ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 U/ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 vial contains 10 ml equivalent to 1,000 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with a syringe
NovoRapid vials are for use with insulin syringes with the corresponding unit scale.

NovoRapid vial is accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula)

should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting.
ATC code: A10AB05.

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.

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

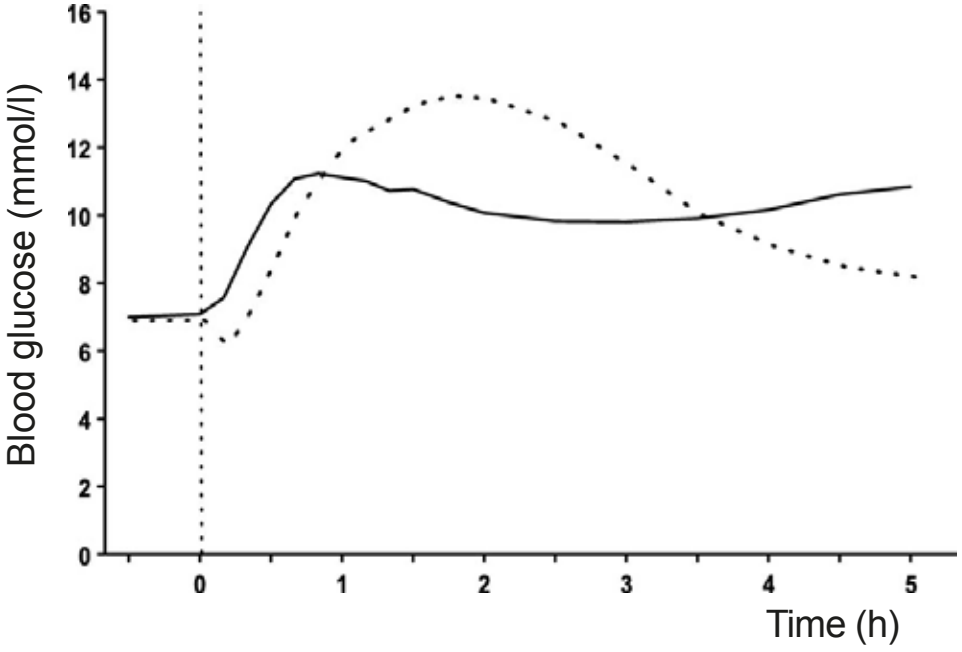

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

Special populations

Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.
Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat

slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

Special populations

Elderly (≥ 65 years old)
The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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

Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze.

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

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml solution in vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap.

Pack sizes of 1 or 5 vials of 10 ml or a multipack of 5 packs of 1 x 10 ml vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Needles and syringes must not be shared.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

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.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/001
EU/1/99/119/008
EU/1/99/119/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

NovoRapid Penfill 100 U/ml solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 cartridge contains 3 ml equivalent to 300 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge. Penfill.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with an insulin delivery system
NovoRapid Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.

NovoRapid Penfill is accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting. ATC code: A10AB05.

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.

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

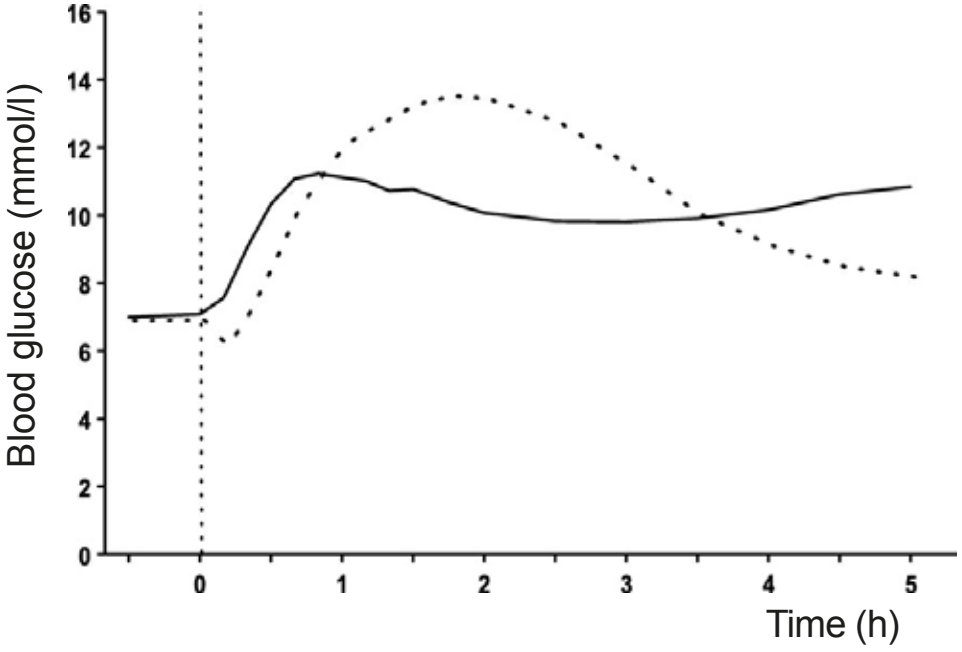

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

Special populations

Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

Special populations

Elderly (≥ 65 years old)
The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

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 from light.

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene).

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

6.6 Special precautions for disposal and other handling

Needles and NovoRapid Penfill must not be shared. The cartridge must not be refilled.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

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

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

In case of emergency in current NovoRapid users (hospitalisation or insulin pen malfunction), NovoRapid can be withdrawn with an U100 insulin syringe from a cartridge.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/003
EU/1/99/119/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

NovoRapid NovoLet 100 U/ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen. NovoLet.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with NovoLet
NovoRapid NovoLet is a pre-filled pen designed to be used with NovoFine needles. NovoLet delivers 2-78 units in increments of 2 units.

NovoRapid NovoLet is accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting.
ATC code: A10AB05.

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.

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

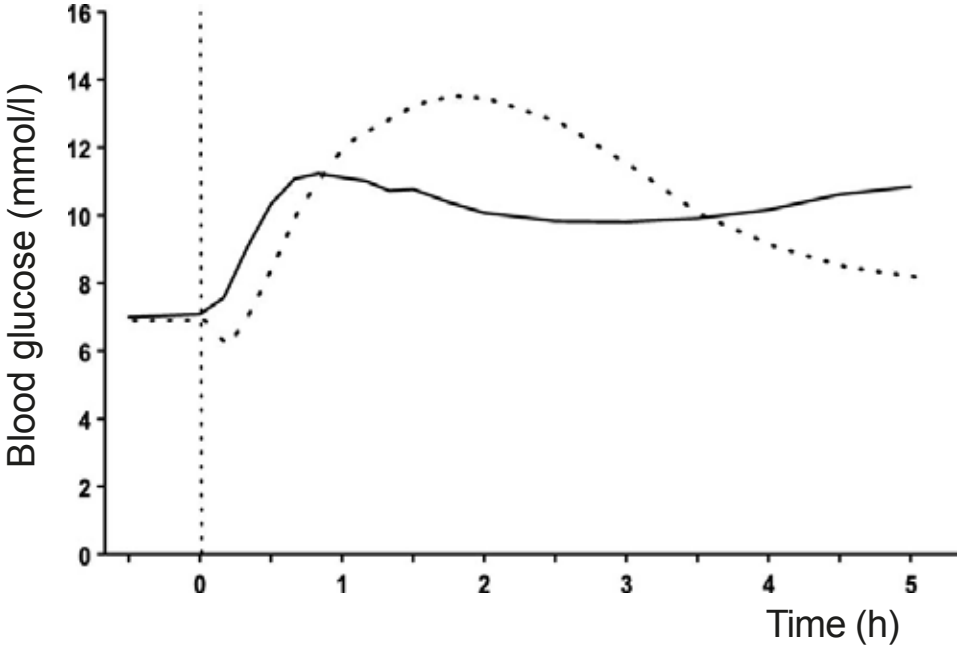

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

Special populations

Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

Special populations

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The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze.

Keep the pen cap on NovoLet in order to protect from light.

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

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

6.6 Special precautions for disposal and other handling

Needles and NovoRapid NovoLet must not be shared. The cartridge must not be refilled.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

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

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

In case of emergency in current NovoRapid users (hospitalisation or insulin pen malfunction), NovoRapid can be withdrawn with an U100 insulin syringe from a NovoLet.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/005
EU/1/99/119/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

NovoRapid FlexPen 100 U/ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen. FlexPen.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with FlexPen
NovoRapid FlexPen is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. FlexPen delivers 1-60 units in increments of 1 unit.

NovoRapid FlexPen is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting.
ATC code: A10AB05.

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.

