ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 U/ml, solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart* ..... 100 U/ml

* produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with diabetes mellitus.

4.2 Posology and method of administration

NovoRapid has a faster onset and a shorter duration of action than soluble human insulin.
Due to the faster onset of action, NovoRapid should generally be given immediately before the meal. When necessary NovoRapid can be given soon after the meal.

Dosage of NovoRapid is individual and determined on the basis of the physician's advice in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin given at least once a day.

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

NovoRapid is administered subcutaneously by injection in the abdominal wall, the thigh, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. 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. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity. As with all insulins, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. However, the faster onset of action compared to soluble human insulin is maintained regardless of injection site.

If necessary, NovoRapid may also be administered intravenously (see section 6.6) which should be carried out by health care professionals.

NovoRapid may be used for Continuous Subcutaneous Insulin Infusion (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.

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 alternative insulin available in case of pump system failure.

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

No studies have been performed in children under the age of 2 years.

NovoRapid can be used in children in preference to soluble insulin human when a rapid onset of action might be beneficial. For example, in the timing of the injections in relation to meals.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to insulin aspart or to any of the excipients.

4.4 Special warnings and special precautions for use

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

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.

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.

NovoRapid should be administered in immediate relation to a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

Concomitant illness, especially infections, usually increases the patient’s insulin requirements.

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

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage. Patients taking NovoRapid may require an increased number of daily injections or a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

NovoRapid contains metacresol, which in rare cases may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral hypoglycaemic agents (OHAs), octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

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

Beta-blocking agents may mask the symptoms of hypoglycaemia.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There is limited clinical experience with NovoRapid in pregnancy.

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

Intensified monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

There are no restrictions on treatment with NovoRapid during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid dosage may need to be adjusted.

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 in order to avoid hypoglycaemia whilst 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

Adverse drug reactions observed in patients using NovoRapid are mainly dose-dependent and due to the pharmacologic effect of insulin. As for other insulin products, hypoglycaemia, in general is the most frequently occurring undesirable effect. 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.

In clinical trials and during marketed use the frequency varies with patient population and dose regimens therefore no specific frequency can be presented. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to insulin aspart are listed below. The frequencies are defined as: Uncommon (> 1/1,000, < 1/100) and rare (> 1/10,000, < 1/1,000). Isolated spontaneous cases are presented as very rare defined as (< 1/10,000).

Immune system disorders
Uncommon - Urticaria, rash, eruptions

Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Rare - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders
Uncommon - Refraction disorder
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon - Local hypersensitivity
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions
Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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 requirements are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carry sugar containing products
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulins and analogues, fast-acting. ATC code A10AB05.

The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells - and simultaneously inhibit the output of glucose 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.

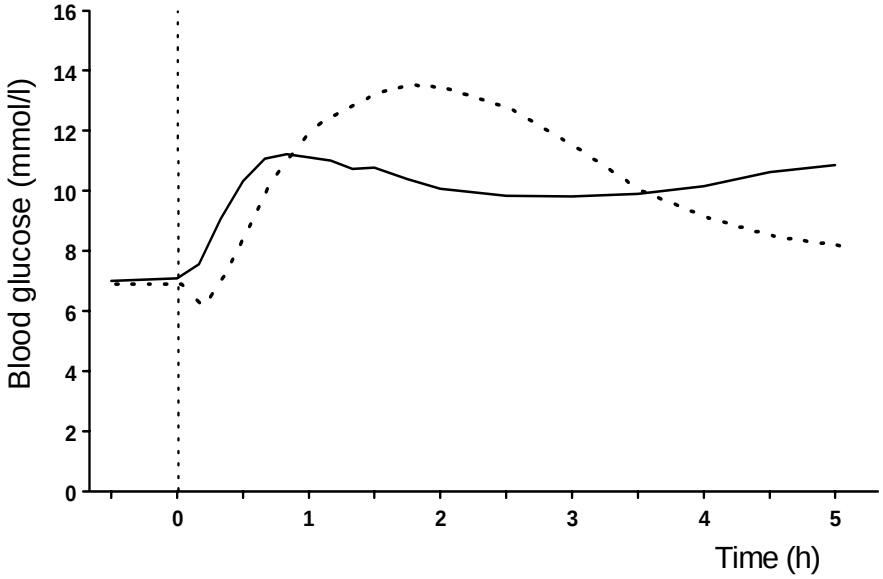

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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.

Adults. 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.

Children and adolescents. 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.

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.

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

5.2 Pharmacokinetic properties

In NovoRapid substitution of the 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.

The pharmacokinetics has not been investigated in elderly or patients with impaired renal or liver function.

Children and adolescents. 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

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. Acute, one month and twelve months toxicity studies produced no toxicity findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid and/or Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to the insulin may cause degradation of the insulin, e.g. if the medicinal product contains thiol or sulphites.

6.3 Shelf life

30 months.

The in-use shelf life is 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
In order to protect from light keep the container in the outer carton.

Vials in use or carried as a spare: Do not refrigerate. Do not store above 30°C.

6.5 Nature and contents of container

Glass vial (Type 1) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of solution.

Cartons of 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

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

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.

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.

NovoRapid should not be used if it does not appear clear and colourless.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 7 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart∗ ..... 100 U/ml

∗ produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with diabetes mellitus.

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NovoRapid has a faster onset and a shorter duration of action than soluble human insulin.
Due to the faster onset of action, NovoRapid should generally be given immediately before the meal. When necessary NovoRapid can be given soon after a meal.

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

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

No studies have been performed in children under the age of 2 years.

NovoRapid can be used in children in preference to soluble insulin human when a rapid onset of action might be beneficial. For example, in the timing of injections in relation to meals.

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Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

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Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There is limited clinical experience with NovoRapid in pregnancy.

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

Intensified monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

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Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon - Local hypersensitivity
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions
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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:

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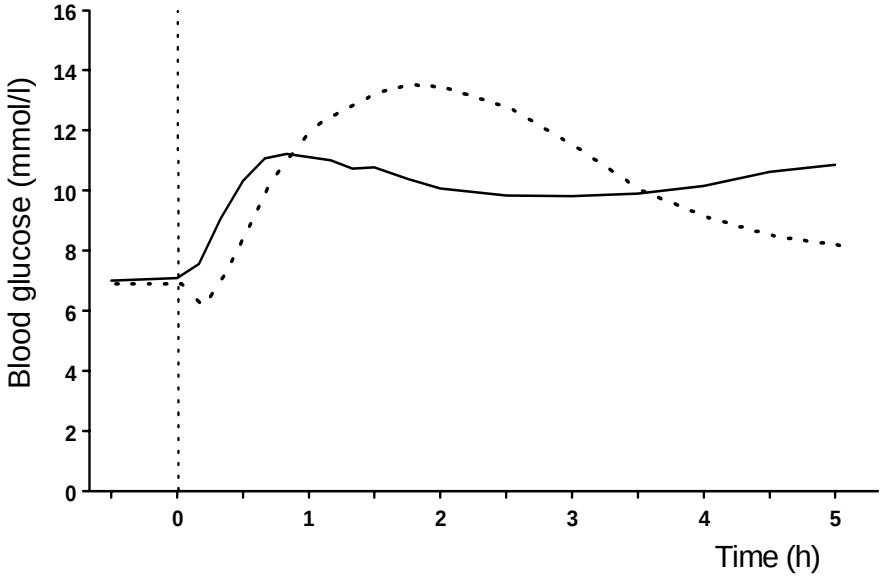
NovoRapid produces a more rapid onset of action compared to soluble human insulin, together with a lower glucose concentration, as assessed within the first four hours after a meal. NovoRapid has a shorter duration of action compared to soluble human insulin after subcutaneous injection.



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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.

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

5.2 Pharmacokinetic properties

In NovoRapid substitution of the amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid Penfill 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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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. Acute, one month and twelve months toxicity studies produced no toxicity findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid and/or Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to the insulin may cause degradation of the insulin, e.g. if the medicinal product contains thiol or sulphites.

