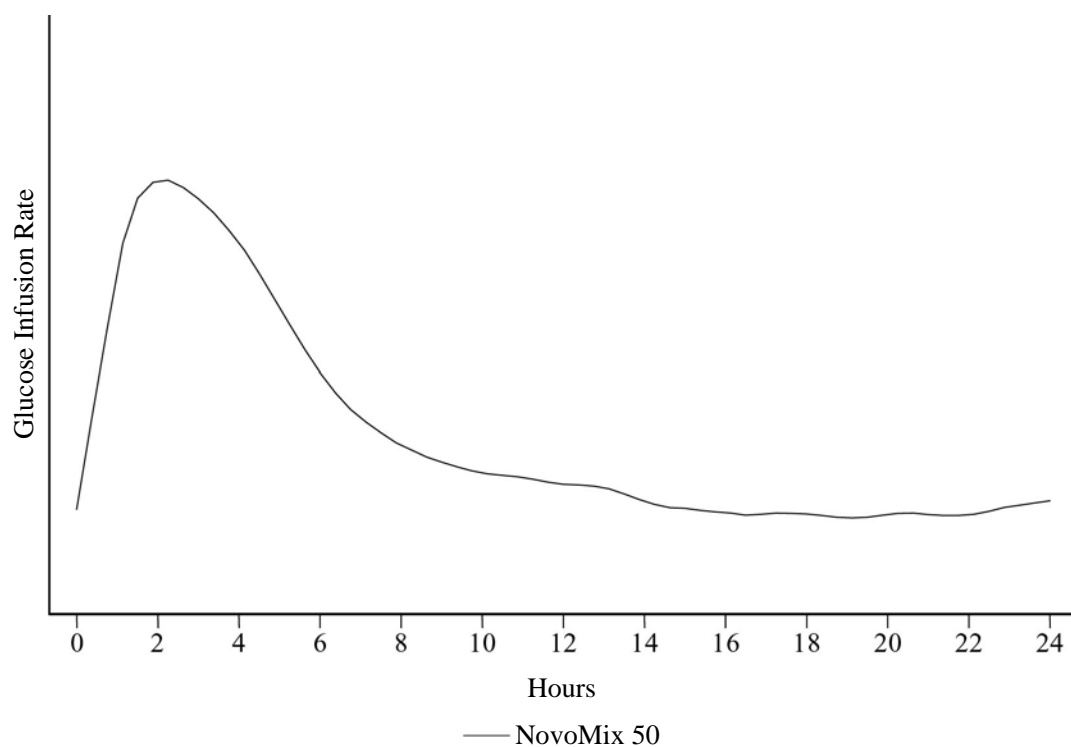


Figure 1: Activity Profile for NovoMix 50 in Healthy Caucasian Subjects.

Insulin aspart is equipotent to human insulin on a molar basis.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

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 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 unit/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 have not been investigated in paediatrics, elderly patients or in patients with renal or hepatic impairment.

5.3 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 and development.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Protamine sulfate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening: 2 years.

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

6.4 Special precautions for storage

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

NovoMix 50 Penfill

During use or 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.

NovoMix 50 FlexPen

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze. Keep the cap on FlexPen in order to protect it from light.

6.5 Nature and contents of container

NovoMix 50 Penfill

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene). The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 1, 5 and 10 cartridges. Not all pack sizes may be marketed.

NovoMix 50 FlexPen

3 ml suspension in 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. The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 1, 5 and 10 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After removing NovoMix 50 Penfill or NovoMix 50 FlexPen from the refrigerator, it is recommended to allow NovoMix 50 Penfill or NovoMix 50 FlexPen to reach room temperature before resuspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the resuspended liquid is not uniformly white, cloudy and aqueous.

The necessity of resuspending the NovoMix 50 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Needles, cartridges and pre-filled pens must not be shared.

The cartridge must not be refilled.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

NovoMix 50 Penfill
EU/1/00/142/011
EU/1/00/142/012
EU/1/00/142/013

NovoMix 50 FlexPen
EU/1/00/142/014
EU/1/00/142/015
EU/1/00/142/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 August 2000

Date of last renewal: 2 July 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 70 Penfill 100 units/ml suspension for injection in cartridge
NovoMix 70 FlexPen 100 units/ml suspension for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoMix 70 Penfill

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 70/30 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units.

NovoMix 70 FlexPen

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 70/30 (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 units.

*Insulin aspart is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NovoMix 70 is indicated for treatment of diabetes mellitus in adults.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin aspart, is expressed in units, whereas the potency of human insulin is expressed in international units.

NovoMix 70 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. NovoMix 70 may fully or partially meet this requirement.

In patients with type 2 diabetes, NovoMix 70 can be given as monotherapy or in combination with metformin when the blood glucose is inadequately controlled with metformin alone.

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

Special populations

In elderly patients (≥ 65 years old) and in patients with hepatic or renal impairment, glucose

monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

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

Paediatric population

The safety and efficacy of NovoMix 70 in children below 18 years of age have not been established. No data are available.

Transfer from other insulin medicinal products

Transfer to NovoMix 70 from other insulin preparations may require adjustment of dose and timing of administration. Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoMix 70 is a biphasic suspension of the insulin analogue, insulin aspart. The suspension contains rapid-acting and intermediate-acting insulin aspart in the ratio 70/30.

NovoMix 70 is for subcutaneous administration **only**.

NovoMix 70 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 (see sections 4.4 and 4.8). The influence of different injection sites on the absorption of NovoMix 70 has not been investigated. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoMix 70 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix 70 can be given soon after a meal.

For detailed user instructions, please refer to the package leaflet.

NovoMix 70 Penfill

Administration with an insulin delivery system

NovoMix 70 Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. NovoMix 70 Penfill is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

NovoMix 70 FlexPen

Administration with FlexPen

NovoMix 70 FlexPen is a pre-filled pen (colour-coded) designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1–60 units in increments of 1 unit. NovoMix 70 FlexPen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NovoMix 70 must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. NovoMix 70 is not to be used in insulin infusion pumps.

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, NovoMix must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.2, 4.8 and 4.9).

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.

Since NovoMix 70 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 NovoMix 70 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 NovoMix 70.

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 NovoMix 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 NovoMix 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.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix and other insulin products.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with NovoMix 70 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 NovoMix 70 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoMix 70 dose may need to be adjusted.

Fertility

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding fertility.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions observed in patients using NovoMix are mainly due to the pharmacological effect of insulin aspart.

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 Description of selected adverse reactions 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 a 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.

Tabulated list of adverse reactions

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).

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*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Oedema
	Uncommon – Injection site reactions

* 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 (see section 4.4).

Paediatric population

The safety and efficacy of NovoMix 70 in children below 18 years of age have not been established. No data are available.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 70 is a biphasic suspension of 70% soluble insulin aspart (rapid-acting human insulin analogue) and 30% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue).

Mechanism of action and pharmacodynamic effects

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 70 is a biphasic insulin, which contains 70% 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 the meal) when compared to soluble human insulin. The crystalline phase (30%) consists of protamine-crystallised insulin aspart, which has an activity profile similar to that of human NPH insulin.