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

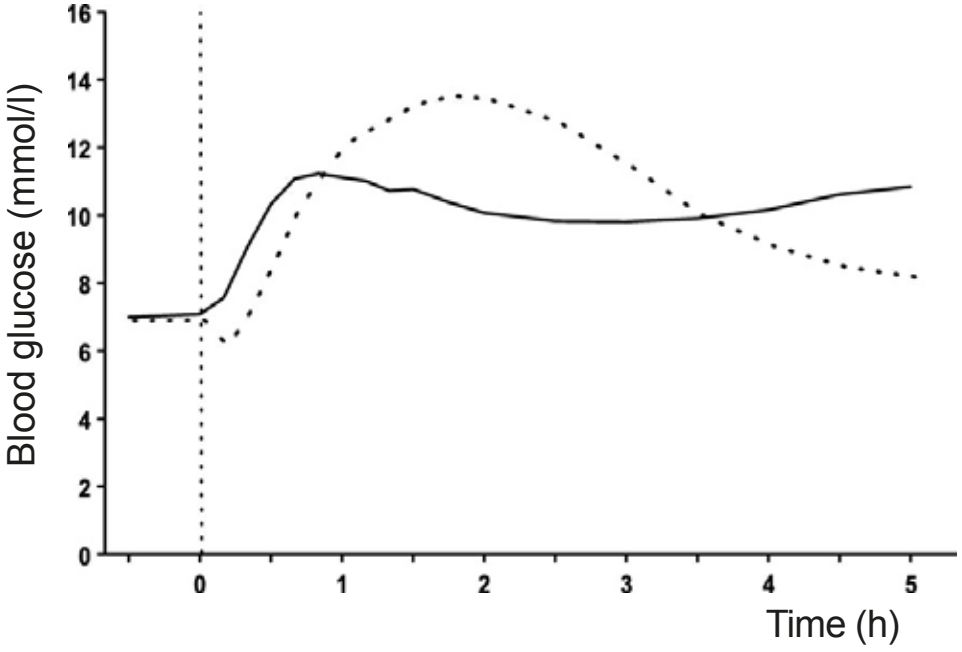

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

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Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

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Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin

concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

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The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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

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Metacresol
Zinc chloride
Disodium phosphate dihydrate

Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

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Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze.

Keep the pen cap on FlexPen in order to protect from light.

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

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

Needles and NovoRapid FlexPen must not be shared. The cartridge must not be refilled.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

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

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

In case of emergency in current NovoRapid users (hospitalisation or insulin pen malfunction), NovoRapid can be withdrawn with an U100 insulin syringe from a FlexPen.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/009
EU/1/99/119/010
EU/1/99/119/011
EU/1/99/119/017
EU/1/99/119/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

NovoRapid InnoLet 100 U/ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen. InnoLet.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with InnoLet
NovoRapid InnoLet is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. InnoLet delivers 1-50 units in increments of 1 unit.

NovoRapid InnoLet is accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting. ATC code: A10AB05.

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.

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

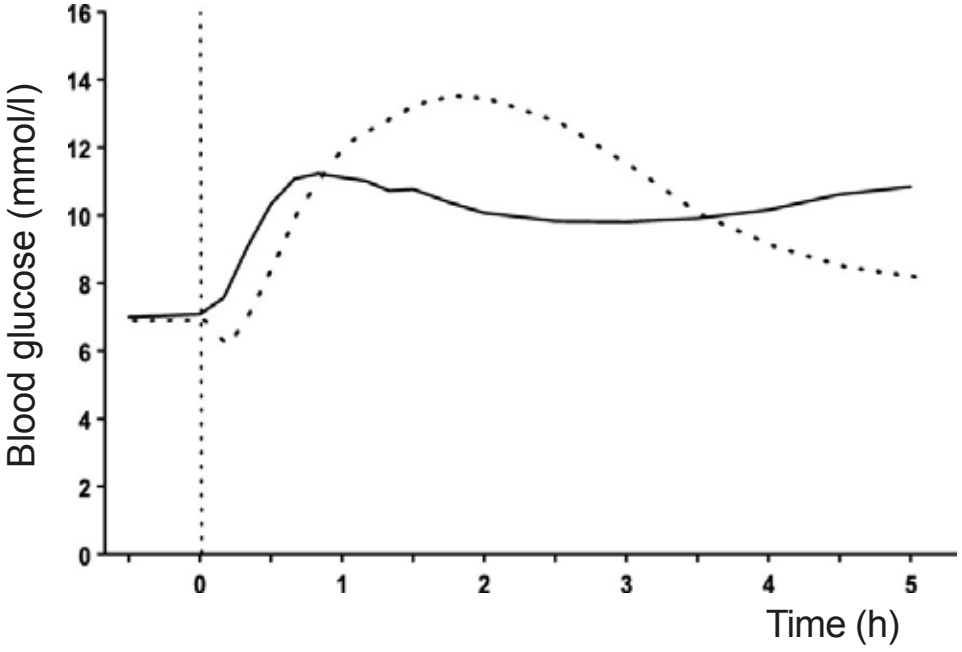


Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

Special populations

Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

Special populations

Elderly (≥ 65 years old)
The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze.

Keep the pen cap on InnoLet in order to protect from light.

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

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

Needles and NovoRapid InnoLet must not be shared. The cartridge must not be refilled.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

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

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

In case of emergency in current NovoRapid users (hospitalisation or insulin pen malfunction), NovoRapid can be withdrawn with an U100 insulin syringe from an InnoLet.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/012
EU/1/99/119/013
EU/1/99/119/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

NovoRapid FlexTouch 100 U/ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 100 U insulin aspart* (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 U.

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

Excipient with known effect:

100 U NovoRapid contains approximately 30 mcmol sodium, i.e. NovoRapid contains less than 1 mmol sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen. FlexTouch.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

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

NovoRapid dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. Moreover NovoRapid can be used for continuous subcutaneous insulin infusion (CSII) in pump systems or be administered intravenously by healthcare professionals. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 U/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by NovoRapid and the remainder by intermediate-acting or long-acting insulin.

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)
NovoRapid can be used in elderly patients.

As with all insulin medicinal products, 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.
As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

NovoRapid can be used in children and adolescents aged 2 years and above in preference to soluble human insulin when a rapid onset of action might be beneficial (see sections 5.1 and 5.2). For example, in the timing of the injections in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. NovoRapid should only be used in this age group under careful medical supervision.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the NovoRapid dose and the dose of the basal insulin may be necessary. NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoRapid is a rapid–acting insulin analogue.
NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin medicinal products, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. Compared to soluble human insulin the faster onset of action of NovoRapid is maintained regardless of the injection site. As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, NovoRapid should generally be given immediately before a meal. When necessary NovoRapid can be given soon after a meal.

Administration with FlexTouch
NovoRapid FlexTouch is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. FlexTouch delivers 1-80 units in increments of 1 unit.

NovoRapid FlexTouch is colour–coded and accompanied by a package leaflet with detailed instructions for use to be followed.

Continuous Subcutaneous Insulin Infusion (CSII)
NovoRapid may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, NovoRapid should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering NovoRapid by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, NovoRapid can be administered intravenously which should be carried out by healthcare professionals.

For intravenous use, infusion systems with NovoRapid 100 U/ml at concentrations from 0.05 U/ml to 1.0 U/ml insulin aspart in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose inclusive 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 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.

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 NovoRapid must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 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.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since NovoRapid should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoRapid 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 may help to reduce 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 NovoRapid.

Combination of NovoRapid 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 NovoRapid 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.

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 sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid (insulin aspart) can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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

Breast-feeding

There are no restrictions on treatment with NovoRapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid 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. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using NovoRapid are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

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

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

* see section c

c. Description of selected adverse reactions

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

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

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

Lipodystrophy:
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. 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.

e. Other special populations

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

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, fast-acting.
ATC code: A10AB05.

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.

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

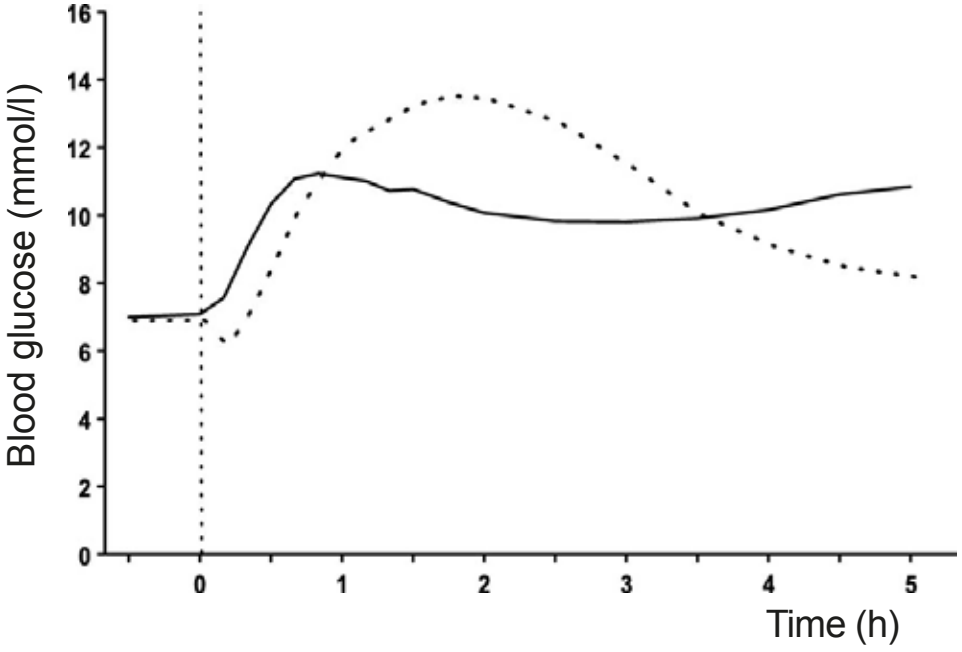


Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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

Clinical efficacy

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with NovoRapid compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, NovoRapid reduced glycosylated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of doubtful clinical significance.