6.3 Shelf life

30 months.

The in-use shelf life is 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
In order to protect from light keep the container in the outer carton.

NovoRapid Penfill in use or carried as a spare: Do not refrigerate. Do not store above 30°C.

6.5 Nature and contents of container

A glass (Type 1) cartridge which contains a piston (bromobutyl rubber) and is closed with a disc (bromobutyl/polyisoprene rubber) containing 3 ml of solution.

Cartons of 5 or 10 cartridges.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

NovoRapid Penfill should only be used in combination with products that are compatible with them and allow the Penfill to function safely and effectively.

NovoRapid Penfill is for use by one person only. The cartridge must not be refilled.

NovoRapid Penfill is designed to be used with the Novo Nordisk insulin delivery system and NovoFine needles.

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.

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.

NovoRapid should not be used if it does not appear clear and colourless.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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: 7 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart* ..... 100 U/ml

* produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with diabetes mellitus.

4.2 Posology and method of administration

NovoRapid has a faster onset and a shorter duration of action than soluble human insulin.
Due to the faster onset of action, NovoRapid should generally be given immediately before the meal. When necessary NovoRapid can be given soon after the meal.

Dosage of NovoRapid is individual and determined on the basis of the physician's advice in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin given at least once a day.

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

NovoRapid is administered subcutaneously in the abdominal wall, the thigh, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. 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. As with all insulins the duration of action will vary according to the dose, injection site, blood flow, temperature and the level of physical activity. As with all insulins, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. However, the faster onset of action compared to soluble human insulin is maintained regardless of injection site.

If necessary, NovoRapid may also be administered intravenously (see section 6.6) which should be carried out by health care professionals.

NovoRapid may be used for Continuous Subcutaneous Insulin Infusion (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.

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 alternative insulin available in case of pump system failure.

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

No studies have been performed in children under the age of 2 years.

NovoRapid can be used in children in preference to soluble insulin human when a rapid onset of action might be beneficial. For example, in the timing of the injections in relation to meals.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to insulin aspart or to any of the excipients.

4.4 Special warnings and special precautions for use

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

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.

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.

NovoRapid should be administered in immediate relation to a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

Concomitant illness, especially infections, usually increases the patient’s insulin requirements.

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

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage. Patients taking NovoRapid may require an increased number of daily injections or a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

NovoRapid contains metacresol, which in rare cases may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral hypoglycaemic agents (OHAs), octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

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

Beta-blocking agents may mask the symptoms of hypoglycaemia.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There is limited clinical experience with NovoRapid in pregnancy.

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

Intensified monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

There are no restrictions on treatment with NovoRapid during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid dosage may need to be adjusted.

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 in order to avoid hypoglycaemia whilst 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

Adverse drug reactions observed in patients using NovoRapid are mainly dose-dependent and due to the pharmacologic effect of insulin. As for other insulin products, hypoglycaemia, in general is the most frequently occurring undesirable effect. 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.

In clinical trials and during marketed use the frequency varies with patient population and dose regimens therefore no specific frequency can be presented. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to insulin aspart are listed below. The frequencies are defined as: Uncommon (> 1/1,000, < 1/100) and rare (> 1/10,000, < 1/1,000). Isolated spontaneous cases are presented as very rare defined as (< 1/10,000).

Immune system disorders
Uncommon - Urticaria, rash, eruptions

Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Rare - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders
Uncommon - Refraction disorder
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon - Local hypersensitivity
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions
Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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 requirements are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carry sugar containing products
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulins and analogues, fast-acting. ATC code A10AB05.

The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells - and simultaneously inhibit the output of glucose 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.

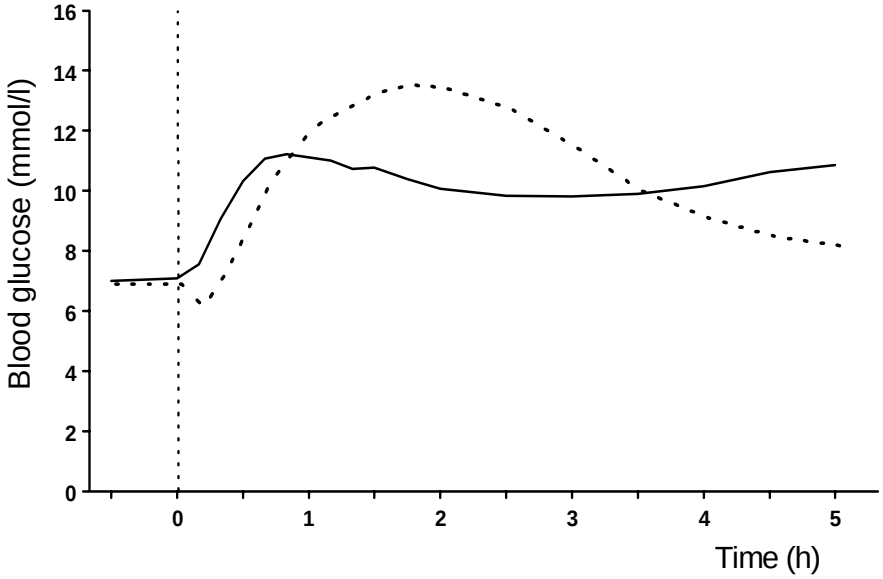

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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.

Adults. 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.

Children and adolescents. 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.

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.

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

5.2 Pharmacokinetic properties

In NovoRapid substitution of the amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. NovoRapid NovoLet 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.

The pharmacokinetics has not been investigated in elderly or patients with impaired renal or liver function.

Children and adolescents. 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

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. Acute, one month and twelve months toxicity studies produced no toxicity findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid and /or Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to the insulin may cause degradation of the insulin, e.g. if the medicinal product contains thiol or sulphites.

6.3 Shelf life

30 months.

The in-use shelf life is 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
In order to protect from light keep the cap on when NovoRapid NovoLet is not in use.

NovoRapid NovoLet in use or carried as a spare: Do not refrigerate. Do not store above 30°C.

6.5 Nature and contents of container

A glass (Type 1) cartridge which contains a piston (bromobutyl rubber) and is closed with a disc (bromobutyl/polyisoprene rubber) containing 3 ml of solution in a multidose disposable pre-filled pen with a pen injector (plastic).

Cartons of 5 or 10 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

NovoRapid NovoLet should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

NovoRapid NovoLet is for use by one person only. NovoRapid NovoLet must not be refilled.

NovoFine needles are designed to be used with NovoRapid NovoLet.

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.

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.

NovoRapid should not be used if it does not appear clear and colourless.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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: 7 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart* ..... 100 U/ml

* produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with diabetes mellitus.

4.2 Posology and method of administration

NovoRapid has a faster onset and a shorter duration of action than soluble human insulin.
Due to the faster onset of action, NovoRapid should generally be given immediately before the meal. When necessary NovoRapid can be given soon after the meal.

Dosage of NovoRapid is individual and determined on the basis of the physician's advice in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin given at least once a day.

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

NovoRapid is administered subcutaneously in the abdominal wall, the thigh, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. 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. As with all insulins the duration of action will vary according to the dose, injection site, blood flow, temperature and the level of physical activity. As with all insulins, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. However, the faster onset of action compared to soluble human insulin is maintained regardless of injection site.

If necessary, NovoRapid may also be administered intravenously (see section 6.6) which should be carried out by health care professionals.

NovoRapid may be used for Continuous Subcutaneous Insulin Infusion (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.

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 alternative insulin available in case of pump system failure.

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

No studies have been performed in children under the age of 2 years.

NovoRapid can be used in children in preference to soluble insulin human when a rapid onset of action might be beneficial. For example, in the timing of the injections in relation to meals.

FlexPen are pre-filled pens designed to be used with NovoFine short cap needles. The needle box is marked with an **S**. FlexPen delivers 1-60 units in increments of 1 unit. Detailed instruction accompanying the device must be followed.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to insulin aspart or to any of the excipients.

4.4 Special warnings and special precautions for use

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

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.

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.