When NovoMix 70 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 (Figure 1).

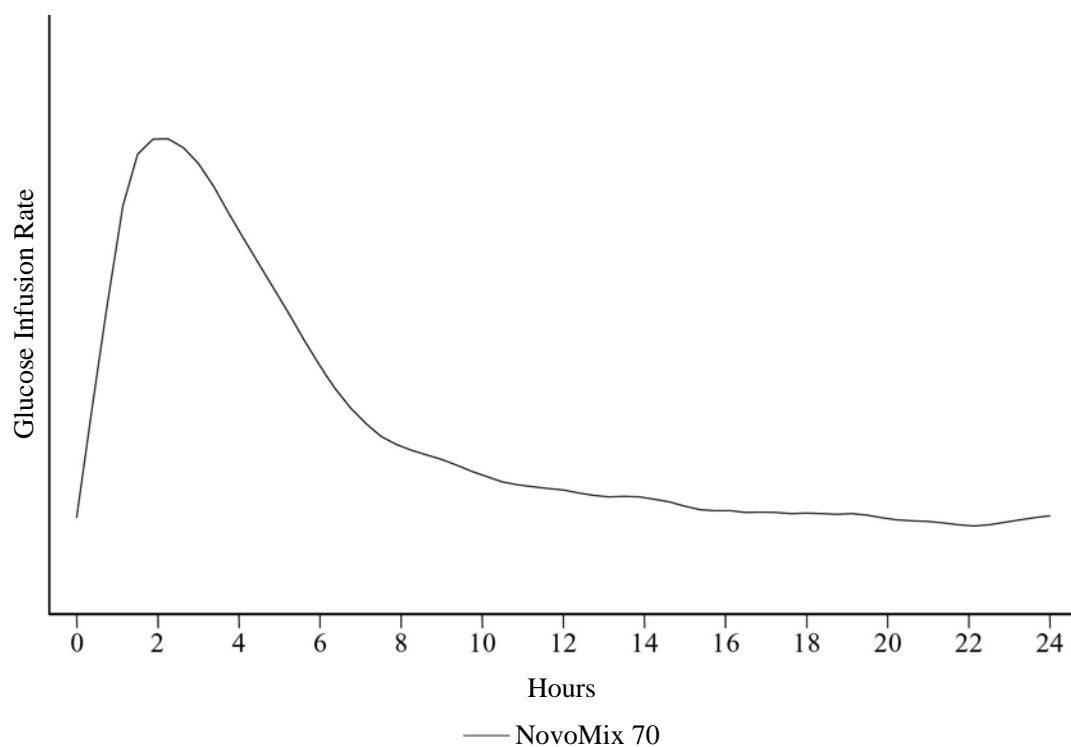


Figure 1: Activity Profile for NovoMix 70 in Healthy Caucasian Subjects.

Insulin aspart is equipotent to human insulin on a molar basis.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

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 NovoMix 70 comprises 70% of the total insulin; this is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 30% 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 645 ± 185 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.30 unit/kg body weight. In type 2 patients with diabetes, the maximum concentration was reached about 75 minutes after dosing. In type 1 patients with diabetes a mean maximum serum concentration of 721 ± 184 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.30 unit/kg body weight.

Special populations

The pharmacokinetics of NovoMix 70 have not been investigated in paediatrics, elderly patients or in patients with renal or hepatic impairment.

5.3 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 and development.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Protamine sulfate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening: 2 years.

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

6.4 Special precautions for storage

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

NovoMix 70 Penfill

During use or 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.

NovoMix 70 FlexPen

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze. Keep the cap on FlexPen in order to protect it from light.

6.5 Nature and contents of container

NovoMix 70 Penfill

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene). The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 1, 5 and 10 cartridges. Not all pack sizes may be marketed.

NovoMix 70 FlexPen

3 ml suspension in 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. The cartridge contains a glass ball to facilitate resuspension.

Pack sizes of 1, 5 and 10 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After removing NovoMix 70 Penfill or NovoMix 70 FlexPen from the refrigerator, it is recommended to allow NovoMix 70 Penfill or NovoMix 70 FlexPen to reach room temperature before resuspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the resuspended liquid is not uniformly white, cloudy and aqueous.

The necessity of resuspending the NovoMix 70 suspension immediately before use is to be stressed to the patient.

NovoMix 70 which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Needles, cartridges and pre-filled pens must not be shared.

The cartridge must not be refilled.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

NovoMix 70 Penfill

EU/1/00/142/017

EU/1/00/142/018

EU/1/00/142/019

NovoMix 70 FlexPen

EU/1/00/142/020

EU/1/00/142/021

EU/1/00/142/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 August 2000

Date of last renewal: 2 July 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

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

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Name and address of the manufacturers responsible for batch release

NovoMix 30 Penfill and NovoMix 30 FlexPen:

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

Novo Nordisk Production SAS
45, Avenue d'Orléans
F-28000 Chartres
France

NovoMix 50 Penfill and NovoMix 50 FlexPen:

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

NovoMix 70 Penfill and NovoMix 70 FlexPen:

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the results of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 30 Penfill 100 units/ml
Suspension for injection in cartridge
30% soluble insulin aspart and 70% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

5 x 3 ml cartridges
10 x 3 ml cartridges

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous.
For use by one person only

8. EXPIRY DATE

EXP
During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)
During use: Do not refrigerate. Store below 30°C
Do not freeze
Keep the cartridge in the outer carton in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/004 5 cartridges of 3 ml
EU/1/00/142/005 10 cartridges of 3 ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NovoMix 30 Penfill

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 30 Penfill 100 units/ml
Suspension for injection
30% soluble insulin aspart and 70% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
Penfill

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 30 FlexPen 100 units/ml
Suspension for injection in pre-filled pen
30% soluble insulin aspart and 70% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70 (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
10 x 3 ml pre-filled pens
1 x 3 ml pre-filled pen + 7 NovoFine needles
1 x 3 ml pre-filled pen + 7 NovoTwist needles

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Needles are not included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous
For use by one person only
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP

During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)

During use: Do not refrigerate. Store below 30°C

Do not freeze

Keep the cap on the pen in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/023 1 pen of 3 ml

EU/1/00/142/009 5 pens of 3 ml

EU/1/00/142/010 10 pens of 3 ml

EU/1/00/142/024 1 pen of 3 ml and 7 NovoFine needles

EU/1/00/142/025 1 pen of 3 ml and 7 NovoTwist needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NovoMix 30 FlexPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 30 FlexPen 100 units/ml
Suspension for injection
30% soluble insulin aspart and 70% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
FlexPen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 50 Penfill 100 units/ml
Suspension for injection in cartridge
50% soluble insulin aspart and 50% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 50/50 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 x 3 ml cartridge
5 x 3 ml cartridges
10 x 3 ml cartridges

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous.
For use by one person only