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

Special populations

Elderly (≥ 65 years old)
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 human insulin in the elderly were similar to those seen in healthy subjects and in younger subjects with diabetes.

Paediatric population

A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

Pregnancy

A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.
In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

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

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In NovoRapid substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30–40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50–90) minutes). The intra-individual variability in time to maximum concentration is significantly less for NovoRapid than for soluble human insulin, whereas the intra-individual variability in C_{max} for NovoRapid is larger.

Special populations

Elderly (≥ 65 years old)
The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger subjects with type 2 diabetes and slightly lower than in subjects with type 1 diabetes.

Hepatic impairment
A single dose pharmacokinetic study of insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Renal impairment
A single dose pharmacokinetic study of insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and t_{max} of insulin aspart was found. Data were limited in subjects with moderate and severe renal impairment. Subjects with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

The pharmacokinetic and pharmacodynamic properties of NovoRapid were 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 NovoRapid.

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
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to NovoRapid may cause degradation of insulin aspart, e.g. if the medicinal product contains thiols or sulphites.
This medicinal product must not be mixed with other medicinal products, except with NPH (Neutral Protamine Hagedorn) insulin and infusion fluids as described in section 4.2.

6.3 Shelf life

Before opening: 30 months.

During use or when carried as a spare: The product must be stored for a maximum of 4 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate. Do not freeze.

Keep the pen cap on FlexTouch in order to protect from light.

For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

Pack sizes of 1 (with or without needles), 5 (without needles) or a multipack with 2 x 5 (without needles) pre-filled pens of 3 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Needles and NovoRapid FlexTouch must not be shared. The cartridge must not be refilled.

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

NovoRapid which has been frozen must not be used.

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

NovoRapid may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

In case of emergency in current NovoRapid users (hospitalisation or insulin pen malfunction), NovoRapid can be withdrawn with an U100 insulin syringe from a FlexTouch Pen.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/119/019
EU/1/99/119/020
EU/1/99/119/021
EU/1/99/119/022
EU/1/99/119/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 30 April 2009

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

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
Hallas Allé
DK-4400 Kalundborg
Denmark

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

Name and address of the manufacturers responsible for batch release

NovoRapid Vial, NovoLet, InnoLet and FlexTouch:

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

NovoRapid Penfill and FlexPen:

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

Novo Nordisk Production SAS
45, Avenue d'Orléans
F-28002 Chartres
France

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

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 Units/ml
Solution for injection
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial contains 10 ml equivalent to 1,000 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.

1 vial of 10 ml
5 vials of 10 ml
Multipack: 5 packs of 1 x 10 ml vials.

5. METHOD AND ROUTES OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before 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 WARNING, IF NECESSARY

Use only solution if water clear, colourless and aqueous

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 vial in the outer carton in order to protect 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/1/99/119/001 1 vial of 10 ml
EU/1/99/119/008 5 vials of 10 ml
EU/1/99/119/015 Multipack: 5 packs of 1 x 10 ml vials

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoRapid

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 Units/ml
Solution for injection
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial contains 10 ml equivalent to 1,000 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.

1 x 10 ml vials. This is a multipack of 5 vials and not for sale as individual vials

5. METHOD AND ROUTES OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before 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 WARNING, IF NECESSARY

Use only solution if water clear, colourless and aqueous

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 vial in the outer carton in order to protect 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 NUMBER

EU/1/99/119/015

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (VIAL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml
1 vial of 10 ml contains 1,000 U

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid Penfill 100 Units/ml
Solution for injection in cartridge
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 cartridge of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a cartridge. Penfill.

5 x 3 ml cartridges
10 x 3 ml cartridges

5. METHOD AND ROUTES OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before 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

Use only solution if water clear, colourless 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 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/1/99/119/003 5 cartridges of 3 ml
EU/1/99/119/006 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

NovoRapid Penfill

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid Penfill 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

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. NovoLet)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid NovoLet 100 Units/ml
Solution for injection in pre-filled pen
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. NovoLet.

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

5. METHOD AND ROUTES OF ADMINISTRATION

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

Use only solution if water clear, colourless and aqueous
For use by one person only
Designed to be used with NovoFine disposable needles

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 pen cap on in order to protect 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/1/99/119/005 5 pens of 3 ml
EU/1/99/119/007 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

NovoRapid NovoLet

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. NovoLet)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid NovoLet 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

NovoLet

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

NovoRapid FlexPen 100 Units/ml
Solution for injection in pre-filled pen
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. FlexPen.

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 ROUTES OF ADMINISTRATION

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

Use only solution if water clear, colourless 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 pen cap on in order to protect 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/1/99/119/011 1 pen of 3 ml
EU/1/99/119/009 5 pens of 3 ml
EU/1/99/119/010 10 pens of 3 ml
EU/1/99/119/017 1 pen of 3 ml and 7 NovoFine needles
EU/1/99/119/018 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

NovoRapid FlexPen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid FlexPen 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

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 (PRE-FILLED PEN. InnoLet)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid InnoLet 100 Units/ml
Solution for injection in pre-filled pen
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. InnoLet.

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

5. METHOD AND ROUTES OF ADMINISTRATION

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

Use only solution if water clear, colourless 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 pen cap on in order to protect 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/1/99/119/012 1 pen of 3 ml
EU/1/99/119/013 5 pens of 3 ml
EU/1/99/119/014 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

NovoRapid InnoLet

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. InnoLet)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid InnoLet 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

InnoLet

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. FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid FlexTouch 100 Units/ml
Solution for injection in pre-filled pen
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. FlexTouch.

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
2 x (5 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 ROUTES OF ADMINISTRATION

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

Use only solution if water clear, colourless 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 pen cap on in order to protect 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/1/99/119/019 1 pen of 3 ml
EU/1/99/119/020 5 pens of 3 ml
EU/1/99/119/021 5 pens of 3 ml. This is part of a multipack of 10 pens and not for sale as individual pens
EU/1/99/119/022 1 pen of 3 ml and 7 NovoFine needles
EU/1/99/119/023 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

NovoRapid FlexTouch

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (PRE–FILLED PEN. FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid FlexTouch 100 Units/ml
Solution for injection in pre-filled pen
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen of 3 ml contains 300 U. 1 ml solution contains 100 U insulin aspart (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. FlexTouch.

2 x (5 x 3 ml). This is a multipack of 10 pre-filled pens and not for sale as individual pre-filled pens

5. METHOD AND ROUTES OF ADMINISTRATION

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

Use only solution if water clear, colourless 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 pen cap on in order to protect 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 NUMBER

EU/1/99/119/021

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

NovoRapid FlexTouch 100 Units/ml
Solution for injection
Insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

FlexTouch

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

NovoRapid 100 Units/ml solution for injection in vial
Insulin aspart

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 with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NovoRapid is and what it is used for

NovoRapid is a modern insulin (insulin analogue) with a rapid–acting effect. Modern insulin products are improved versions of human insulin.

NovoRapid is used to reduce the high blood sugar level in adults, adolescents and children aged 2 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. Treatment with NovoRapid helps to prevent complications from your diabetes.

NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

2. What you need to know before you use NovoRapid

Do not use NovoRapid

- ► 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).
- ► If the protective cap is loose or missing. Each vial has a protective, tamper–proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

► Check the label to make sure it is the right type of insulin.
► Remove the protective cap.
► Always use a new needle for each injection to prevent contamination.
► Needles and syringes must not be shared.

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 of your injections.

Other medicines and NovoRapid

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. 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)
- Sulphonamides (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], or salbutamol, 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 NovoRapid

► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

Ask your doctor, nurse or pharmacist for advice before taking this 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, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

NovoRapid has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

NovoRapid contains sodium

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

3. How to use NovoRapid

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.

NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to take NovoRapid

<u>If you use only one type of insulin</u>
1. Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.
2. Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.