NovoRapid should be administered in immediate relation to a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

Concomitant illness, especially infections, usually increases the patient’s insulin requirements.

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

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage. Patients taking NovoRapid may require an increased number of daily injections or a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

NovoRapid contains metacresol, which in rare cases may cause allergic reactions.

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 hypoglycaemic agents (OHAs), octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

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

Beta-blocking agents may mask the symptoms of hypoglycaemia.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There is limited clinical experience with NovoRapid in pregnancy.

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

Intensified monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

There are no restrictions on treatment with NovoRapid during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid dosage may need to be adjusted.

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 in order to avoid hypoglycaemia whilst 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

Adverse drug reactions observed in patients using NovoRapid are mainly dose-dependent and due to the pharmacologic effect of insulin. As for other insulin products, hypoglycaemia, in general is the most frequently occurring undesirable effect. 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.

In clinical trials and during marketed use the frequency varies with patient population and dose regimens therefore no specific frequency can be presented. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to insulin aspart are listed below. The frequencies are defined as: Uncommon (> 1/1,000, < 1/100) and rare (> 1/10,000, < 1/1,000). Isolated spontaneous cases are presented as very rare defined as (< 1/10,000).

Immune system disorders
Uncommon - Urticaria, rash, eruptions

Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Rare - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders
Uncommon - Refraction disorder
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon - Local hypersensitivity
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions
Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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 requirements are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carry sugar containing products
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the

patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulins and analogues, fast-acting. ATC code A10AB05.

The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells - and simultaneously inhibit the output of glucose 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.

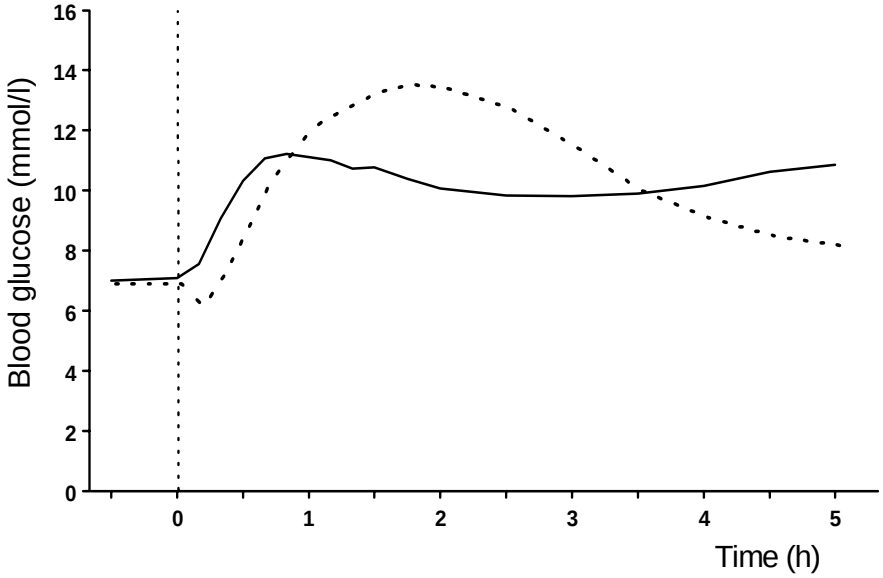

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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.

Adults. 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

Children and adolescents. 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.

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.

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

5.2 Pharmacokinetic properties

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 FlexPen 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.

The pharmacokinetics has not been investigated in elderly or patients with impaired renal or liver function.

Children and adolescents. 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

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. Acute, one month and twelve months toxicity studies produced no toxicity findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid and/or Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to the insulin may cause degradation of the insulin, e.g. if the medicinal product contains thiol or sulphites.

6.3 Shelf life

30 months.

The in-use shelf life is 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
In order to protect from light keep the cap on when NovoRapid FlexPen is not in use.

NovoRapid FlexPen in use or carried as a spare: Do not refrigerate. Do not store above 30°C.

6.5 Nature and contents of container

A glass (Type 1) cartridge which contains a piston (bromobutyl rubber) and is closed with a disc (bromobutyl/polyisoprene rubber) containing 3 ml of solution in a multidose disposable pre-filled pen with a pen injector (plastic).

Cartons of 1, 5 or 10 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

NovoRapid FlexPen should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

NovoRapid FlexPen is for use by one person only. NovoRapid FlexPen must not be refilled.

NovoFine **S** needles are designed to be used with NovoRapid FlexPen.

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.

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.

NovoRapid should not be used if it does not appear clear and colourless.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 1999
Date of last renewal: 7 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart* ..... 100 U/ml

* produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with diabetes mellitus.

4.2 Posology and method of administration

NovoRapid has a faster onset and a shorter duration of action than soluble human insulin.
Due to the faster onset of action, NovoRapid should generally be given immediately before the meal. When necessary NovoRapid can be given soon after the meal.

Dosage of NovoRapid is individual and determined on the basis of the physician's advice in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin given at least once a day.

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

NovoRapid is administered subcutaneously in the abdominal wall, the thigh, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. 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. As with all insulins the duration of action will vary according to the dose, injection site, blood flow, temperature and the level of physical activity. As with all insulins, subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites. However, the faster onset of action compared to soluble human insulin is maintained regardless of injection site.

If necessary, NovoRapid may also be administered intravenously (see section 6.6) which should be carried out by health care professionals.

NovoRapid may be used for Continuous Subcutaneous Insulin Infusion (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.

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 alternative insulin available in case of pump system failure.

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

No studies have been performed in children under the age of 2 years.

NovoRapid can be used in children in preference to soluble insulin human when a rapid onset of action might be beneficial. For example, in the timing of injections in relation to meals.

InnoLet are pre-filled pens designed to be used with NovoFine short cap needles. The needle box is marked with an **S**. InnoLet delivers 1-50 units in increments of 1 unit. Detailed instruction accompanying the device must be followed.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to insulin aspart or to any of the excipients.

4.4 Special warnings and special precautions for use

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

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.

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.

NovoRapid should be administered in immediate relation to a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

Concomitant illness, especially infections, usually increases the patient’s insulin requirements.

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

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage. Patients taking NovoRapid may require an increased number of daily injections or a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

NovoRapid contains metacresol, which in rare cases may cause allergic reactions.

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 hypoglycaemic agents (OHAs), octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

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

Beta-blocking agents may mask the symptoms of hypoglycaemia.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There is limited clinical experience with NovoRapid in pregnancy.

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

Intensified monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

There are no restrictions on treatment with NovoRapid during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoRapid dosage may need to be adjusted.

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 in order to avoid hypoglycaemia whilst 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

Adverse drug reactions observed in patients using NovoRapid are mainly dose-dependent and due to the pharmacologic effect of insulin. As for other insulin products, hypoglycaemia, in general is the most frequently occurring undesirable effect. 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.

In clinical trials and during marketed use the frequency varies with patient population and dose regimens therefore no specific frequency can be presented. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgment are considered related to insulin aspart are listed below. The frequencies are defined as: Uncommon (> 1/1,000, < 1/100) and rare (> 1/10,000, < 1/1,000). Isolated spontaneous cases are presented as very rare defined as (< 1/10,000).

Immune system disorders
Uncommon - Urticaria, rash, eruptions

Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Rare - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders
Uncommon - Refraction disorder
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon - Local hypersensitivity
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions
Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

4.9 Overdose

A specific overdose of 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 constantly carry sugar containing products
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the

patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulins and analogues, fast-acting. ATC code A10AB05.

The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells - and simultaneously inhibit the output of glucose 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.