8. EXPIRY DATE

EXP
During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)
During use: Do not refrigerate. Store below 30°C
Do not freeze
Keep the cartridge in the outer carton in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/011 1 cartridge of 3 ml
EU/1/00/142/012 5 cartridges of 3 ml
EU/1/00/142/013 10 cartridges of 3 ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NovoMix 50 Penfill

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 50 Penfill 100 units/ml
Suspension for injection
50% soluble insulin aspart and 50% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
Penfill

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON (PRE-FILLED PEN. FlexPen)****1. NAME OF THE MEDICINAL PRODUCT**

NovoMix 50 FlexPen 100 units/ml
Suspension for injection in pre-filled pen
50% soluble insulin aspart and 50% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units 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 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
10 x 3 ml pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Needles are not included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous
For use by one person only
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP

During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)

During use: Do not refrigerate. Store below 30°C

Do not freeze

Keep the cap on the pen in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/014 1 pen of 3 ml

EU/1/00/142/015 5 pens of 3 ml

EU/1/00/142/016 10 pens of 3 ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoMix 50 FlexPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 50 FlexPen 100 units/ml
Suspension for injection
50% soluble insulin aspart and 50% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
FlexPen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 70 Penfill 100 units/ml
Suspension for injection in cartridge
70% soluble insulin aspart and 30% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 70/30 (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 x 3 ml cartridge
5 x 3 ml cartridges
10 x 3 ml cartridges

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous
For use by one person only

8. EXPIRY DATE

EXP
During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)
During use: Do not refrigerate. Store below 30°C
Do not freeze
Keep the cartridge in the outer carton in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/017 1 cartridge of 3 ml
EU/1/00/142/018 5 cartridges of 3 ml
EU/1/00/142/019 10 cartridges of 3 ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NovoMix 70 Penfill

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 70 Penfill 100 units/ml
Suspension for injection
70% soluble insulin aspart and 30% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
Penfill

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT

NovoMix 70 FlexPen 100 units/ml
Suspension for injection in pre-filled pen
70% soluble insulin aspart and 30% insulin aspart crystallised with protamine

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml suspension contains 100 units soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 70/30 (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 units

3. 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

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
10 x 3 ml pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Needles are not included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Resuspend according to instructions
Only use resuspension if uniformly white, cloudy and aqueous
For use by one person only
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP

During use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator (2°C to 8°C)

During use: Do not refrigerate. Store below 30°C

Do not freeze

Keep the cap on the pen in order to protect it from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/00/142/020 1 pen of 3 ml

EU/1/00/142/021 5 pens of 3 ml

EU/1/00/142/022 10 pens of 3 ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoMix 70 FlexPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoMix 70 FlexPen 100 units/ml
Suspension for injection
70% soluble insulin aspart and 30% insulin aspart crystallised with protamine
SC use

2. METHOD OF ADMINISTRATION

Resuspend according to instructions
FlexPen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NovoMix 30 Penfill 100 units/ml suspension for injection in a cartridge 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoMix 30 is and what it is used for
2. What you need to know before you use NovoMix 30
3. How to use NovoMix 30
4. Possible side effects
5. How to store NovoMix 30
6. Contents of the pack and other information

1. What NovoMix 30 is and what it is used for

NovoMix 30 is a modern insulin (insulin analogue) with both a rapid-acting and an intermediate-acting effect, in the ratio 30/70. Modern insulin products are improved versions of human insulin.

NovoMix 30 is used to reduce the high blood sugar level in adults, adolescents and children aged 10 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar.

NovoMix 30 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 24 hours.

In treatment of type 2 diabetes mellitus, NovoMix 30 may be used in combination with tablets for diabetes and/or with injectable antidiabetic products.

2. What you need to know before you use NovoMix 30

Do not use NovoMix 30

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If the cartridge or the device containing the cartridge is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 30.
- ▶ 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.

If any of these apply, do not use NovoMix 30. Talk to your doctor, nurse or pharmacist for advice.

Before using NovoMix 30

- ▶ Check the label to make sure it is the right type of insulin.
- ▶ Always check the cartridge, including the rubber plunger at the bottom of the cartridge. Do not use it if any damage is seen or if the rubber plunger has been drawn above the white label band at the bottom of the cartridge. This could be the result of an insulin leakage. If you suspect that the cartridge is damaged, take it back to your supplier. See your pen manual for further instructions.
- ▶ Always use a new needle for each injection to prevent contamination.
- ▶ Needles and NovoMix 30 Penfill must not be shared.
- ▶ NovoMix 30 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 30). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Children and adolescents

- NovoMix 30 can be used in adolescents and children aged 10 years and above.
- There is limited experience with NovoMix 30 in children aged 6–9 years.
- No data are available for NovoMix 30 in children below 6 years of age.

Other medicines and NovoMix 30

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 30

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 30 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 30

NovoMix 30 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 30 is essentially ‘sodium-free’.

3. How to use NovoMix 30

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

NovoMix 30 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, NovoMix 30 can be given soon after a meal. See How and where to inject, below for information.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

When NovoMix 30 is used in combination with tablets for diabetes and/or with injectable antidiabetic products your dose may have to be adjusted by your doctor.

Use in children and adolescents

NovoMix 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. Limited clinical data exists for children aged 6–9 years. No data are available for NovoMix 30 in children below 6 years of age.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 30 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 30 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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.

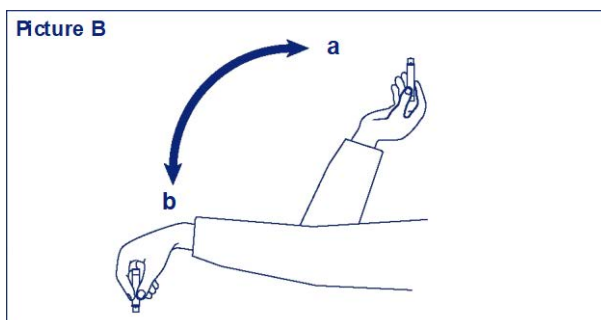
- ▶ Do not refill the cartridge.
- ▶ NovoMix 30 Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.
- ▶ If you are treated with NovoMix 30 Penfill and another insulin Penfill cartridge, you should use two insulin delivery systems, one for each type of insulin.
- ▶ Always carry a spare Penfill cartridge in case the one in use is lost or damaged.

Resuspension of NovoMix 30

Always check if there is enough insulin left (at least 12 units) in the cartridge to allow even resuspension. If there is not enough insulin left, use a new one. See your pen manual for further instructions.

- ▶ **Every time you use a new NovoMix 30 Penfill** (before you put the cartridge into the insulin delivery system)
 - 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) (see picture **A**).
- Move the cartridge up and down between positions a and b (see picture **B**) 10 times so that the glass ball moves from one end of the cartridge to the other.
- Repeat the rolling and moving procedures (see pictures **A** and **B**) until the liquid does appear uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white, cloudy and aqueous.
- Complete the other stages of injection without delay.
- ▶ **For every following injection**
- Move the delivery system with the cartridge inside up and down between a and b (see picture **B**) at least 10 times until the liquid appears uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white, cloudy and aqueous.
- Complete the other stages of injection without delay.