<u>If you have to mix two types of insulin</u>
1. Just before use, roll the long–acting (cloudy) insulin between your hands until the liquid is uniformly white and cloudy.
2. Draw into the syringe the same amount of air as the dose of long–acting insulin. Inject the air into the vial containing long–acting insulin and pull out the needle.
3. Draw into the syringe the same amount of air as the dose of NovoRapid. Inject the air into the vial containing NovoRapid. Turn the vial and syringe upside down and draw up the prescribed dose of NovoRapid. Expel any air from the syringe and check that the dose is correct.
4. Push the needle into the vial of long–acting insulin, turn the vial and syringe upside down and draw out the dose you have been prescribed. Expel any air from the syringe and check the dose. Inject the mixture immediately.
5. Always mix NovoRapid and long–acting insulin in the same sequence.

How to inject NovoRapid

- ► Inject the insulin under the skin. Use the injection technique advised by your doctor or nurse.
- ► Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.
- ► Discard the needle after each injection.

For use in an infusion pump system

NovoRapid should never be mixed with any other insulin when used in a pump.
Follow the instructions and recommendations from your doctor regarding the use of NovoRapid in a pump. Before use of NovoRapid in the pump system, you must have received a comprehensive

instruction in the use and information about any actions to be taken in case of illness, too high or too low blood sugar or failure of the pump system.

- Before inserting the needle, use soap and water to clean your hands and the skin where the needle is inserted to avoid any infection at the infusion site.
- When you fill a new reservoir, be certain not to leave large air bubbles in either the syringe or the tubing.
- Changing of the infusion set (tubing and needle) must be done according to the instructions in the product information supplied with the infusion set.

To get the benefit of insulin infusion, and to detect possible malfunction of the insulin pump, it is recommended that you measure your blood sugar level regularly.

What to do in case of pump system failure

You should always have an alternative delivery method for your insulin available for injection under the skin in case of pump system failure.

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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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 vial label and carton, after 'EXP'. The expiry date refers to the last day of that month.
Keep the vial in the outer carton in order to protect it from light.

Before opening: Store in a refrigerator at 2°C to 8°C. Do not freeze.

During use or when carried as a spare: The product may be stored for a maximum of 4 weeks. Store below 30°C. Do not refrigerate or freeze.

Discard the needle after each injection.

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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each vial contains 1,000 Units of insulin aspart in 10 ml solution for injection.

- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

Pack sizes of 1 or 5 vials of 10 ml or a multipack of 5 packs of 1 x 10 ml vials. Not all pack sizes may be marketed.

The solution is water clear, colourless 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 European Medicines Agency website: http://www.ema.europa.eu.

Package leaflet: Information for the user

NovoRapid Penfill 100 Units/ml solution for injection in cartridge
Insulin aspart

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 with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NovoRapid is and what it is used for

NovoRapid is a modern insulin (insulin analogue) with a rapid–acting effect. Modern insulin products are improved versions of human insulin.

NovoRapid is used to reduce the high blood sugar level in adults, adolescents and children aged 2 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. Treatment with NovoRapid helps to prevent complications from your diabetes.

NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

2. What you need to know before you use NovoRapid

Do not use NovoRapid

- ► 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).
- ► If the cartridge or the device containing the cartridge is dropped, damaged or crushed.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

► Check the label to make sure it is the right type of insulin.
► Always check the cartridge, including the rubber plunger (stopper) 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 a result of leakage of insulin. If you suspect 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 NovoRapid Penfill must not be shared.

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 of your injections.

Other medicines and NovoRapid

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
• 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)
• Sulphonamides (used to treat infections).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
• 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], or salbutamol, 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.

<u>Pioglitazone (tablets used for the treatment of type 2 diabetes)</u>

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 NovoRapid

► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

Ask your doctor, nurse or pharmacist for advice before taking this 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, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

NovoRapid has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

NovoRapid contains sodium

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

3. How to use NovoRapid

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.

NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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
NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

- ► Do not refill the cartridge.
- ► NovoRapid Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.
- ► If you are treated with NovoRapid 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 it is lost or damaged.

How to inject NovoRapid

- ► Inject the insulin under the 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.
- ► Remove and discard the needle after each injection. Always store NovoRapid 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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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.
NovoRapid must be protected from excessive heat and light.

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

During use or when carried as a spare: NovoRapid Penfill that is being used or carried as a spare is not to 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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each cartridge contains 300 Units of insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

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

The solution is water clear, colourless 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-28002 Chartres, France.

This leaflet was last revised in

Other sources of information

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

Package leaflet: Information for the user

NovoRapid NovoLet 100 Units/ml solution for injection in pre–filled pen
Insulin aspart

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 with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NovoRapid is and what it is used for

NovoRapid is a modern insulin (insulin analogue) with a rapid–acting effect. Modern insulin products are improved versions of human insulin.

NovoRapid is used to reduce the high blood sugar level in adults, adolescents and children aged 2 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. Treatment with NovoRapid helps to prevent complications from your diabetes.

NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

2. What you need to know before you use NovoRapid

Do not use NovoRapid

- ► 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).
- ► If NovoLet is dropped, damaged or crushed.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

► 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 NovoRapid NovoLet must not be shared.

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 of your injections.

Other medicines and NovoRapid

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. 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)
- Sulphonamides (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], or salbutamol, 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 NovoRapid

► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

Ask your doctor, nurse or pharmacist for advice before taking this 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, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

NovoRapid has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

NovoRapid contains sodium

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

3. How to use NovoRapid

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.
NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to handle NovoRapid NovoLet

NovoRapid NovoLet is a pre-filled disposable pen containing insulin aspart.

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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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 NovoLet label and carton, after 'EXP'. The expiry date refers to the last day of that month.
Always keep the pen cap on your NovoLet when you are not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and light.

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

During use or when carried as a spare: NovoRapid NovoLet that is being used or carried as a spare is not to 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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each pre–filled pen contains 300 Units of insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

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

The solution is water clear, colourless 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 NovoLet.

This leaflet was last revised in

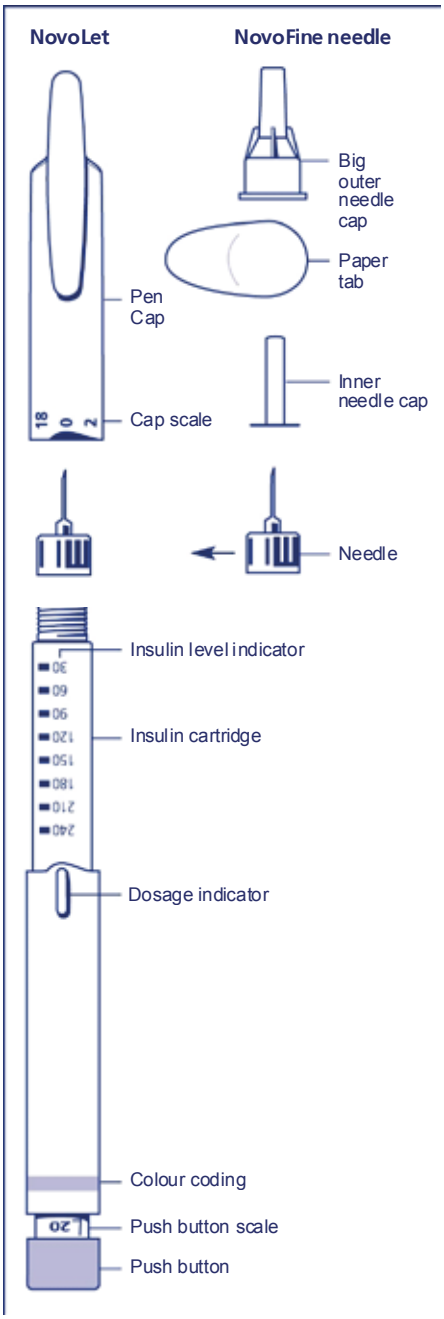
Other sources of information

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

NOVORAPID solution for injection in a pre-filled pen. NovoLet. INSTRUCTIONS FOR USE

Please read the following instructions carefully before using your NovoRapid NovoLet.

- ► Your NovoLet is a simple, compact pre–filled pen. You can dial doses from 2 to 78 units in increments of 2 units.
- ► NovoLet is designed to be used with NovoFine needles.
- ► Always carry a spare insulin delivery device in case your NovoLet is lost or damaged.

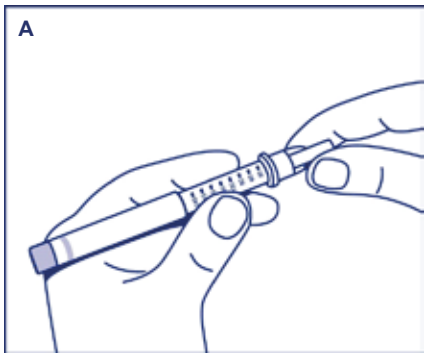


Preparing for injection

Check the label to be sure that your NovoLet contains the correct type of insulin. Take off the pen cap.

- Always use a new needle for each injection to prevent contamination.
- Take a new needle and tear off the paper tab.
- Screw the needle straight and tightly onto your NovoLet (picture **A**).
- Always use a new disposable needle for each injection. Do not bend or damage the needle before use.