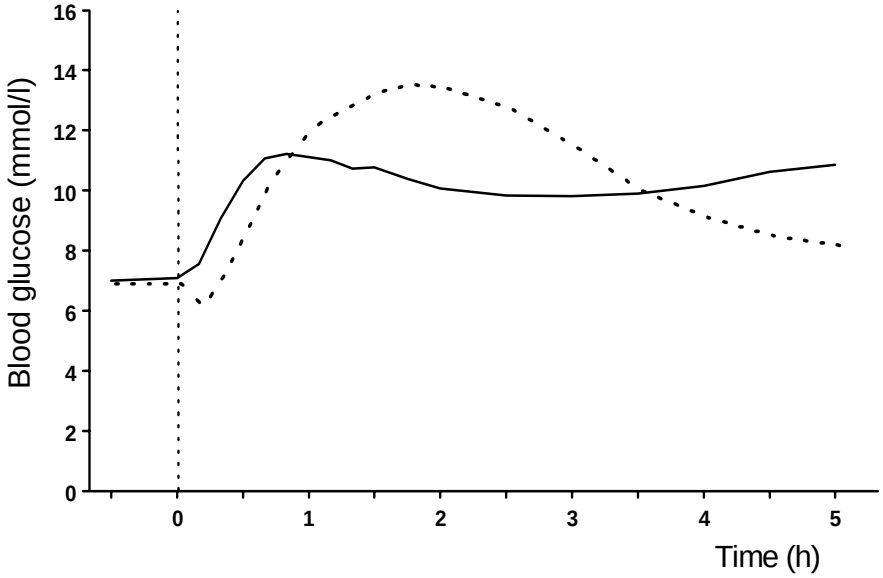

Fig. I. Blood glucose concentrations following a single pre-meal dose of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

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.

Adults. 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.

Children and adolescents. 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.

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.

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

5.2 Pharmacokinetic properties

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.

The pharmacokinetics has not been investigated in elderly or patients with impaired renal or liver function.

Children and adolescents. 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

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. Acute, one month and twelve months toxicity studies produced no toxicity findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid and/or Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to the insulin may cause degradation of the insulin, e.g. if the medicinal product contains thiol or sulphites.

6.3 Shelf life

30 months.

The in-use shelf life is 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
In order to protect from light keep the cap on when NovoRapid Innolet is not in use.

NovoRapid InnoLet in use or carried as a spare: Do not refrigerate. Do not store above 30°C.

6.5 Nature and contents of container

A glass (Type 1) cartridge which contains a piston (bromobutyl rubber) and is closed with a disc (bromobutyl/polyisoprene rubber) containing 3 ml of solution in a multidose disposable pre-filled pen with a pen injector (plastic).

Cartons of 1, 5 or 10 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

NovoRapid InnoLet should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

NovoRapid InnoLet is for use by one person only. NovoRapid InnoLet must not be refilled.

NovoFine **S** needles are designed to be used with NovoRapid InnoLet.

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.

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.

NovoRapid should not be used if it does not appear clear and colourless.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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: 7 September 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

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

Name and address of the manufacturers responsible for batch release

NovoRapid Vial:

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

NovoRapid Penfill:

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

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

Novo Nordisk A/S
Brennum Park
DK-3400 Hilleroed
Denmark

NovoRapid FlexPen:

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

Novo Nordisk A/S
Brennum Park
DK-3400 Hilleroed
Denmark

NovoRapid NovoLet:

Novo Nordisk A/S
Brennum Park
DK-3400 Hilleroed
Denmark

NovoRapid InnoLet:

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

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 U/ml
Solution for injection in a vial
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Keep the container in the outer carton
During use: use within 4 weeks
Do not refrigerate or store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/001

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

NovoRapid 100 U/ml
Solution for injection in a vial
Insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Keep the container in the outer carton
During use: use within 4 weeks
Do not refrigerate or store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/008

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NovoRapid 100 U/ml
Solution for injection
Insulin aspart

2. METHOD OF ADMINISTRATION

SC, IV use

3. EXPIRY DATE

Expiry/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
NovoRapid Penfill is for use with Novo Nordisk insulin devices

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use
NovoRapid Penfill is for use by one person only

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Keep the cartridge in the outer carton
During use: use within 4 weeks
Do not refrigerate or store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/003

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
NovoRapid Penfill is for use with Novo Nordisk insulin devices

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use
NovoRapid Penfill is for use by one person only

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Keep the cartridge in the outer carton
During use: use within 4 weeks
Do not refrigerate or store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/006

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NovoRapid Penfill 100 U/ml
Solution for injection
Insulin aspart

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
NovoRapid NovoLet is designed to be used with NovoFine needles
NovoFine needles are not included

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use
NovoRapid NovoLet is for use by one person only

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Protect from light
During use: use within 4 weeks
Do not refrigerate or store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/005

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
NovoRapid NovoLet is designed to be used with NovoFine needles
NovoFine needles are not included

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use
NovoRapid NovoLet is for use by one person only

8. EXPIRY DATE

Expiry/

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Protect from light
During use: use within 4 weeks
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Novo Allé
DK - 2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/007

13. MANUFACTURER'S BATCH NUMBER

Batch:

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Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NovoRapid NovoLet 100 U/ml
Solution for injection
Insulin aspart

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

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

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1 ml solution contains 100 U (3.5 mg) of insulin aspart (r-DNA),

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

4. PHARMACEUTICAL FORM AND CONTENTS

3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
NovoRapid FlexPen is designed to be used with NovoFine **S** needles
NovoFine **S** needles are not included

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

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7. OTHER SPECIAL WARNING(S), IF NECESSARY

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Expiry/

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Novo Allé
DK - 2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/011

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Batch:

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sodium chloride, hydrochloric acid/sodium hydroxide and
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5 x 3 ml

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Novo Allé
DK - 2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S

EU/1/99/119/009

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

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Solution for injection
Insulin aspart

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

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NovoRapid InnoLet is designed to be used with NovoFine **S** needles
NovoFine **S** needles are not included

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

Keep out of the reach and sight of children

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Expiry/:

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Novo Allé
DK - 2880 Bagsværd
Denmark

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EU/1/99/119/012

13. MANUFACTURER'S BATCH NUMBER

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Novo Allé
DK - 2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/119/013

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13. MANUFACTURER'S BATCH NUMBER

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Solution for injection
Insulin aspart

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET

NovoRapid

Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

NovoRapid 100 U/ml
Solution for injection in a vial
Insulin aspart, rDNA.
The active substance is insulin aspart made by recombinant DNA technology.
1 ml contains 100 U of insulin aspart. 1 vial contains 10 ml equivalent to 1000 U.
The other ingredients are glycerol, phenol, metacresol, zinc chloride, sodium chloride, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.
The solution for injection comes as a clear, colourless, aqueous solution in packs of 1 or 5 vials of 10 ml (not all packs may be marketed).
The marketing authorisation holder and manufacturer is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark.

1. WHAT NOVORAPID IS AND WHAT IT IS USED FOR

NovoRapid is an insulin analogue to treat diabetes. It comes in a 10 ml vial that you use to fill a syringe.
NovoRapid is a rapid-acting insulin for use in adults and children from 2 years of age. It will start to lower your blood sugar 10-20 minutes after you take it, a maximum effect occurs between 1 and 3 hours 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.

2. BEFORE YOU USE NOVORAPID

Do not use NovoRapid

- **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See *4 What to do in an emergency* for more about hypos
- **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see box, below left). Look out for the signs of allergy in *5 Possible side effects*.

Take special care with NovoRapid

- **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose
- **If you are drinking alcohol (also beer and wine):** watch for signs of a hypo and never drink alcohol on an empty stomach
- **If you are exercising** more than usual or if you want to change your usual diet
- **If you are ill:** carry on taking your insulin. Your need for insulin may change
- **If you have an infection, fever or an operation** you may need more insulin than usual
- **If you suffer from diarrhoea, vomiting or eat less than usual** you may also need less insulin than usual
- **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling

- **If you are planning a pregnancy or if you are pregnant or breast-feeding:** please contact your doctor for advice. There is limited clinical experience with NovoRapid in pregnancy
- **If you drive or use tools or machines:** your ability to concentrate or react may be reduced if you have a hypo. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on. You should contact your doctor about the advisability of driving if you have frequent episodes of hypos or reduced or absent warning signs of hypos.

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

There is no clinical experience with NovoRapid in children under the age of 2 years.