How to inject NovoMix 30

- ▶ Inject the insulin under your skin. Use the injection technique advised by your doctor or nurse and as described in your pen manual.
- ▶ Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- ▶ After each injection, be sure to remove and discard the needle and store NovoMix 30 without the needle attached. Otherwise the liquid may leak out, which can cause inaccurate dosing.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 30 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 30 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the cartridge label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the cartridge in the outer carton when you are not using it, in order to protect it from light. NovoMix 30 must be protected from excessive heat and light.

Before opening: NovoMix 30 Penfill that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 30 Penfill, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new NovoMix 30 Penfill. See Resuspension of NovoMix 30 in section 3.

During use or when carried as a spare: NovoMix 30 Penfill that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 30 contains

- The active substance is insulin aspart. NovoMix 30 is a mixture consisting of 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each cartridge contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 30 looks like and contents of the pack

NovoMix 30 is presented as a suspension for injection. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 5 and 10 cartridges of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Novo Nordisk A/S
Novo Allé

DK-2880 Bagsværd, Denmark

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are S6, P5, K7, R7, VG, FG or ZF, the manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.
- If the second and third characters are H7 or T6, the manufacturer is Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France.

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Package leaflet: Information for the user

NovoMix 30 FlexPen 100 units/ml suspension for injection in a pre-filled pen 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoMix 30 is and what it is used for
2. What you need to know before you use NovoMix 30
3. How to use NovoMix 30
4. Possible side effects
5. How to store NovoMix 30
6. Contents of the pack and other information

1. What NovoMix 30 is and what it is used for

NovoMix 30 is a modern insulin (insulin analogue) with both a rapid-acting and an intermediate-acting effect, in the ratio 30/70. Modern insulin products are improved versions of human insulin.

NovoMix 30 is used to reduce the high blood sugar level in adults, adolescents and children aged 10 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar.

NovoMix 30 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 24 hours.

In treatment of type 2 diabetes mellitus, NovoMix 30 may be used in combination with tablets for diabetes and/or with injectable antidiabetic products.

2. What you need to know before you use NovoMix 30

Do not use NovoMix 30

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If FlexPen is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 30.
- ▶ 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.

If any of these apply, do not use NovoMix 30. Talk to your doctor, nurse or pharmacist for advice.

Before using NovoMix 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 NovoMix 30 FlexPen must not be shared.
- ▶ NovoMix 30 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 30). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Children and adolescents

- NovoMix 30 can be used in adolescents and children aged 10 years and above.
- There is limited experience with NovoMix 30 in children aged 6–9 years.
- No data are available for NovoMix 30 in children below 6 years of age.

Other medicines and NovoMix 30

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
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- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
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Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 30

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 30 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 30

NovoMix 30 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 30 is essentially 'sodium-free'.

3. How to use NovoMix 30

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your

doctor, nurse or pharmacist if you are not sure.

NovoMix 30 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, NovoMix 30 can be given soon after a meal. See How and where to inject, below for information.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

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Use in children and adolescents

NovoMix 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. Limited clinical data exists for children aged 6–9 years. No data are available for NovoMix 30 in children below 6 years of age.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 30 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 30 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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 30 FlexPen

NovoMix 30 FlexPen is a pre-filled, colour-coded, disposable pen containing a mixture of rapid-acting and intermediate-acting insulin aspart in the ratio 30/70.

Read carefully the instructions for use included in this package leaflet. You must use the pen as described in the Instructions for use.

Always ensure you use the correct pen before you inject your insulin.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 30 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 30 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the FlexPen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the pen cap on your FlexPen when you are not using it, in order to protect it from light. NovoMix 30 must be protected from excessive heat and light.

Before opening: NovoMix 30 FlexPen that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 30 FlexPen, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new pen. See Instructions for use.

During use or when carried as a spare: NovoMix 30 FlexPen that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 30 contains

- The active substance is insulin aspart. NovoMix 30 is a mixture consisting of 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each pre-filled pen contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 30 looks like and contents of the pack

NovoMix 30 is presented as a suspension for injection in a pre-filled pen. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 1 (with or without needles), 5 (without needles) and 10 (without needles) pre-filled pens of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Novo Nordisk A/S

Novo Allé
DK-2880 Bagsværd, Denmark

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are S6, P5, K7, R7, VG, FG or ZF, the manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.
- If the second and third characters are H7 or T6, the manufacturer is Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France.

Now turn over for information on how to use your FlexPen.

This leaflet was last revised in

Other sources of information

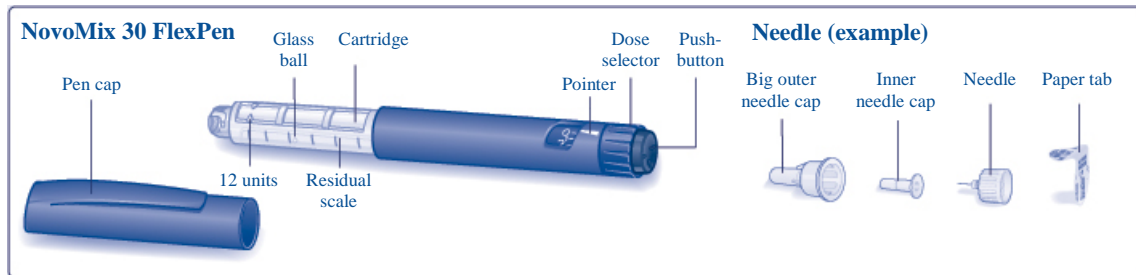
Detailed information on this medicine is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Instruction on how to use NovoMix 30 suspension for injection in FlexPen.

Read the following instructions carefully before using your FlexPen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your FlexPen is a pre-filled 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.
- ▶ Always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



Caring for your pen

- ▶ Your FlexPen must be handled with care. If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.
- ▶ 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.**

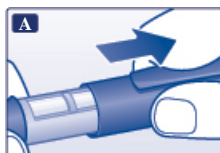
Resuspending your insulin

A

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Every time you use a new pen

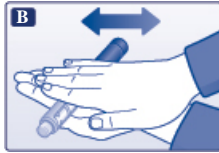
Let the insulin reach room temperature before you use it. This makes it easier to resuspend.
Pull off the pen cap.



B

Before your first injection with a new FlexPen, you must resuspend the insulin:

Roll the pen between your palms 10 times – it is important that the pen is kept **horizontal** (level with the ground).



C

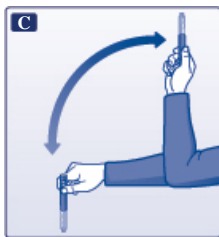
Then move the pen up and down 10 times between the two positions as shown, so the **glass ball moves** from one end of the cartridge to the other.

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

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, cloudy and aqueous.

- ▶ Always make sure that you have resuspended the insulin prior to each injection. This reduces the risk of too high or too low blood sugar level. 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. 12 units are marked on the residual scale. See the big picture on top of this instruction.
- △ Do not use the pen if the **resuspended** insulin does not look **uniformly white, cloudy and aqueous**.