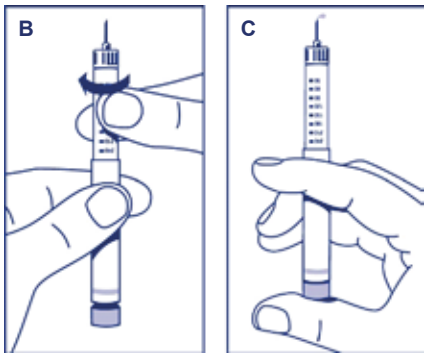
- Pull off the big outer needle cap and the inner needle cap. Do not discard the big outer needle cap.



Priming to expel air prior to each injection

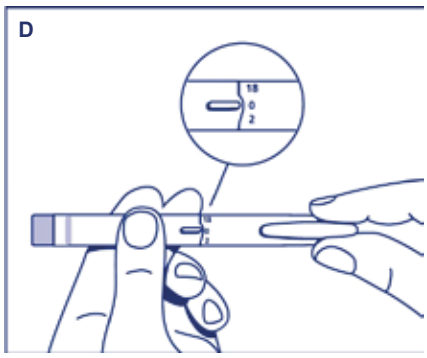
Small amounts of air may collect in the needle and cartridge during normal use.
To avoid injection of air and ensure proper dosing:
- Hold your NovoLet with the needle pointing upwards.
- Tap the cartridge gently with your finger a few times. Any air bubbles will collect at the top of the cartridge.
- Keeping the needle upwards, turn the cartridge for one click in the direction of the arrow (picture **B**).
- Still with the needle upwards, press the push–button fully down (picture **C**).
- A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

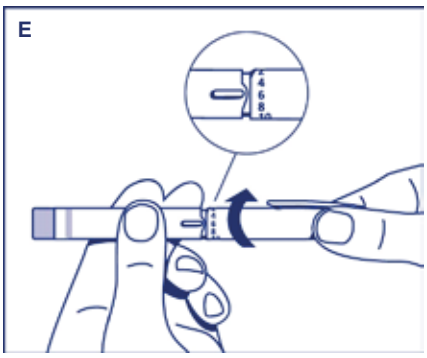
If a drop of insulin still does not appear, the device is defective and must not be used.



Setting the dose

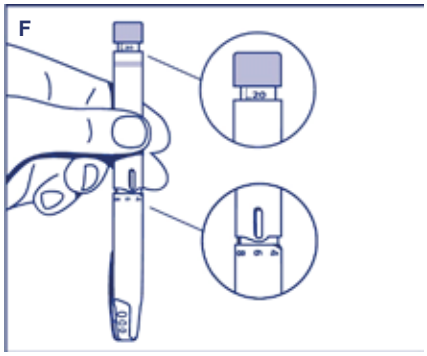
- Put the cap back on the pen, with 0 next to the dosage indicator (picture **D**).
- Check that the push–button is fully down. If it is not, turn the cap until the push–button is fully depressed.
- Hold your NovoLet horizontally. Now you are ready to set the dose you need.
- Turn the cap in the direction of the arrow (picture **E**) to set the right dose. You will feel the cap clicking, and the push–button will rise up.
- Do not put your hand over the push–button when you set the dose. If the push–button cannot rise freely, some of your insulin will be pushed out of the needle.
- The scale on the cap shows 0, 2, 4, 6, 8, 10, 12, 14, 16 and 18 units. For every click you feel when you turn the cap, you set 2 units more. The push–button also rises as you turn the cap.
- The scale under the push–button shows 20, 40 and 60 units. Every time you fully turn the cap, you set 20 units.





Dose examples

To set 8 units:
Turn the cap until **8** is opposite the dose indicator; four clicks.
To select 26 units:
Turn the cap round 1 full turn, so **0** is opposite the dose indicator again. You have now set 20 units. Keep turning the cap until **6** is opposite the dose indicator. On the push–button scale you will see a 20–line.
Add the 6 from the dose indicator to the 20 on the push–button scale. There, you have set **26** units (picture **F**).



To check a dose you set

- Note the figure on the cap next to the dose indicator.
- Note the highest figure you can see on the push–button scale.
- Add the two together to show the dose you set.
- If you have set a wrong dose, simply turn the cap forwards or backwards until you set the right number of units.

The maximum dose is 78 units

- Do not try to set a dose higher than 78 units. Otherwise insulin will leak out of the needle and the dose will be incorrect.
- If you have, by mistake, tried to set a dose over 78 units, follow these steps:
- Turn the cap back as far as you can. Turn it till the push–button is fully down and you can feel resistance.
- Then take the cap off and put it back on again, lining up the 0 next to the dosage indicator. Now set the dose again.
- Remember that 78 units is the maximum dose.
- After the dose is set, remove the cap to inject the insulin. Go straight on to *Injecting the insulin.*

Injecting the insulin

- Insert the needle into your skin. Use the injection technique advised by your doctor.
- Deliver the dose by pressing the push–button all the way in. Be careful only to push the push–button when injecting.
- Keep the push–button fully depressed after the injection until the needle has been withdrawn from the skin. The needle should remain under the skin for at least 6 seconds. This will ensure that the full dose has been delivered.

Subsequent injections

- Always check that the push–button is completely down. If not, turn the cap until the push–button is fully depressed, then proceed as described in Preparing for injection.
- You may hear a clicking sound when you press the push–button. Do not use this to set or check your dose; it may not be accurate.
- You can not set a dose higher than the number of units left in the cartridge.
- You can use the insulin level indicator to estimate how much is left. But you can not use it to set or select your dose.

Removing the needle

- Replace the big outer needle cap and unscrew the needle.
- Dispose of it carefully.

Use a new needle for each injection.
Remove and discard the needle after each injection. Always store your NovoLet without the needle attached. Otherwise the liquid may leak out which can cause inaccurate dosing.
Healthcare professionals, relatives and other carers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle injuries.
Close your NovoLet fully with 0 next to the dosage indicator.
Dispose of your used NovoLet carefully without the needle attached.
Needles and NovoRapid NovoLet must not be shared.

Maintenance

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

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

Package leaflet: Information for the user

NovoRapid FlexPen 100 Units/ml solution for injection in pre–filled pen
Insulin aspart

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 with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NovoRapid is and what it is used for

NovoRapid is a modern insulin (insulin analogue) with a rapid–acting effect. Modern insulin products are improved versions of human insulin.

NovoRapid is used to reduce the high blood sugar level in adults, adolescents and children aged 2 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. Treatment with NovoRapid helps to prevent complications from your diabetes.

NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

2. What you need to know before you use NovoRapid

Do not use NovoRapid

- ► 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).
- ► If FlexPen is dropped, damaged or crushed.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

- ► 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 NovoRapid FlexPen must not be shared.

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 of your injections.

Other medicines and NovoRapid

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. 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)
- Sulphonamides (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], or salbutamol, 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 NovoRapid

► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

Ask your doctor, nurse or pharmacist for advice before taking this 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, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

NovoRapid has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

NovoRapid contains sodium

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

3. How to use NovoRapid

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.
NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to handle NovoRapid FlexPen

NovoRapid FlexPen is a pre-filled, colour–coded, disposable pen containing insulin aspart.

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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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.
NovoRapid must be protected from excessive heat and light.

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

During use or when carried as a spare: NovoRapid FlexPen that is being used or carried as a spare is not to 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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each pre–filled pen contains 300 Units of insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

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 solution is water clear, colourless 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-28002 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 European Medicines Agency website: http://www.ema.europa.eu.

NOVORAPID solution for injection in a pre–filled pen. FlexPen. INSTRUCTIONS FOR USE

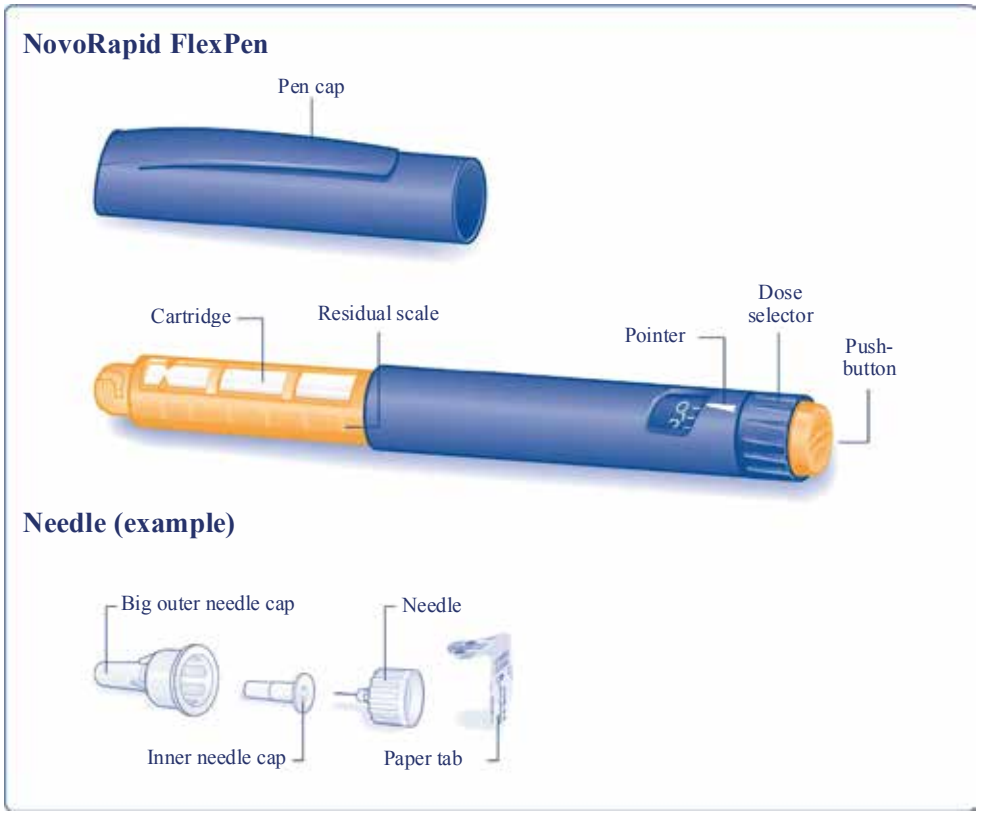
Please read the following instructions carefully before using your NovoRapid FlexPen.