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

Using other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Please consult your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take:
Oral antidiabetic medicinal products, monoamine oxidase (MAO) inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and glucocorticoids (except topical administration), oral contraceptives, thiazides, thyroid hormones, sympathomimetics, danazol, octreotide and sulphonamides.

3. HOW TO USE NOVORAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
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.
Eat a meal or snack containing carbohydrates within 10 minutes of the injection to avoid hypoglycaemia. When necessary, NovoRapid may be given soon after the meal, instead of before the meal.
It is recommended that you measure your blood glucose regularly.

Before using NovoRapid

- **Check the label to make sure** it is the right type of insulin
- **Remove the protective cap**
- **Disinfect** the rubber membrane with a medicinal swab.

NovoRapid should not be used

- **If the protective cap is loose or missing.** Each vial has a protective, tamper-proof plastic cap. If it isn't in perfect condition when you get the vial, return the vial to your supplier
- **If it hasn't been stored correctly** or if it has been frozen (see *6 Storing NovoRapid)*
- **If the insulin does not appear clear and colourless.**

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. NovoRapid may also be given intravenously by health care professionals under close supervision by a doctor.

Always vary the sites you inject, to avoid lumps (see *5 Possible side effects)*. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

How to take this insulin

If you use only one type of insulin

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.

If you have to mix two types of insulin

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 this insulin

- Pinch your skin between two fingers, push the needle into the skin fold and inject the insulin under the skin.
- Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.

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 so as 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 alternative insulin available for injection under the skin in case of pump system failure.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo (hypoglycaemia)

A hypo means your blood sugar level is too low.
The warning signs of a hypo may come on suddenly and can include: 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.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and get medical help straight away. They must not give you any food or drink, as it could choke you.

- ► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
- ► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of your insulin, food or exercise may need to be adjusted.

Using glucagon

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).
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.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5. POSSIBLE SIDE EFFECTS

Like all medicines, NovoRapid can have side effects.
The most common side effect is low blood sugar (hypoglycaemia). See the advice in *4 What to do in an emergency*

Side effects reported uncommonly

(less than 1 in 100)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes of the injection site. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same region.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.
Seek medical advice immediately:
- If signs of allergy spread to other parts of your body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid or one of its ingredients (called a systemic allergic reaction). See also the warning in *2 Before you use NovoRapid*.

Diabetic retinopathy. If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Side effects reported rarely

(less than 1 in 1,000)

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Painful neuropathy. If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If you notice any side effects also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING NOVORAPID

Keep out of the reach and sight of children.
NovoRapid vials that are not being used are to be stored at 2°C – 8°C in the refrigerator, away from the freezer compartment. Do not freeze.
NovoRapid vials that are being used or about to be used are not to be kept in the refrigerator. You can carry them with you and keep them at room temperature (not above 30°C) for up to 4 weeks. Always keep the vial in the outer carton when you're not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and sunlight.
Do not use NovoRapid after the expiry date stated on the label and carton.

This leaflet was last approved

PACKAGE LEAFLET

NovoRapid Penfill

Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

NovoRapid Penfill 100 U/ml
Solution for injection in a cartridge
Insulin aspart, rDNA.
The active substance is insulin aspart made by recombinant DNA technology.
1 ml contains 100 U of insulin aspart. 1 cartridge contains 3 ml equivalent to 300 U.
The other ingredients are glycerol, phenol, metacresol, zinc chloride, sodium chloride, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.
The solution for injection comes as a clear, colourless, aqueous solution in packs of 5 or 10 cartridges of 3 ml (not all packs may be marketed).
The marketing authorisation holder is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark
and manufacturer is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark,
or
Novo Nordisk Production SAS,
45, Avenue d'Orléans F-28002 Chartres, France,
or
Novo Nordisk A/S,
Brennum Park, DK-3400 Hilleroed, Denmark

1. WHAT NOVORAPID IS AND WHAT IT IS USED FOR

NovoRapid is an insulin analogue to treat diabetes. It comes in a 3 ml cartridge, called Penfill, which fits into a delivery system.
NovoRapid is a rapid-acting insulin for use in adults and children from 2 years of age. It will start to lower your blood sugar 10-20 minutes after you take it, a maximum effect occurs between 1 and 3 hours 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.

2. BEFORE YOU USE NOVORAPID

Do not use NovoRapid

- ► **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See *4 What to do in an emergency* for more about hypos
- ► **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see box, below left). Look out for the signs of allergy in *5 Possible side effects*.

Take special care with NovoRapid

- ► **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose

- **If you are drinking alcohol (also beer and wine):** watch for signs of a hypo and never drink alcohol on an empty stomach
- **If you are exercising** more than usual or if you want to change your usual diet
- **If you are ill:** carry on taking your insulin. Your need for insulin may change
- **If you have an infection, fever or an operation** you may need more insulin than usual
- **If you suffer from diarrhoea, vomiting or eat less than usual** you may also need less insulin than usual
- **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling
- **If you are planning a pregnancy or if you are pregnant or breast-feeding:** please contact your doctor for advice. There is limited clinical experience with NovoRapid in pregnancy
- **If you drive or use tools or machines:** your ability to concentrate or react may be reduced if you have a hypo. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on. You should contact your doctor about the advisability of driving if you have frequent episodes of hypos or reduced or absent warning signs of hypos.

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

There is no clinical experience with NovoRapid in children under the age of 2 years.

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

Using other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Please consult your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take:
Oral antidiabetic medicinal products, monoamine oxidase (MAO) inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and glucocorticoids (except topical administration), oral contraceptives, thiazides, thyroid hormones, sympathomimetics, danazol, octreotide and sulphonamides.

3. HOW TO USE NOVORAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
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.
Eat a meal or snack containing carbohydrates within 10 minutes of the injection to avoid hypoglycaemia. When necessary, NovoRapid may be given soon after the meal, instead of before the meal.
It is recommended that you measure your blood glucose regularly.

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). Don't use it if any damage is seen or if there is a gap between the rubber plunger and the white label band. Take it back to your supplier. See your delivery system manual for further instructions
- **Disinfect** the rubber membrane with a medicinal swab.

NovoRapid should not be used

- ► **If the cartridge or the device containing the cartridge is dropped, damaged or crushed,** there is a risk of leakage of insulin
- ► **If it hasn't been stored correctly** or if it has been frozen (see *6 Storing NovoRapid)*
- ► **If the insulin does not appear clear and colourless**.

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. NovoRapid may also be given intravenously by healthcare professionals under close supervision by a doctor.
Always vary the sites you inject, to avoid lumps (see *5 Possible side effects)*. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

NovoRapid Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine needles. If you are treated with NovoRapid Penfill and another insulin Penfill cartridge, you must use two insulin delivery systems, one for each type of insulin.

Do not refill NovoRapid Penfill.
As a precautionary measure, always carry a spare insulin delivery device in case your Penfill is lost or damaged.

How to inject this insulin

- ► **Inject the insulin** under the skin. Use the injection technique advised by your doctor or diabetes nurse and described in your delivery system manual
- ► **Keep the needle under your skin** for at least 6 seconds to make sure that the full dose has been delivered
- ► **After each injection** be sure to discard the needle. Otherwise, the liquid may leak out when the temperature changes.

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 so as 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 alternative insulin available for injection under the skin in case of pump system failure.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo (hypoglycaemia)

A hypo means your blood sugar level is too low.
The warning signs of a hypo may come on suddenly and can include: 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.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and get medical help straight away. They must not give you any food or drink, as it could choke you.

- ► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
- ► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of your insulin, food or exercise may need to be adjusted.

Using glucagon

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).
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.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5. POSSIBLE SIDE EFFECTS

Like all medicines, NovoRapid can have side effects.
The most common side effect is low blood sugar (hypoglycaemia). See the advice in *4 What to do in an emergency.*

Side effects reported uncommonly

(less than 1 in 100)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes of the injection site. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same region.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.
Seek medical advice immediately:
- If signs of allergy spread to other parts of your body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid or one of its ingredients (called a systemic allergic reaction). See also the warning in *2 Before you use NovoRapid*.