Attaching a needle

D

Take a new needle and tear off the paper tab.

Screw the needle straight and tightly onto your FlexPen.



E

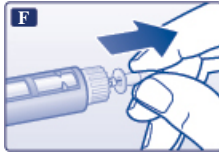
Pull off the big outer needle cap and keep it for later.



F

Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



- ⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- ⚠ Be careful not to bend or damage the needle before use.

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.

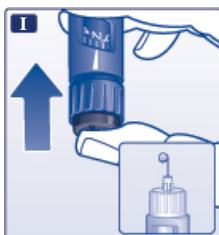


I

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.



- ⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.

- ⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

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.



- ⚠ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
- ⚠ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

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.

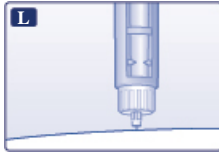
Turning the dose selector will not inject insulin.



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.

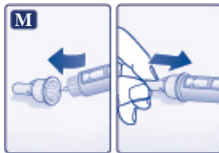
- ▶ Withdraw the needle from the skin, then release the pressure on the push-button.
- ▶ Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



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 your FlexPen.



- ⚠ Always remove the needle after each injection and store your FlexPen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

- ⚠ Caregivers must be very careful when handling used needles to reduce the risk of needle sticks and cross-infection.
- ⚠ Dispose of the used FlexPen carefully without the needle attached.
- ⚠ Never share your pen or your needles with other people. It might lead to cross-infection.
- ⚠ Never share your pen with other people. Your medicine might be harmful to their health.
- ⚠ Always keep your pen and needles out of sight and reach of others, especially children.

Package leaflet: Information for the user

NovoMix 50 Penfill 100 units/ml suspension for injection in a cartridge 50% soluble insulin aspart and 50% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoMix 50 is and what it is used for
2. What you need to know before you use NovoMix 50
3. How to use NovoMix 50
4. Possible side effects
5. How to store NovoMix 50
6. Contents of the pack and other information

1. What NovoMix 50 is and what it is used for

NovoMix 50 is a modern insulin (insulin analogue) with both a rapid-acting and an intermediate-acting effect, in the ratio 50/50. Modern insulin products are improved versions of human insulin.

NovoMix 50 is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. NovoMix 50 may be used in combination with metformin.

NovoMix 50 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 14–24 hours.

2. What you need to know before you use NovoMix 50

Do not use NovoMix 50

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If the cartridge or the device containing the cartridge is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 50.
- ▶ 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.

If any of these apply, do not use NovoMix 50. Talk to your doctor, nurse or pharmacist for advice.

Before using NovoMix 50

- ▶ Check the label to make sure it is the right type of insulin.
- ▶ Always check the cartridge, including the rubber plunger at the bottom of the cartridge. Do not use it if any damage is seen or if the rubber plunger has been drawn above the white label band at the bottom of the cartridge. This could be the result of an insulin leakage. If you suspect that the cartridge is damaged, take it back to your supplier. See your pen manual for further instructions.
- ▶ Always use a new needle for each injection to prevent contamination.
- ▶ Needles and NovoMix 50 Penfill must not be shared.
- ▶ NovoMix 50 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 50). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and NovoMix 50

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 50

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 50 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 50

NovoMix 50 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 50 is essentially 'sodium-free'.

3. How to use NovoMix 50

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

NovoMix 50 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, NovoMix 50 can be given soon after a meal.

See How and where to inject, below for information.

When NovoMix 50 is used in combination with metformin the dose should be adjusted.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents

No clinical studies with NovoMix 50 have been carried out in children and adolescents under the age of 18 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 50 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 50 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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.

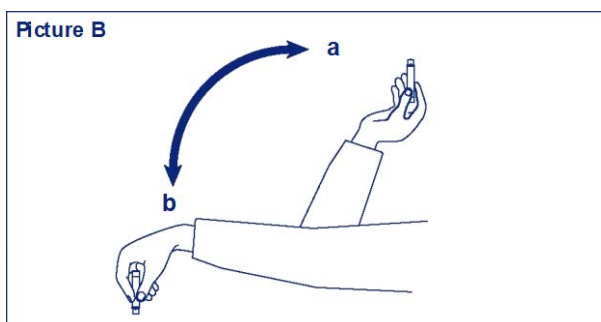
- ▶ Do not refill the cartridge.
- ▶ NovoMix 50 Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.
- ▶ If you are treated with NovoMix 50 Penfill and another insulin Penfill cartridge, you should use two insulin delivery systems, one for each type of insulin.
- ▶ Always carry a spare Penfill cartridge in case the one in use is lost or damaged.

Resuspension of NovoMix 50

Always check if there is enough insulin left (at least 12 units) in the cartridge to allow even resuspension. If there is not enough insulin left, use a new one. See your pen manual for further instructions.

- ▶ **Every time you use a new NovoMix 50 Penfill** (before you put the cartridge into the insulin delivery system)
 - 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) (see picture **A**).
 - Move the cartridge up and down between positions a and b (see picture **B**) 10 times so that the glass ball moves from one end of the cartridge to the other.
 - Repeat the rolling and moving procedures (see pictures **A** and **B**) until the liquid does appear uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white and cloudy.
 - Complete the other stages of injection without delay.
- ▶ **For every following injection**

- Move the delivery system with the cartridge inside up and down between a and b (see picture **B**) at least 10 times until the liquid appears uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white, cloudy and aqueous.
- If the moving procedure alone is not enough to give a uniformly white, cloudy and aqueous liquid, repeat the rolling and moving procedures described above until the liquid appears uniformly white, cloudy and aqueous.
- Complete the other stages of injection without delay.



How to inject NovoMix 50

- ▶ Inject the insulin under your skin. Use the injection technique advised by your doctor or nurse and as described in your pen manual.
- ▶ Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- ▶ After each injection, be sure to remove and discard the needle and store NovoMix 50 without the needle attached. Otherwise the liquid may leak out, which can cause inaccurate dosing.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 50 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 50 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the cartridge label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the cartridge in the outer carton when you are not using it, in order to protect it from light. NovoMix 50 must be protected from excessive heat and light.

Before opening: NovoMix 50 Penfill that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 50 Penfill, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new NovoMix 50 Penfill. See Resuspension of NovoMix 50 in section 3.

During use or when carried as a spare: NovoMix 50 Penfill that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 50 contains

- The active substance is insulin aspart. NovoMix 50 is a mixture consisting of 50% soluble insulin aspart and 50% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each cartridge contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 50 looks like and contents of the pack

NovoMix 50 is presented as a suspension for injection. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 1, 5 and 10 cartridges of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

Package leaflet: Information for the user

NovoMix 50 FlexPen 100 units/ml suspension for injection in a pre-filled pen 50% soluble insulin aspart and 50% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoMix 50 is and what it is used for
2. What you need to know before you use NovoMix 50
3. How to use NovoMix 50
4. Possible side effects
5. How to store NovoMix 50
6. Contents of the pack and other information

1. What NovoMix 50 is and what it is used for

NovoMix 50 is a modern insulin (insulin analogue) with both a rapid-acting and an intermediate-acting effect, in the ratio 50/50. Modern insulin products are improved versions of human insulin.