Your FlexPen is a unique dial–a–dose insulin pen.

► You can select doses from 1 to 60 units in increments of 1 unit.

► FlexPen is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.

► Always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



Maintenance

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

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

► **Do not refill your FlexPen.**

Preparing your NovoRapid FlexPen

Check the label to make sure that your FlexPen contains the correct type of insulin.

A
Pull off the pen cap.

B
Take a new needle and tear off the paper tab.

Screw the needle straight and tightly onto your FlexPen.

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

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

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

Checking the insulin flow

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

E
Turn the dose selector to select 2 units.

F
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.

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

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

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

Selecting your dose

Check that the dose selector is set at 0.

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

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

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

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

Making the injection

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

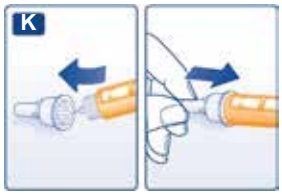
I
Inject the dose by pressing the push–button all the way in until 0 lines up with the pointer. Be careful only to push the push–button when injecting.

Turning the dose selector will not inject insulin.

J
► 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.

K
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.



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

Package leaflet: Information for the user

NovoRapid InnoLet 100 Units/ml solution for injection in pre–filled pen
Insulin aspart

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 with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What NovoRapid is and what it is used for

NovoRapid is a modern insulin (insulin analogue) with a rapid–acting effect. Modern insulin products are improved versions of human insulin.

NovoRapid is used to reduce the high blood sugar level in adults, adolescents and children aged 2 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. Treatment with NovoRapid helps to prevent complications from your diabetes.

NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

2. What you need to know before you use NovoRapid

Do not use NovoRapid

- ► 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).
- ► If InnoLet is dropped, damaged or crushed.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

► 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 NovoRapid InnoLet must not be shared.

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 of your injections.

Other medicines and NovoRapid

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. 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)
- Sulphonamides (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], or salbutamol, 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 NovoRapid

► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

Ask your doctor, nurse or pharmacist for advice before taking this 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, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

NovoRapid has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

NovoRapid contains sodium

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

3. How to use NovoRapid

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.

NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to handle NovoRapid InnoLet

NovoRapid InnoLet is a pre-filled disposable pen containing insulin aspart.

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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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 InnoLet label and carton, after 'EXP'. The expiry date refers to the last day of that month.
Always keep the pen cap on your InnoLet when you are not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and light.

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

During use or when carried as a spare: NovoRapid InnoLet that is being used or carried as a spare is not to 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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each pre–filled pen contains 300 Units of insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

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

The solution is water clear, colourless 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 InnoLet.

This leaflet was last revised in

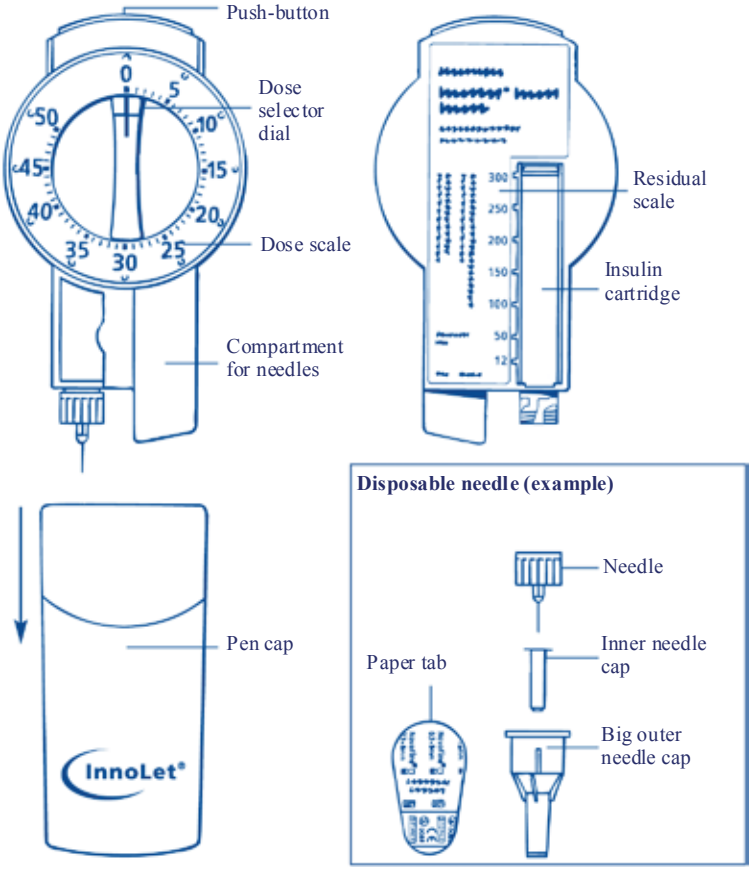
Other sources of information

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

NOVORAPID solution for injection in a pre–filled pen. InnoLet. INSTRUCTIONS FOR USE

Please read the following instructions carefully before using your NovoRapid InnoLet.

- ► Your InnoLet is a simple, compact pre–filled pen able to deliver 1 to 50 units in increments of 1 unit.
- ► InnoLet 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 InnoLet is lost or damaged.

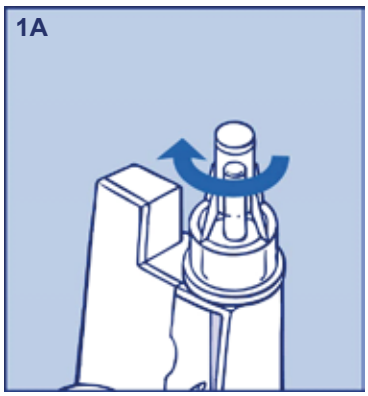


Preparing for injection

Check the label to be sure that your InnoLet contains the correct type of insulin.
Take off the pen cap (as shown by the arrow).

Attaching the needle

- Always use a new needle for each injection to prevent contamination.
- Take a new needle and tear off the paper tab.
- Screw the needle straight and tightly onto your InnoLet (picture **1A**).
- Always use a new disposable needle for each injection. Do not bend or damage the needle before use.
- Pull off the big outer needle cap and the inner needle cap. You may want to store the big outer needle cap in the compartment.

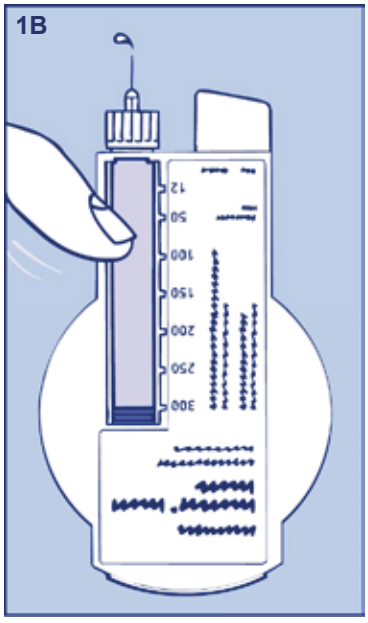


Priming to expel air prior to each injection

Small amounts of air may collect in the needle and cartridge during normal use.
To avoid injection of air and ensure proper dosing:

- Dial 2 units by turning the dose selector clockwise.
- Hold your InnoLet with the needle upwards and tap the cartridge gently with your finger a few times (picture **1B**) to make any air bubbles collect at the top of the cartridge.
- Keeping the needle upwards, press the push–button and the dose selector returns to 0.
- A drop of insulin should appear at the needle tip (picture **1B**). If not, change the needle and repeat the procedure no more than 6 times.

