**NovoMix® 30** Penfill®
100 U/ml
Suspension for injection in a cartridge.

**Qualitative and quantitative composition**
1 ml of the suspension contains 100 U of 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 U.
*Insulin aspart produced by recombinant DNA technology in *Saccharomyces cerevisiae.*

**Pharmaceutical form:** White suspension for injection in a cartridge. Penfill®.

**Therapeutic indications:** Treatment of patients with diabetes mellitus requiring insulin.

**Posology**
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 drugs and/or GLP-1 receptor agonists.

**How to start**
Insulin naïve patients: For patients with type 2 diabetes, the recommended starting dose of NovoMix® 30 is 6 U at breakfast and 6 U at dinner (evening meal). However, it can also be initiated once daily with 12 U at dinner (evening meal).

**How to switch**
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 following titration guideline*). As with all insulin products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see *Transfer from other insulin products*).

**How to intensify**
NovoMix® 30 can be intensified from once daily to twice daily. 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 (50:50).
From NovoMix® 30 twice daily to thrice daily: the morning dose can be split into morning and lunchtime doses (thrice daily dosing).

**How to adjust the dose**
- Adjust the dose of NovoMix® 30 on the basis of the lowest pre-meal blood glucose level from the three previous days.
- Always change the mealtime dose preceding the measurement.
- Dose adjustment can be made once a week until target $HbA_{1c}$ is reached.
- The dose should not be increased if hypoglycaemia occurred within these days.
- Adjustment of dosage may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

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 U |
| 4.4–6.1 mmol/l | 80–110 mg/dl | 0 |
| 6.2–7.8 mmol/l | 111–140 mg/dl | +2 U |
| 7.9–10 mmol/l | 141–180 mg/dl | +4 U |
| >10 mmol/l | >180 mg/dl | +6 U |

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.

**Special populations**
As with all insulin products, in special populations, glucose monitoring should be intensified and the insulin aspart dosage adjusted on an individual basis.
Elderly: NovoMix® 30 can be used in elderly patients; however there is limited experience with the use of NovoMix® 30 in combination with OADs in patients older than 75 years.
Renal and hepatic impairment: Renal or hepatic impairment may reduce the patient's insulin requirements.
Paediatric population: NovoMix® 30 can be used in children and adolescents aged 10 years and above when premixed insulin is preferred. Limited clinical data exist for children aged 6 to 9 years (see *Pharmacodynamic properties*).
No data are available for NovoMix® 30 in children below 6 years of age.

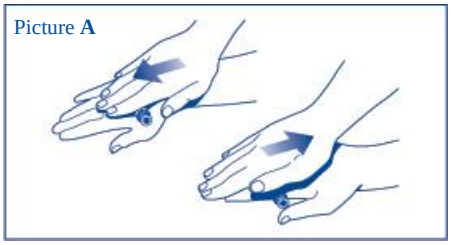
**Method of administration**
NovoMix® 30 is for subcutaneous administration only. NovoMix® 30 must not be administered intravenously as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. NovoMix® 30 is not to be used in insulin infusion pumps.
NovoMix® 30 is administered 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 *Special warnings and precautions for use* and *Undesirable effects*). As with all insulin products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
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.

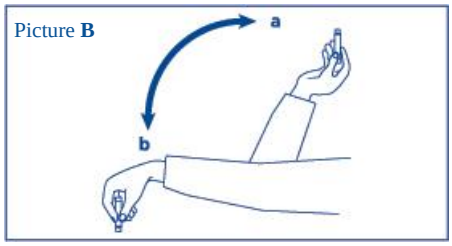
**Resuspension of the insulin**
Check that there are at least 12 units of insulin left in the cartridge to allow even resuspension. If there are less than 12 units left, use a new cartridge.

**Every time you use a new** NovoMix® 30 Penfill® cartridge (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 and cloudy. 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 and cloudy.
- Complete the other stages of injection without delay.

Picture **A**






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

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

To be used as prescribed by doctor only. If experience dizziness or fainting, please consult your doctor immediately.

**Hyperglycaemia (high blood sugar)**
Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

**Hypoglycaemia (low blood sugar)**
Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see *Undesirable effects* and *Overdose*).
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 *Posology*.

Since NovoMix® 30 should be administered in immediate relation to a meal, the rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements. Concomitant diseases 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 products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

**Transfer from other insulin 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 (human insulin, insulin analogue) and/or method of manufacture may result in the need for a change in dosage. Patients transferred to NovoMix® 30 from another type of insulin may require an increased number of daily injections or a change in dosage from that used with their usual insulin products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

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

**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.

**Interaction with other medicinal products and other forms of interaction**
A number of medicinal products are known to interact with the glucose metabolism.
**The following substances may reduce the patient's insulin requirements:**
Oral antidiabetic products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOIs), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.
**The following substances may increase the patient's insulin requirements:**
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta-blocking agents may mask the symptoms of hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the insulin requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

**Pregnancy and lactation**
There is limited clinical experience with NovoMix® 30 in pregnancy.
NovoMix® 30 has not been investigated in pregnant women. However, data from two randomised controlled clinical trials (157 and 14 insulin aspart-exposed pregnancies, respectively, in basal-bolus regimen) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to soluble human insulin.
In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

There are no restrictions on treatment with NovoMix® 30 during lactation. Insulin treatment of the breast-feeding mother presents no risk to the baby. However, the NovoMix® 30 dosage may need to be adjusted.