Diabetic retinopathy. If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Side effects reported rarely

(less than 1 in 1,000)

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Painful neuropathy. If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If you notice any side effects also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING NOVORAPID

Keep out of the reach and sight of children.
NovoRapid Penfill that is not being used is to be stored at 2°C – 8°C in the refrigerator, away from the freezer compartment. Do not freeze.
NovoRapid Penfill that is being used or about to be used is not to be kept in the refrigerator. You can carry it with you and keep it at room temperature (not above 30°C) for up to 4 weeks.
Always keep the cartridge in the outer carton when you're not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and sunlight.
Do not use NovoRapid after the expiry date stated on the label and carton.

This leaflet was last approved

PACKAGE LEAFLET

NovoRapid NovoLet

Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This side of the leaflet:

Overleaf: How to use your NovoLet.

NovoRapid NovoLet 100 U/ml
Solution for injection in a pre-filled pen
Insulin aspart, rDNA.
The active substance is insulin aspart made by recombinant DNA technology.
1 ml contains 100 U of insulin aspart. 1 pre-filled pen contains 3 ml equivalent to 300 U.
The other ingredients are glycerol, phenol, metacresol, zinc chloride, sodium chloride, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.
The solution for injection comes as a clear, colourless, aqueous solution in packs of 5 or 10 pre-filled pens of 3 ml (not all packs may be marketed).
The marketing authorisation holder is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark
and manufacturer is
Novo Nordisk A/S,
Brennum Park, DK-3400 Hilleroed, Denmark

1. WHAT NOVORAPID IS AND WHAT IT IS USED FOR

NovoRapid is an insulin analogue to treat diabetes. It comes in a 3 ml pre-filled pen, called NovoLet – see overleaf for detailed instructions.
NovoRapid is a rapid-acting insulin for use in adults and children from 2 years of age. It will start to lower your blood sugar 10-20 minutes after you take it, a maximum effect occurs between 1 and 3 hours 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.

2. BEFORE YOU USE NOVORAPID

Do not use NovoRapid

- **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See *4 What to do in an emergency* for more about hypos
- **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see box, below left). Look out for the signs of allergy in *5 Possible side effects*.

Take special care with NovoRapid

- **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose
- **If you are drinking alcohol (also beer and wine):** watch for signs of a hypo and never drink alcohol on an empty stomach
- **If you are exercising** more than usual or if you want to change your usual diet
- **If you are ill:** carry on taking your insulin. Your need for insulin may change
- **If you have an infection, fever or an operation** you may need more insulin than usual
- **If you suffer from diarrhoea, vomiting or eat less than usual** you may also need less insulin than usual
- **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling
- **If you are planning a pregnancy or if you are pregnant or breast-feeding:** please contact your doctor for advice. There is limited clinical experience with NovoRapid in pregnancy
- **If you drive or use tools or machines:** your ability to concentrate or react may be reduced if you have a hypo. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on. You should contact your doctor about the advisability of driving if you have frequent episodes of hypos or reduced or absent warning signs of hypos.

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

There is no clinical experience with NovoRapid in children under the age of 2 years.

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

Using other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Please consult your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take:
Oral antidiabetic medicinal products, monoamine oxidase (MAO) inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and glucocorticoids (except topical administration), oral contraceptives, thiazides, thyroid hormones, sympathomimetics, danazol, octreotide and sulphonamides.

3. HOW TO USE NOVORAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
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.
Eat a meal or snack containing carbohydrates within 10 minutes of the injection to avoid hypoglycaemia. When necessary, NovoRapid may be given soon after the meal, instead of before the meal.
It is recommended that you measure your blood glucose regularly.

Injecting the insulin

See overleaf for detailed instructions.

Before using NovoRapid

► **Check the label to make sure** it is the right type of insulin.

NovoRapid should not be used

► **If the NovoLet is dropped, damaged or crushed**, there is a risk of leakage of insulin
► **If it hasn't been stored correctly** or if it has been frozen (see *6 Storing NovoRapid*)
► **If the insulin does not appear clear and colourless.**

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. NovoRapid may also be given intravenously by healthcare professionals under close supervision by a doctor.
Always vary the sites you inject, to avoid lumps (see *5 Possible side effects*). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

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 so as 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 alternative insulin available for injection under the skin in case of pump system failure.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo (hypoglycaemia)

A hypo means your blood sugar level is too low.
The warning signs of a hypo may come on suddenly and can include: 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.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and get medical help straight away. They must not give you any food or drink, as it could choke you.
► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of your insulin, food or exercise may need to be adjusted.

Using glucagon

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:
- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).
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.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5. POSSIBLE SIDE EFFECTS

Like all medicines, NovoRapid can have side effects.
The most common side effect is low blood sugar (hypoglycaemia). See the advice in *4 What to do in an emergency*

Side effects reported uncommonly

(less than 1 in 100)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes of the injection site. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same region.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.
Seek medical advice immediately:
- If signs of allergy spread to other parts of your body, or

- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid or one of its ingredients (called a systemic allergic reaction). See also the warning in *2 Before you use NovoRapid*.

Diabetic retinopathy. If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Side effects reported rarely

(less than 1 in 1,000)

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Painful neuropathy. If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If you notice any side effects also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING NOVORAPID

Keep out of the reach and sight of children.
NovoRapid NovoLet that is not being used is to be stored at 2°C – 8°C in the refrigerator, away from the freezer compartment. Do not freeze.
NovoRapid NovoLet that is being used or about to be used is not to be kept in the refrigerator. You can carry them with you and keep them at room temperature (not above 30°C) for up to 4 weeks. Always keep the pen cap on your NovoLet when you're not using it in order to protect it from light. NovoRapid must be protected from excessive heat and sunlight. Do not use NovoRapid after the expiry date stated on the label and carton.

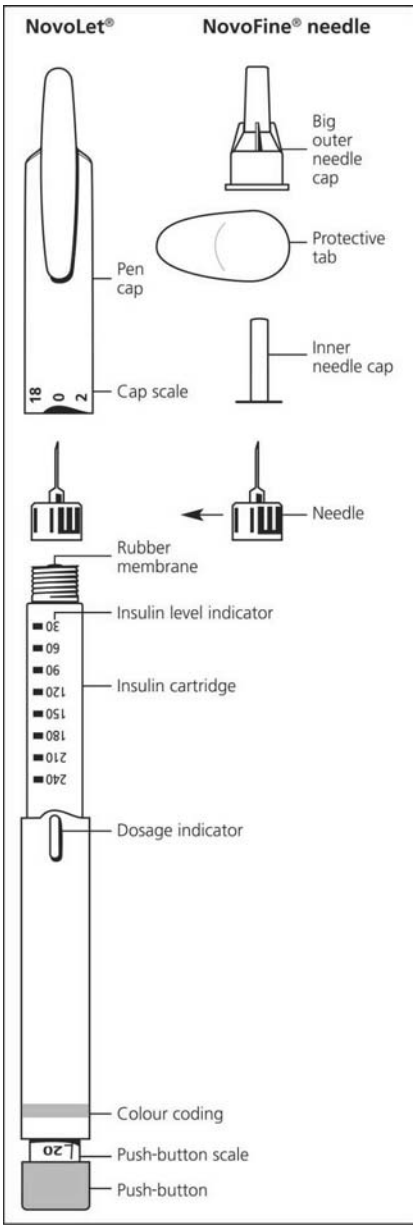
Now turn for information on how to use your NovoLet.

This leaflet was last approved

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

Introduction

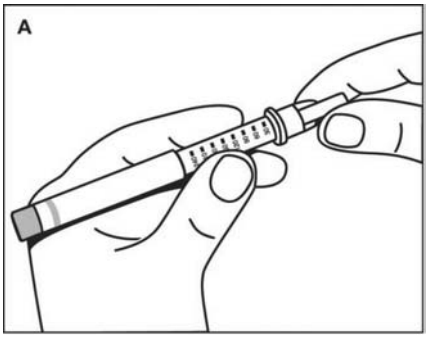
NovoRapid NovoLet is a simple, compact pre-filled pen. You can dial doses from 2 to 78 units in increments of 2 units. NovoRapid NovoLet is designed to be used with NovoFine needles.
As a precautionary measure, always carry a spare insulin delivery device in case your NovoLet is lost or damaged.