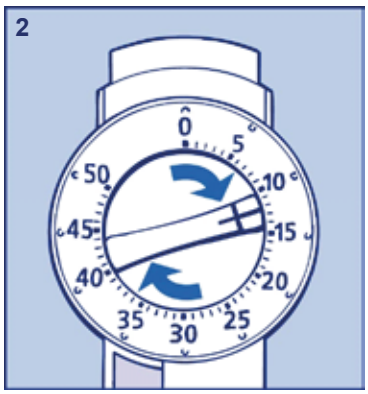
If a drop of insulin still does not appear, the device is defective and must not be used.



Setting the dose

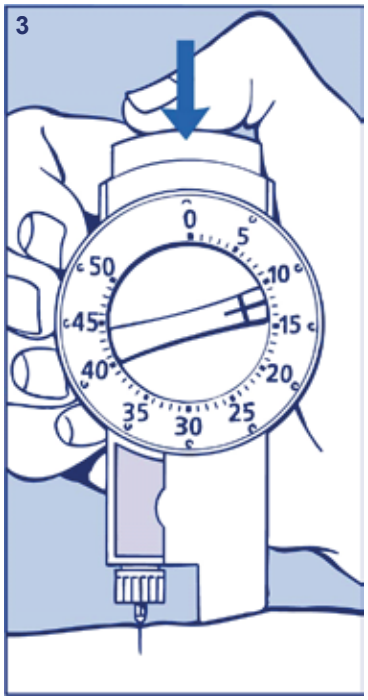
- Always check that the push–button is fully depressed and the dose selector is set to 0.
- Dial the number of units required by turning the dose selector clockwise (picture **2**). Do not use the residual scale to measure your dose of insulin.
- You will hear a click for every single unit dialled. The dose can be corrected by turning the dial either way. Do not turn the dial to correct the dose when the needle is inserted in the skin.

You cannot set a dose larger than the number of units remaining in the cartridge.



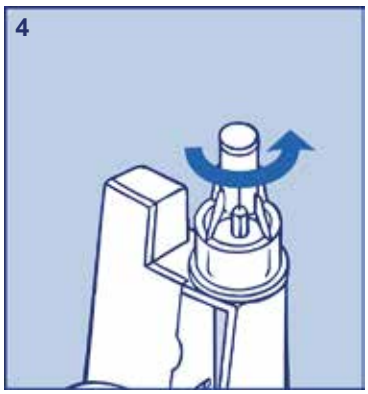
Injecting the insulin

- Insert the needle into your skin. Use the injection technique advised by your doctor.
- Deliver the dose by pressing the push–button fully down (picture **3**). You will hear clicks as the dose selector returns to 0.
- After the injection, the needle should remain under the skin for **at least 6 seconds** to ensure that the full dose has been delivered.
- Make sure not to block the dose selector while injecting, as the dose selector must be allowed to return to 0 when you press the push–button.



Removing the needle

- Replace the big outer needle cap and unscrew the needle (picture **4**). Dispose of it carefully.



Use a new needle for each injection.
Remove and discard the needle after each injection. Always store your InnoLet without the needle attached. Otherwise the liquid may leak out which can cause inaccurate dosing.
Healthcare professionals, relatives and other carers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Dispose of your used InnoLet carefully without the needle attached.
Needles and NovoRapid InnoLet must not be shared.

Maintenance

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

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

Package leaflet: Information for the user

NovoRapid FlexTouch 100 Units/ml solution for injection in pre–filled pen
Insulin aspart

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.
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NovoRapid will start to lower your blood sugar 10–20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3–5 hours. Due to this short action NovoRapid should normally be taken in combination with intermediate–acting or long–acting insulin preparations. Moreover NovoRapid can be used for continuous infusion in a pump system.

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Do not use NovoRapid

- ► 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).
- ► If FlexTouch is dropped, damaged or crushed.
- ► If it has not been stored correctly or been frozen (see section 5, How to store NovoRapid).
- ► If the insulin does not appear water clear, colourless, and aqueous.

If any of these applies, do not use NovoRapid. Talk with your doctor, nurse or pharmacist for advice.

Before using NovoRapid

► 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 NovoRapid FlexTouch must not be shared.

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.
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- Anabolic steroids (such as testosterone)
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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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► 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. NovoRapid can be used during 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 NovoRapid during breast–feeding.

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► Please ask your doctor whether you can drive a car or operate a machine:
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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.

NovoRapid 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, NovoRapid 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.

Use in children and adolescents

NovoRapid can be used in children instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

No clinical studies with NovoRapid have been carried out in children under the age of 2 years. Therefore only use NovoRapid in children below this age, if your doctor have specifically told you to.

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

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary NovoRapid can be given directly into a vein but this must only be done by healthcare professionals.

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), the upper arm or the front of your thighs. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to handle NovoRapid FlexTouch

NovoRapid FlexTouch is a pre-filled, colour–coded, disposable pen containing insulin aspart.

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 NovoRapid in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heart beat; 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 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 symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such a low blood sugar that makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with 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 (become 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 due to risk of suffocation.

Serious allergic reactions to NovoRapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affact 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 heart beat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

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, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

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

Changes at the injection site (lipodystrophy): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the

injection site, tell your doctor or nurse. These reactions can become more severe, or they may change the absorption of your insulin, if you inject in such a site.

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

If you get any side effects, talk with your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject 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 NovoRapid

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 FlexTouch label and carton, after 'EXP'. The expiry date refers to the last day of that month.
Always keep the pen cap on your FlexTouch when you are not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and light.

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

During use or when carried as a spare: NovoRapid FlexTouch that is being used or carried as a spare is not to 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 NovoRapid contains

- The active substance is insulin aspart. Each ml contains 100 Units of insulin aspart. Each pre–filled pen contains 300 Units of insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What NovoRapid looks like and contents of the pack

NovoRapid is presented as a solution for injection.

Pack sizes of 1 (with or without needles) or 5 (without needles) or a multipack with 2 x 5 (without needles) pre–filled pens of 3 ml. Not all pack sizes may be marketed.

The solution is water clear, colourless 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 FlexTouch.

This leaflet was last revised in

Other sources of information

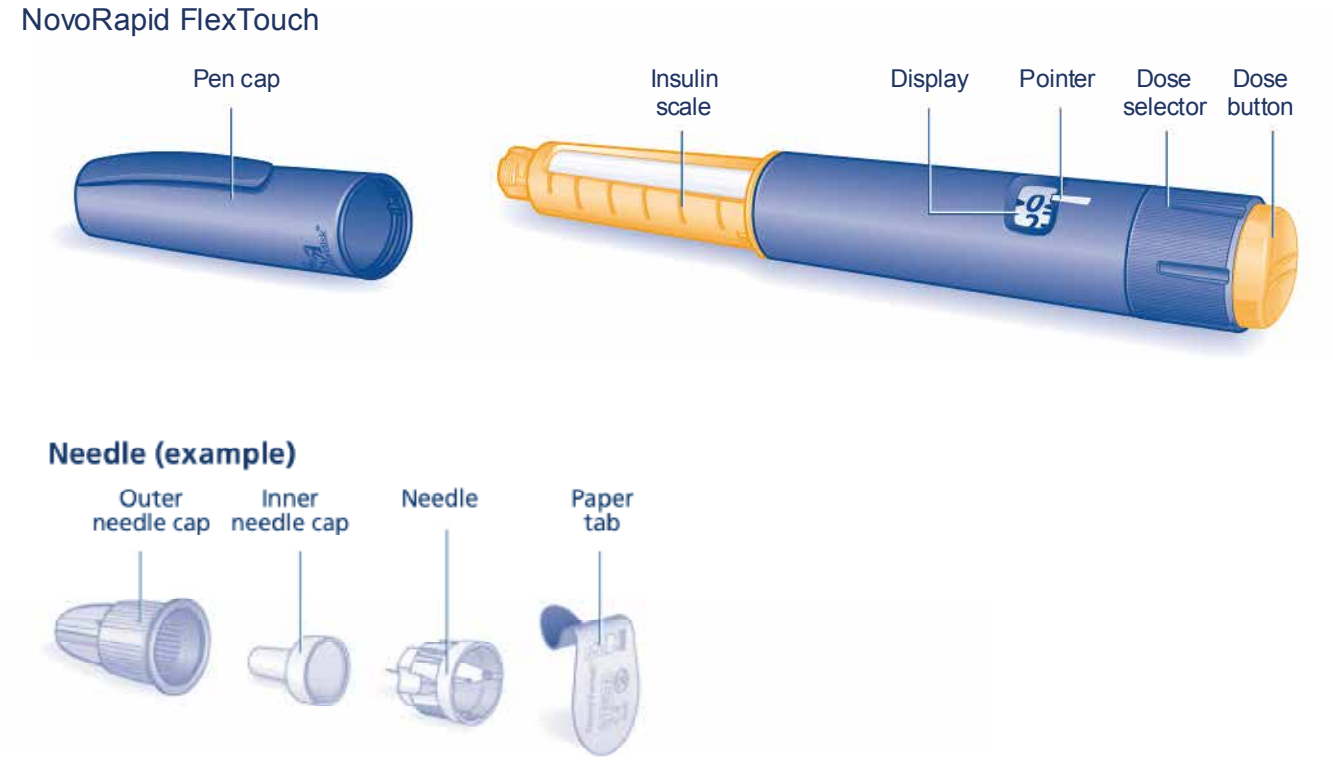
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

Instructions on how to use NovoRapid FlexTouch

Please read these instructions carefully before using your NovoRapid FlexTouch pen. Use the coloured label to make sure that your FlexTouch pen contains the type of insulin you need.