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

**Undesirable effects**

**a. Summary of the safety profile**
Adverse reactions observed in patients using NovoMix® are mainly due to the pharmacologic effect of insulin.
The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c. *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.

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

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

* see section c
† ADR from postmarketing sources

**c. Description of selected adverse reactions**
Anaphylactic reactions: The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in

breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life-threatening.

Hypoglycaemia: The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.
In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control. During clinical trials, the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

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 *Special warnings and precautions for use*).

**Overdose**
A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:
- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

**Pharmacodynamic properties**
Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting. ATC code: A10AD05.
NovoMix® 30 is a biphasic suspension of soluble insulin aspart (rapid-acting insulin analogue) and insulin aspart crystallised with protamine (intermediate-acting insulin analogue). The suspension contains rapid-acting and intermediate-acting insulin aspart in the ratio 30/70. Insulin aspart is equipotent to human insulin on a molar basis.

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

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.

In a 3-month trial comparing NovoMix® 30 with biphasic human insulin 30 administration before breakfast and dinner in patients with type 1 and type 2 diabetes, NovoMix® 30 resulted in significantly 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 compared to biphasic human insulin 30, administration of NovoMix® 30 before breakfast and dinner resulted in significantly better postprandial blood glucose control (average prandial glucose increments over breakfast, lunch and dinner). While fasting blood glucose was higher in patients treated with

NovoMix® 30, the overall glycaemic control measured by glycosylated haemoglobin was similar.

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. $HbA_{1c}$ 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 treatment following the dosing guideline, 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 126 mg/dl (from 252 mg/dl at baseline to 127.8 mg/dl).
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 higher 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 was 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.

Elderly: The pharmacodynamic properties of NovoMix® 30 have not been investigated in the elderly. However, a randomised, double-blind, cross-over PK/PD trial, comparing insulin aspart with soluble human insulin was performed in elderly patients with type 2 diabetes (19 patients aged 65–83 years, mean age 70 years). The relative differences in the pharmacodynamic properties ($GIR_{max}$, $AUC_{GIR,\ 0\text{-}120\ min}$) between insulin aspart and soluble human insulin in the elderly were similar to those seen in healthy subjects and in younger patients with diabetes.

**Pharmacokinetic properties**
In insulin aspart, substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with human insulin. The insulin aspart in the soluble phase of NovoMix® 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 U/kg body weight. The mean half-life ($t_{½}$) 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.

Elderly: The pharmacokinetic properties of NovoMix® 30 have not been investigated in the elderly patients. However, the relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly patients (65–83 years, mean age 70 years) with type 2 diabetes, were similar to those observed in healthy subjects and in younger patients with diabetes. A decreased absorption rate was observed in elderly patients, resulting in a later $t_{max}$ (82 (interquartile range: 60–120) minutes), whereas $C_{max}$ was similar to that observed in younger patients with type 2 diabetes and slightly lower than in patients with type 1 diabetes.

Renal and hepatic impairment: The pharmacokinetics of NovoMix® 30 has not been investigated in patients with renal or hepatic impairment.

Paediatric population: The pharmacokinetics of NovoMix® 30 has 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.

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

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

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

**Special precautions for storage**
**Storage when not in use:** Store in a refrigerator (2°C–8°C). Keep away from the cooling element. Do not freeze.
The expiry date is printed on the label and carton.
After removing NovoMix® 30 Penfill® from the refrigerator, it is recommended to allow NovoMix® 30 Penfill® to reach room temperature before resuspending the insulin as instructed for the first time use.
**Storage during use or when carried as a spare:** NovoMix® 30 Penfill® that is being used or carried as a spare is not to be kept in the refrigerator. It can be kept at room temperature (below 30°C) for up to 4 weeks.
Keep the cartridge in the outer carton in order to protect from light.
NovoMix® 30 must be protected from excessive heat and light.

**Nature and contents of container**
3 ml suspension cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) in a carton. The cartridge contains a glass ball to facilitate resuspension.
Pack sizes of 5 or 10 cartridges. Not all pack sizes may be marketed.

**Special precautions for disposal and other handling**
Needles and NovoMix® 30 Penfill® must not be shared. The cartridge must not be refilled. NovoMix® 30 must not be used if the resuspended liquid does not appear uniformly white and cloudy.
The necessity of resuspending the NovoMix® 30 Penfill® 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.

**Product Owner:**
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

**Manufactured by:**
1. Novo Nordisk Produção Farmacêutica do Brasil Ltda., Montes Claros - Minas Gerais, Brazil
2. Novo Nordisk Production SAS, Chartres, France

**Imported by:**
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