NovoMix 50 is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. NovoMix 50 may be used in combination with metformin.

NovoMix 50 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 14–24 hours.

2. What you need to know before you use NovoMix 50

Do not use NovoMix 50

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If FlexPen is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 50.
- ▶ 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.

If any of these apply, do not use NovoMix 50. Talk to your doctor, nurse or pharmacist for advice.

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 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 50). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and NovoMix 50

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 50

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 50 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 50

NovoMix 50 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 50 is essentially 'sodium-free'.

3. How to use NovoMix 50

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

NovoMix 50 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, NovoMix 50 can be given soon after a meal. See How and where to inject, below for information.

When NovoMix 50 is used in combination with metformin the dose should be adjusted.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one

type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents

No clinical studies with NovoMix 50 have been carried out in children and adolescents under the age of 18 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 50 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 50 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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

NovoMix 50 FlexPen is a pre-filled, colour-coded, disposable pen containing a mixture of rapid-acting and intermediate-acting insulin aspart in the ratio 50/50.

Read carefully the instructions for use included in this package leaflet. You must use the pen as described in the Instructions for use.

Always ensure you use the correct pen before you inject your insulin.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 50 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 50 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the FlexPen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the pen cap on your FlexPen when you are not using it, in order to protect it from light. NovoMix 50 must be protected from excessive heat and light.

Before opening: NovoMix 50 FlexPen that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 50 FlexPen, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new pen. See Instructions for use.

During use or when carried as a spare: NovoMix 50 FlexPen that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 50 contains

- The active substance is insulin aspart. NovoMix 50 is a mixture consisting of 50% soluble insulin aspart and 50% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each pre-filled pen contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 50 looks like and contents of the pack

NovoMix 50 is presented as a suspension for injection in a pre-filled pen. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 1, 5 and 10 pre-filled pens of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

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

Now turn over for information on how to use your FlexPen.

This leaflet was last revised in

Other sources of information

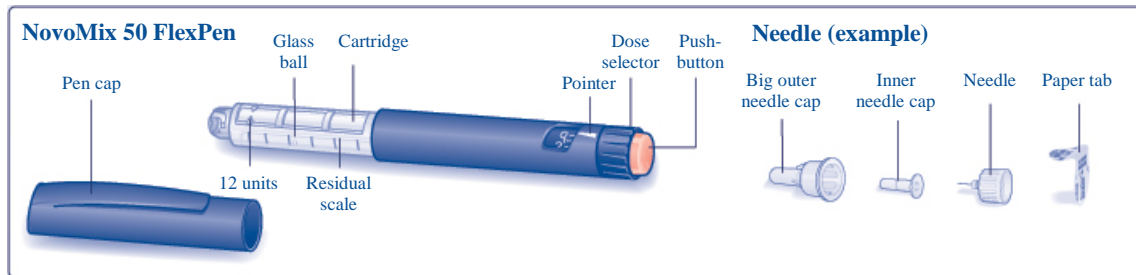
Detailed information on this medicine is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Instruction on how to use NovoMix 50 suspension for injection in FlexPen.

Read the following instructions carefully before using your FlexPen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your FlexPen is a pre-filled 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.
- ▶ Always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



Caring for your pen

- ▶ Your FlexPen must be handled with care. If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.
- ▶ 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.**

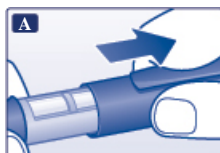
Resuspending your insulin

A

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Every time you use a new pen

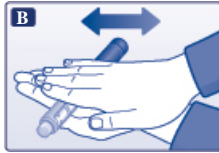
Let the insulin reach room temperature before you use it. This makes it easier to resuspend.
Pull off the pen cap.



B

Before your first injection with a new FlexPen, you must resuspend the insulin:

Roll the pen between your palms 10 times – it is important that the pen is kept **horizontal** (level with the ground).



C

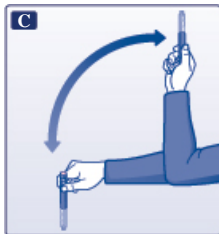
Then move the pen up and down 10 times between the two positions as shown, so the **glass ball moves** from one end of the cartridge to the other.

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

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, cloudy and aqueous. If the moving procedure alone is not enough to give a uniformly white, cloudy and aqueous liquid, repeat the rolling and moving procedures (see B and C) until the liquid does appear uniformly white, cloudy and aqueous.

- ▶ Always make sure that you have resuspended the insulin prior to each injection. This reduces the risk of too high or too low blood sugar level. 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. 12 units are marked on the residual scale. See the big picture on top of this instruction.

- ⚠ Do not use the pen if the **resuspended** insulin does not look **uniformly white, cloudy and aqueous**.

Attaching a needle

D

Take a new needle and tear off the paper tab.

Screw the needle straight and tightly onto your FlexPen.



E

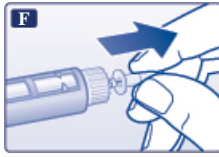
Pull off the big outer needle cap and keep it for later.



F

Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



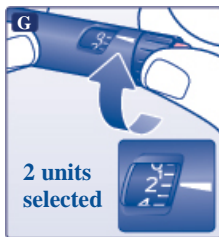
- ⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- ⚠ Be careful not to bend or damage the needle before use.

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.



- ⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.
- ⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

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.



- ⚠ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
- ⚠ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Making the injection

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

K

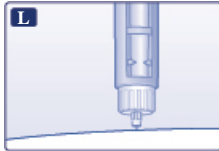
Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.



L

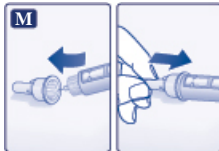
- ▶ Keep the **push-button fully depressed** and let the needle remain under the skin for **at least 6 seconds**. This will make sure you get the full dose.
- ▶ Withdraw the needle from the skin, then release the pressure on the push-button.
- ▶ Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



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 your FlexPen.



- ⚠ Always remove the needle after each injection and store your FlexPen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

- ⚠ Caregivers must be very careful when handling used needles to reduce the risk of needle sticks and cross-infection.
- ⚠ Dispose of the used FlexPen carefully without the needle attached.
- ⚠ Never share your pen or your needles with other people. It might lead to cross-infection.
- ⚠ Never share your pen with other people. Your medicine might be harmful to their health.
- ⚠ Always keep your pen and needles out of sight and reach of others, especially children.

Package leaflet: Information for the user

NovoMix 70 Penfill 100 units/ml suspension for injection in a cartridge 70% soluble insulin aspart and 30% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoMix 70 is and what it is used for
2. What you need to know before you use NovoMix 70
3. How to use NovoMix 70
4. Possible side effects
5. How to store NovoMix 70
6. Contents of the pack and other information

1. What NovoMix 70 is and what it is used for

NovoMix 70 is a modern insulin (insulin analogue) with both a rapid-acting and an intermediate-acting effect, in the ratio 70/30. Modern insulin products are improved versions of human insulin.