Your NovoRapid FlexTouch pen is an easy–to–use pre–filled insulin pen with a light–touch dose button.

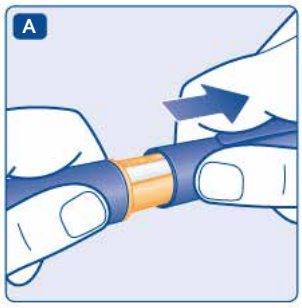
NovoRapid FlexTouch contains 300 units of insulin and delivers doses from 1 to 80 units, in increments of 1 unit. NovoRapid FlexTouch is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.



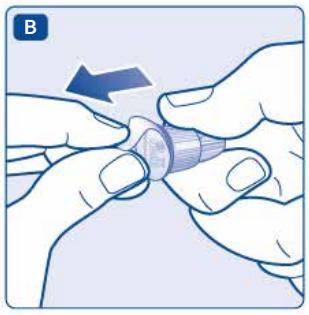
Preparing your NovoRapid FlexTouch pen

Check the coloured label on your NovoRapid FlexTouch pen to make sure that it contains the type of insulin you need.

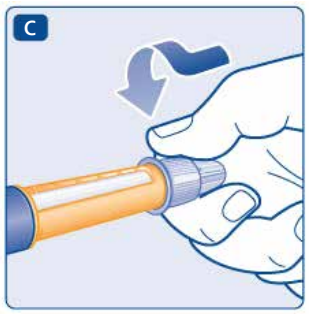
A Pull off the pen cap.



B Take a new disposable needle and tear off the paper tab.



C Screw the needle straight onto the pen. Make sure the needle is on tight.

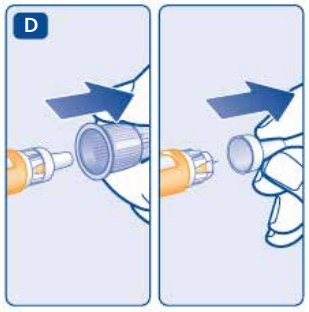


D Pull off the outer needle cap and save it.
You will need it after the injection, to safely remove the needle from the pen.

Pull off the inner needle cap and throw it away.

If you try to put it back on, you may accidentally hurt yourself with the needle.

A drop of insulin may appear at the needle tip. This is normal.

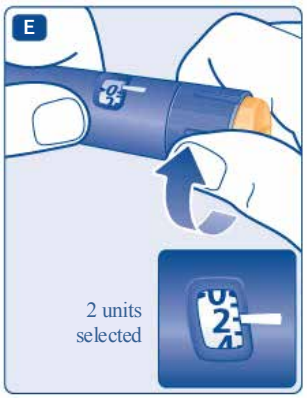


- Always use a new needle for each injection as this will prevent contamination and blocked needles.
- Never bend or damage the needle.

Checking the insulin flow

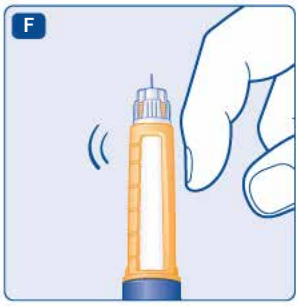
Make sure that you receive your full dose by always checking the insulin flow before you select and inject your dose.

E Turn the dose selector to select 2 units.



F Hold the pen with the needle pointing up.

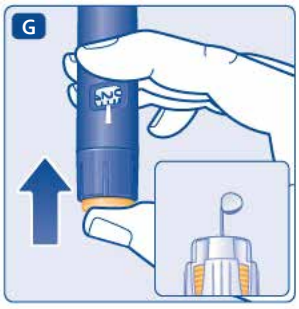
Tap the top of the pen a few times to let any air bubbles rise to the top.



G Press the dose button with your thumb until the display returns to zero. The figure 0 lines up with the pointer. A drop of insulin will appear at the needle tip.

If no drop appears, repeat steps **E** to **G** up up to 6 times. If no drop appears after these new attempts, change the needle and repeat steps **E** to **G** once more.

Do not use the pen if a drop of insulin still does not appear.



- Always make sure that a drop appears at the needle tip before you inject.

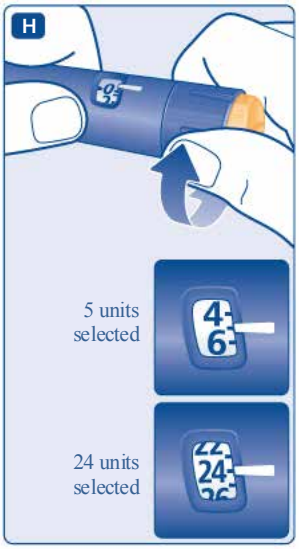
Selecting your dose

Use the dose selector on your NovoRapid FlexTouch pen to ensure exact and easy dose selection. You can select up to 80 units per dose.

H Select the dose you need. You can turn the dose selector forwards or backwards. Stop when the right number of units lines up with the pointer.

The dose selector clicks differently when turned forwards, backwards or past the number of units left.

When the pen contains less than 80 units, the display stops at the number of units left.



- How much insulin is left?

  You can use the insulin scale to see approximately how much insulin is left in the pen.

  You can use the display to see exactly how much insulin is left – if the pen contains less than 80 units: Turn the dose selector until the display stops. The figure that lines up with the pointer shows how many units are left.

- Never use the pen clicks to count the number of units you **select**. Only the display and pointer will indicate the exact number of units.

- Never use the insulin scale to measure how much insulin to inject. Only the display and pointer will indicate the exact number of units.

Injecting your dose

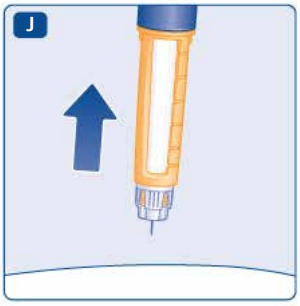
Make sure that you receive your full dose by using the right injection technique.

I Insert the needle into your skin as your doctor or nurse has shown you. Make sure you can see the display. Press the dose button until the display returns to zero. The figure 0 lines up with the pointer, and you may hear or feel a click.

- After the display has returned to zero, leave the needle under the skin for **at least 6 seconds** to make sure that you get your full dose.

J Remove the needle from the skin.

After that, you may see a drop of insulin at the needle tip. This is normal and has no effect on the dose you just received.

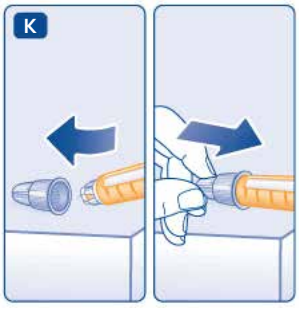


- Remove and discard the needle after each injection to prevent blocked needles. If the needle is blocked, you will **not** receive your full dose.

K Lead the needle tip into the outer needle cap on a flat surface. Do not touch the needle or the cap.

Once the needle is covered, carefully push the outer needle cap completely on and then unscrew the needle. Dispose of it carefully, and put the pen cap back on after every use.

When the pen is empty, throw it away without a needle on as instructed by your doctor, nurse, pharmacist or local authorities.



- Never use the pen clicks to count the number of units you **inject**. Only the display and pointer will indicate the exact number of units.

- Never touch the display when you inject, as this can block the injection.
- Never put the inner needle cap back on once you have removed it from the needle. This reduces the risk of hurting yourself with the needle.
- Always store the pen without a needle attached. This prevents contamination, infection and leakage of insulin and ensures accurate dosing.

Caring for your NovoRapid FlexTouch pen

Your NovoRapid FlexTouch pen is accurate and safe to use. However, you must take care of it:

- Do not drop your pen or knock it against hard surfaces. If you do drop it or suspect that something is wrong with it, always screw on a new disposable needle and check the insulin flow before you inject.
- Do not try to refill your pen – it is pre–filled.
- Do not try to repair your pen or pull it apart.
- Do not expose your pen to dust, dirt or any kind of liquid.
- Do not try to wash, soak or lubricate your pen. If necessary, clean it with a mild detergent on a moistened cloth.
- See section 5, How to store NovoRapid in this leaflet for information on how to store your pen.
- **Important information**
- Always carry an extra NovoRapid FlexTouch in case you lose or damage your current pen. Also carry new disposable needles.
- Always keep your pen and needles out of reach of others, especially children.
- Needles and NovoRapid FlexTouch must not be shared.
- Caregivers should be most careful when handling used needles to avoid hurting themselves.