NovoMix 70 is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. NovoMix 70 may be used in combination with metformin.

NovoMix 70 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 14–24 hours.

2. What you need to know before you use NovoMix 70

Do not use NovoMix 70

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If the cartridge or the device containing the cartridge is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 70.
- ▶ 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.

If any of these apply, do not use NovoMix 70. Talk to your doctor, nurse or pharmacist for advice.

Before using NovoMix 70

- ▶ Check the label to make sure it is the right type of insulin.
- ▶ Always check the cartridge, including the rubber plunger at the bottom of the cartridge. Do not use it if any damage is seen or if the rubber plunger has been drawn above the white label band at the bottom of the cartridge. This could be the result of an insulin leakage. If you suspect that the cartridge is damaged, take it back to your supplier. See your pen manual for further instructions.
- ▶ Always use a new needle for each injection to prevent contamination.
- ▶ Needles and NovoMix 70 Penfill must not be shared.
- ▶ NovoMix 70 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 70). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and NovoMix 70

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)

- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 70

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 70 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 70

NovoMix 70 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 70 is essentially 'sodium-free'.

3. How to use NovoMix 70

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

NovoMix 70 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of

the injection to avoid low blood sugar. When necessary, NovoMix 70 can be given soon after a meal. See How and where to inject, below for information.

When NovoMix 70 is used in combination with metformin the dose should be adjusted.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents

No clinical studies with NovoMix 70 have been carried out in children and adolescents under the age of 18 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 70 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 70 Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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.

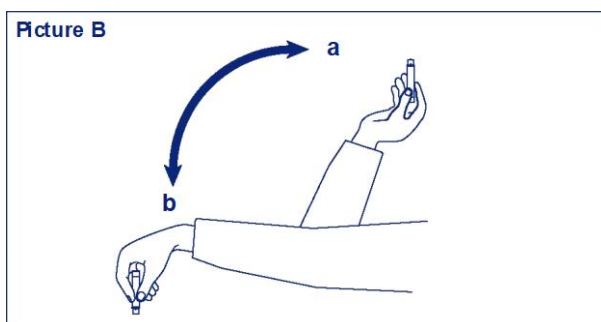
- ▶ Do not refill the cartridge.
- ▶ NovoMix 70 Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.
- ▶ If you are treated with NovoMix 70 Penfill and another insulin Penfill cartridge, you should use two insulin delivery systems, one for each type of insulin.
- ▶ Always carry a spare Penfill cartridge in case the one in use is lost or damaged.

Resuspension of NovoMix 70

Always check if there is enough insulin left (at least 12 units) in the cartridge to allow even resuspension. If there is not enough insulin left, use a new one. See your pen manual for further instructions.

- ▶ **Every time you use a new NovoMix 70 Penfill** (before you put the cartridge into the insulin delivery system)
 - 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) (see picture **A**).
 - Move the cartridge up and down between positions a and b (see picture **B**) 10 times so that the glass ball moves from one end of the cartridge to the other.
 - Repeat the rolling and moving procedures (see pictures **A** and **B**) until the liquid appears uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white, cloudy and aqueous.
 - Complete the other stages of injection without delay.
- ▶ **For every following injection**

- Move the delivery system with the cartridge inside up and down between a and b (see picture **B**) at least 10 times until the liquid appears uniformly white, cloudy and aqueous. Do not use the cartridge if the resuspended insulin does not look uniformly white, cloudy and aqueous.
- If the moving procedure alone is not enough to give a uniformly white, cloudy and aqueous liquid, repeat the rolling and moving procedures described above until the liquid appears uniformly white, cloudy and aqueous.
- Complete the other stages of injection without delay.



How to inject NovoMix 70

- ▶ Inject the insulin under your skin. Use the injection technique advised by your doctor or nurse and as described in your pen manual.
- ▶ Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- ▶ After each injection, be sure to remove and discard the needle and store NovoMix 70 without the needle attached. Otherwise the liquid may leak out, which can cause inaccurate dosing.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 70 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 70 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 70

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the cartridge label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the cartridge in the outer carton when you are not using it, in order to protect it from light. NovoMix 70 must be protected from excessive heat and light.

Before opening: NovoMix 70 Penfill that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 70 Penfill, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new NovoMix 70 Penfill. See Resuspension of NovoMix 70 in section 3.

During use or when carried as a spare: NovoMix 70 Penfill that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 70 contains

- The active substance is insulin aspart. NovoMix 70 is a mixture consisting of 70% soluble insulin aspart and 30% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each cartridge contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 70 looks like and contents of the pack

NovoMix 70 is presented as a suspension for injection. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 1, 5 and 10 cartridges of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

Package leaflet: Information for the user

NovoMix 70 FlexPen 100 units/ml suspension for injection in a pre-filled pen 70% soluble insulin aspart and 30% insulin aspart crystallised with protamine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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2. What you need to know before you use NovoMix 70
3. How to use NovoMix 70
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1. What NovoMix 70 is and what it is used for

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NovoMix 70 is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. NovoMix 70 may be used in combination with metformin.

NovoMix 70 will start to lower your blood sugar 10–20 minutes after you inject it, the maximum effect occurs between 1 and 4 hours after the injection, and the effect lasts for up to 14–24 hours.

2. What you need to know before you use NovoMix 70

Do not use NovoMix 70

- ▶ If you are allergic to insulin aspart or any of the other ingredients in this medicine (see section 6, Contents of the pack and other information).
- ▶ If you suspect hypoglycaemia (low blood sugar) is starting, see a) Summary of serious and very common side effects in section 4.
- ▶ In insulin infusion pumps.
- ▶ If FlexPen is dropped, damaged or crushed.
- ▶ If it has not been stored correctly or if it has been frozen, see section 5, How to store NovoMix 70.
- ▶ 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.

If any of these apply, do not use NovoMix 70. Talk to your doctor, nurse or pharmacist for advice.

Before using NovoMix 70

- ▶ 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 70 FlexPen must not be shared.
- ▶ NovoMix 70 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:

- ▶ If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ▶ If you are ill, carry on taking your insulin and consult your doctor.
- ▶ If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use NovoMix 70). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and NovoMix 70

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking NovoMix 70

- ▶ If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

- ▶ If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is limited clinical experience with insulin aspart in pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- ▶ There are no restrictions on treatment with NovoMix 70 during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

- ▶ Please ask your doctor whether you can drive a car or operate a machine:
 - If you have frequent hypoglycaemia.
 - If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Important information about some of the ingredients in NovoMix 70

NovoMix 70 contains less than 1 mmol sodium (23 mg) per dose, i.e. NovoMix 70 is essentially 'sodium-free'.

3. How to use NovoMix 70

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

NovoMix 70 is generally taken immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, NovoMix 70 can be given soon after a meal. See How and where to inject, below for information.

When NovoMix 70 is used in combination with metformin the dose should be adjusted.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one

type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents

No clinical studies with NovoMix 70 have been carried out in children and adolescents under the age of 18 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

NovoMix 70 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly). NovoMix 70 FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

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 (see section 4, Possible side effects). 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 70 FlexPen

NovoMix 70 FlexPen is a pre-filled, colour-coded, disposable pen containing a mixture of rapid-acting and intermediate-acting insulin aspart in the ratio 70/30.

Read carefully the instructions for use included in this package leaflet. You must use the pen as described in the Instructions for use.

Always ensure you use the correct pen before you inject your insulin.

If you take more insulin than you should

If you take too much insulin, your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin, your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:

- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking NovoMix 70 in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:

- ▶ If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ▶ When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ▶ If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink because you may choke.

Serious allergic reactions to NovoMix 70 or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life-threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ▶ If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects

May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally, this soon disappears. If not, contact your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects

May affect less than 1 in 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:

- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:

- ▶ If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ▶ These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store NovoMix 70

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the FlexPen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Always keep the pen cap on your FlexPen when you are not using it, in order to protect it from light. NovoMix 70 must be protected from excessive heat and light.

Before opening: NovoMix 70 FlexPen that is not being used must be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

Before you use NovoMix 70 FlexPen, remove it from the refrigerator. It is recommended to resuspend the insulin as instructed every time you use a new pen. See Instructions for use.

During use or when carried as a spare: NovoMix 70 FlexPen that is being used or carried as a spare should not be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoMix 70 contains

- The active substance is insulin aspart. NovoMix 70 is a mixture consisting of 70% soluble insulin aspart and 30% insulin aspart crystallised with protamine. 1 ml contains 100 units of insulin aspart. Each pre-filled pen contains 300 units of insulin aspart in 3 ml suspension for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulfate, hydrochloric acid, sodium hydroxide and water for injections.

What NovoMix 70 looks like and contents of the pack

NovoMix 70 is presented as a suspension for injection in a pre-filled pen. The cartridge contains a glass ball to facilitate resuspension. After resuspension, the liquid should appear uniformly white, cloudy and aqueous. Do not use the insulin, if it does not look uniformly white, cloudy and aqueous after resuspension.

Pack sizes of 1, 5 and 10 pre-filled pens of 3 ml. Not all pack sizes may be marketed.

The suspension is cloudy, white and aqueous.

Marketing Authorisation Holder and Manufacturer

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

Now turn over for information on how to use your FlexPen.

This leaflet was last revised in

Other sources of information

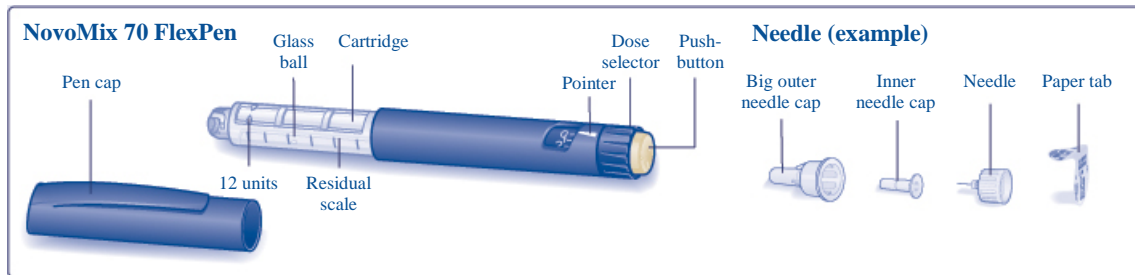
Detailed information on this medicine is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Instruction on how to use NovoMix 70 suspension for injection in FlexPen.

Read the following instructions carefully before using your FlexPen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your FlexPen is a pre-filled 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.
- ▶ Always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



Caring for your pen

- ▶ Your FlexPen must be handled with care. If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.
- ▶ 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.**

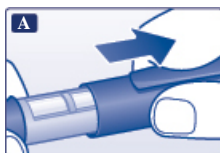
Resuspending your insulin

A

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Every time you use a new pen

Let the insulin reach room temperature before you use it. This makes it easier to resuspend.
Pull off the pen cap.



B

Before your first injection with a new FlexPen, you must resuspend the insulin:

Roll the pen between your palms 10 times – it is important that the pen is kept **horizontal** (level with the ground).



C

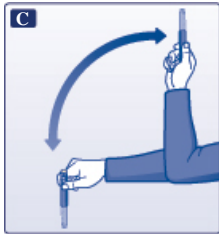
Then move the pen up and down 10 times between the two positions as shown, so the **glass ball moves** from one end of the cartridge to the other.

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

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, cloudy and aqueous. If the moving procedure alone is not enough to give a uniformly white, cloudy and aqueous liquid, repeat the rolling and moving procedures (see B and C) until the liquid does appear uniformly white, cloudy and aqueous.

- ▶ Always make sure that you have resuspended the insulin prior to each injection. This reduces the risk of too high or too low blood sugar level. 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. 12 units are marked on the residual scale. See the big picture on top of this instruction.

- ⚠ Do not use the pen if the **resuspended** insulin does not look **uniformly white, cloudy and aqueous**.

Attaching a needle

D

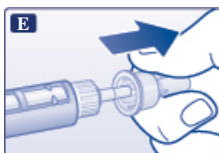
Take a new needle and tear off the paper tab.

Screw the needle straight and tightly onto your FlexPen.



E

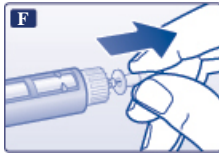
Pull off the big outer needle cap and keep it for later.



F

Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



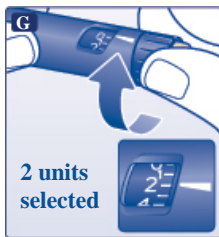
- ⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- ⚠ Be careful not to bend or damage the needle before use.

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.



- △ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.
- △ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Selecting your dose

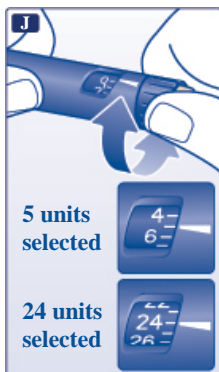
Check that the dose selector is set at 0.

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.



- △ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
- △ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Making the injection

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

K

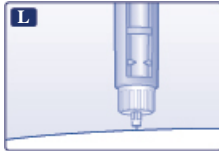
Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.



L

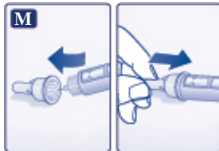
- ▶ Keep the **push-button fully depressed** and let the needle remain under the skin for **at least 6 seconds**. This will make sure you get the full dose.
- ▶ Withdraw the needle from the skin, then release the pressure on the push-button.
- ▶ Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



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 your FlexPen.



- ⚠ Always remove the needle after each injection and store your FlexPen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

- ⚠ Caregivers must be very careful when handling used needles to reduce the risk of needle sticks and cross-infection.
- ⚠ Dispose of the used FlexPen carefully without the needle attached.
- ⚠ Never share your pen or your needles with other people. It might lead to cross-infection.
- ⚠ Never share your pen with other people. Your medicine might be harmful to their health.
- ⚠ Always keep your pen and needles out of sight and reach of others, especially children.