Getting started

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

- **Disinfect the rubber membrane** with a medicinal swab
- **Remove the protective tab** from a NovoFine needle
- **Screw the needle straight and tightly** onto NovoRapid NovoLet (picture **A**)
- **Pull off the big outer needle cap and the inner needle cap**. Do not discard the big outer needle cap.

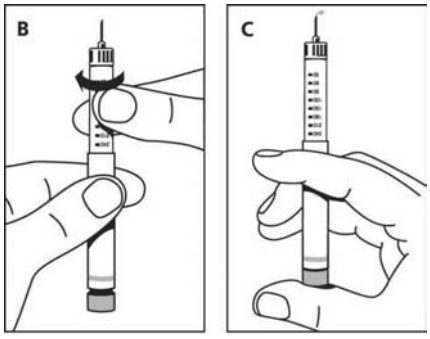


Priming to expel air

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 NovoRapid 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.

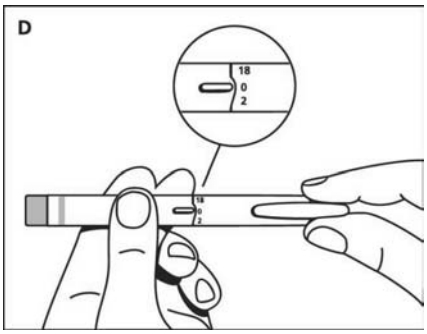
If a drop of insulin still does not appear, the device is defective and must not be used.

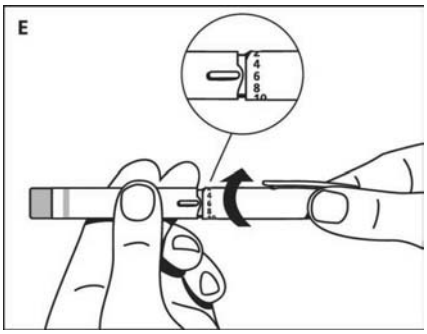


Setting the dose

- **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 isn't, turn the cap until the push-button is fully depressed
- **Hold your NovoRapid NovoLet horizontally.** Now you're ready to set the dose you need

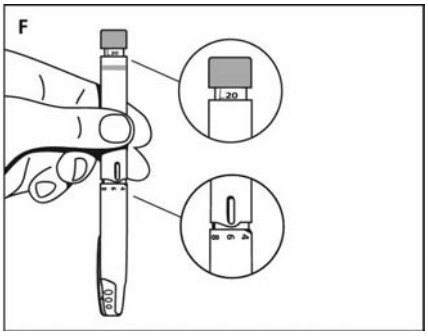
- **Turn the cap in the direction of the arrow** (picture **E**) to set the right dose. You'll feel the cap clicking, and the push-button will rise up
- **Don't put your hand over the push-button** when you set the dose. If the push-button cannot rise freely, some of your insulin will be pushed out of 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.





Dosage examples

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



To check a dose you set

- **Note the figure on the cap** next to the dosage 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

- **Don't 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 must 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 *Getting started*
- **You may hear a clicking sound when you press the push-button.** Don't use this to set or check your dose; it may not be accurate
- **You can't 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't 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 the needle after each injection. Otherwise, the liquid may leak out when the temperature changes.
Health care professionals, relatives and other carers must follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Close your NovoRapid NovoLet fully with 0 next to the dosage indicator.
Dispose of your used NovoRapid NovoLet carefully without the needle attached.

Maintenance

Your NovoRapid NovoLet is designed to work accurately and safely. It must be handled with care.
You can clean the exterior of your NovoRapid NovoLet by wiping it with a medicinal swab. Do not soak it, wash or lubricate it. This may damage the mechanism.
Do not refill NovoRapid NovoLet.

PACKAGE LEAFLET

NovoRapid FlexPen

Read all of this leaflet carefully **before you start using this medicine.** Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This side of the leaflet:

Overleaf: How to use your FlexPen.

NovoRapid FlexPen 100 U/ml
Solution for injection in a pre-filled pen
Insulin aspart, rDNA.
The active substance is insulin aspart made by recombinant DNA technology.
1 ml contains 100 U of insulin aspart. 1 pre-filled pen contains 3 ml equivalent to 300 U.
The other ingredients are glycerol, phenol, metacresol, zinc chloride, sodium chloride, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.
The solution for injection comes as a clear, colourless, aqueous solution in packs of 1, 5 or 10 pre-filled pens of 3 ml (not all packs may be marketed).
The marketing authorisation holder is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark
and manufacturer is
Novo Nordisk A/S,
Brennum Park, DK-3400 Hilleroed, Denmark
or
Novo Nordisk Production SAS
45, Avenue d'Orléans F-28002 Chartres, France.

1. WHAT NOVORAPID IS AND WHAT IT IS USED FOR

NovoRapid is an insulin analogue to treat diabetes. It comes in a 3 ml pre-filled pen, called FlexPen – see overleaf for detailed instructions.
NovoRapid is a rapid-acting insulin for use in adults and children from 2 years of age. It will start to lower your blood sugar 10-20 minutes after you take it, a maximum effect occurs between 1 and 3 hours 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.

2. BEFORE YOU USE NOVORAPID

Do not use NovoRapid

► **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See *4 What to do in an emergency* for more about hypos

- **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see box, below left). Look out for the signs of allergy in *5 Possible side effects*.

Take special care with NovoRapid

- **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose
- **If you are drinking alcohol (also beer and wine):** watch for signs of a hypo and never drink alcohol on an empty stomach
- **If you are exercising** more than usual or if you want to change your usual diet
- **If you are ill:** carry on taking your insulin. Your need for insulin may change
- **If you have an infection, fever or an operation** you may need more insulin than usual
- **If you suffer from diarrhoea, vomiting or eat less than usual** you may also need less insulin than usual
- **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling
- **If you are planning a pregnancy or if you are pregnant or breast-feeding:** please contact your doctor for advice. There is limited clinical experience with NovoRapid in pregnancy
- **If you drive or use tools or machines:** your ability to concentrate or react may be reduced if you have a hypo. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on. You should contact your doctor about the advisability of driving if you have frequent episodes of hypos or reduced or absent warning signs of hypos.

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

There is no clinical experience with NovoRapid in children under the age of 2 years.

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

Using other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Please consult your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take:
Oral antidiabetic medicinal products, monoamine oxidase (MAO) inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and glucocorticoids (except topical administration), oral contraceptives, thiazides, thyroid hormones, sympathomimetics, danazol, octreotide and sulphonamides.

3. HOW TO USE NOVORAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
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.
Eat a meal or snack containing carbohydrates within 10 minutes of the injection to avoid hypoglycaemia. When necessary, NovoRapid may be given soon after the meal, instead of before the meal.
It is recommended that you measure your blood glucose regularly.

Injecting the insulin

See overleaf for detailed instructions.

Before using NovoRapid

► **Check the label to make sure** it is the right type of insulin.

NovoRapid should not be used

► **If the FlexPen is dropped, damaged or crushed**, there is a risk of leakage of insulin
► **If it hasn't been stored correctly** or if it has been frozen (see *6 Storing NovoRapid*)
► **If the insulin does not appear clear and colourless.**

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. NovoRapid may also be given intravenously by healthcare professionals under close supervision by a doctor.
Always vary the sites you inject, to avoid lumps (see *5 Possible side effects*). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

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 so as 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 alternative insulin available for injection under the skin in case of pump system failure.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo (hypoglycaemia)

A hypo means your blood sugar level is too low.
The warning signs of a hypo may come on suddenly and can include: 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.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and get medical help straight away. They must not give you any food or drink, as it could choke you.

- ► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
- ► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of your insulin, food or exercise may need to be adjusted.

Using glucagon

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).
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.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5. POSSIBLE SIDE EFFECTS

Like all medicines, NovoRapid can have side effects.
The most common side effect is low blood sugar (hypoglycaemia). See the advice in *4 What to do in an emergency.*

Side effects reported uncommonly

(less than 1 in 100)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes of the injection site. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same region.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.
Seek medical advice immediately:
- If signs of allergy spread to other parts of your body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid or one of its ingredients (called a systemic allergic reaction). See also the warning in *2 Before you use NovoRapid*.

Diabetic retinopathy. If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Side effects reported rarely

(less than 1 in 1,000)

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Painful neuropathy. If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If you notice any side effects also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING NOVORAPID

Keep out of the reach and sight of children.
NovoRapid FlexPen that is not being used is to be stored at 2°C – 8°C in the refrigerator, away from the freezer compartment. Do not freeze.
NovoRapid FlexPen that is being used or about to be used is not to be kept in the refrigerator You can carry them with you and keep them at room temperature (not above 30°C) for up to 4 weeks. Always keep the pen cap on your FlexPen when you're not using it in order to protect it from light. NovoRapid must be protected from excessive heat and sunlight. Do not use NovoRapid after the expiry date stated on the label and carton.

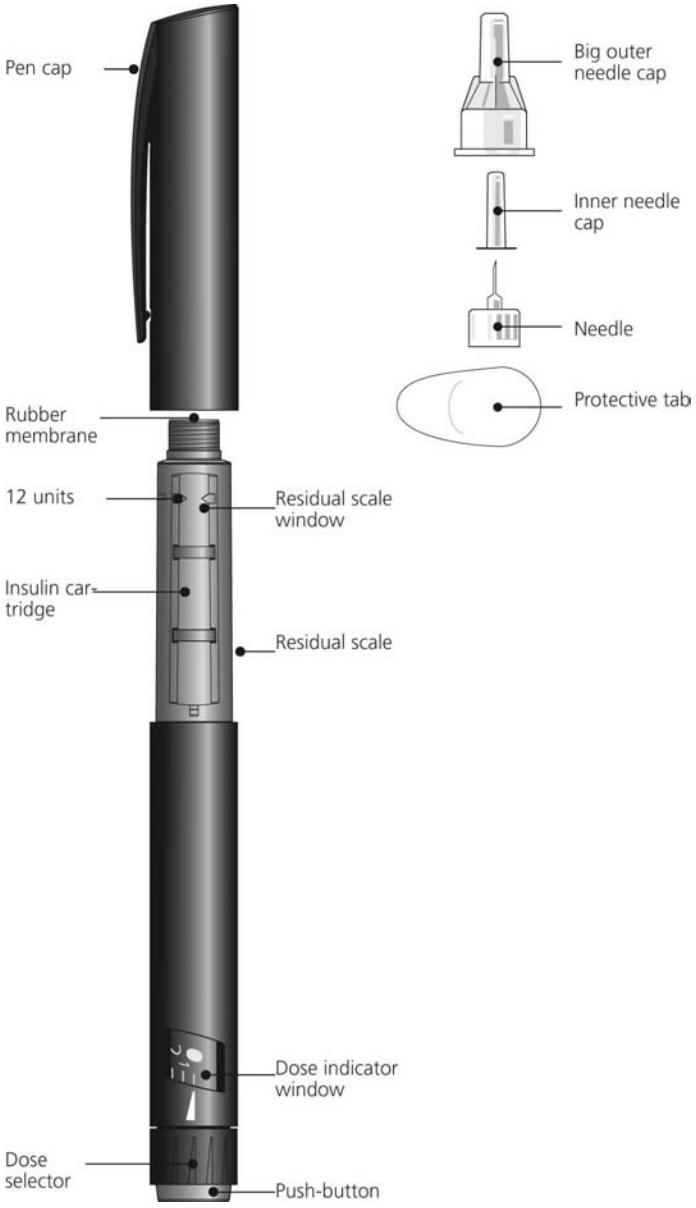
Now turn for information on how to use your FlexPen.

This leaflet was last approved

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

Introduction

NovoRapid FlexPen is a unique dial-a-dose insulin pen. You can dial doses from 1 to 60 units in increments of 1 unit. NovoRapid FlexPen is designed to be used with NovoFine **S** needles of 8 mm or shorter in length. Look for an **S** on the needle box. The **S** stands for short cap.
As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen is lost or damaged.

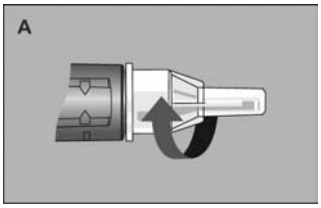


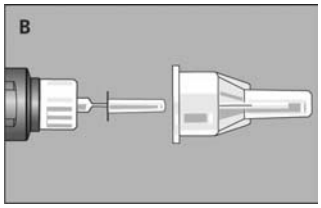
Getting started

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

- **Disinfect the rubber membrane** with a medicinal swab
- **Remove the protective tab** from a NovoFine **S** short cap needle
- **Screw the needle straight and tightly** onto NovoRapid FlexPen (picture **A**)

- **Pull off the big outer needle cap and the inner needle cap** (picture **B**). Do not discard the big outer needle cap.



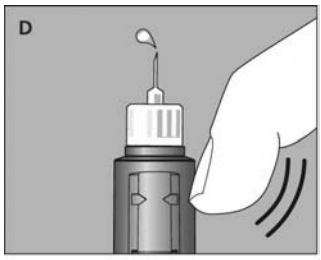


Priming to expel air

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:

- **Dial 2 units** (picture **C**)
- **Hold NovoRapid 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 (picture **D**)
- **Keeping the needle upwards, press the push-button all the way in.** The dose selector returns to zero
- **A drop of insulin should appear at the needle tip**. If not, change the needle and repeat the procedure no more than 6 times.

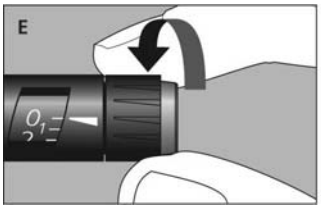
If a drop of insulin still does not appear, the device is defective, and must not be used.



Setting the dose

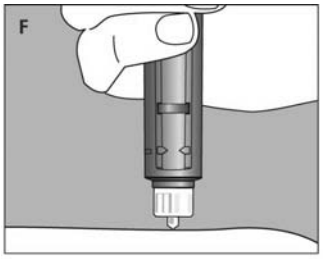
- **Check that the dose selector is set at zero**
- **Dial the number of units you need to inject** (picture **E**)**.**

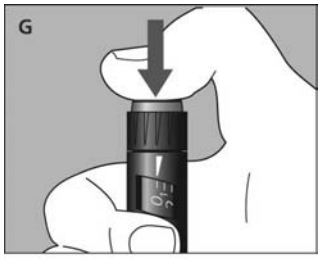
The dose can be corrected either up or down by turning the dose selector in either direction. When dialling back, be careful not to push the push-button as insulin will come out.
Do not use the residual scale to measure your dose of insulin.
You cannot set a dose larger than the number of units left in the cartridge.



Injecting the insulin

- **Insert the needle into your skin** (picture **F**). Use the injection technique advised by your doctor
- **Deliver the dose by pressing the push-button all the way in** (picture **G**). 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 must remain under the skin for at least 6 seconds. This will ensure that the full dose has been delivered.

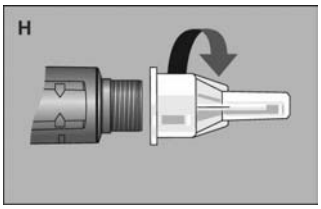




Removing the needle

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

Use a new needle for each injection.
Remove the needle after each injection. Otherwise, the liquid may leak out when the temperature changes.
Health care professionals, relatives and other carers must follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Dispose of the used NovoRapid FlexPen carefully without the needle attached.



Maintenance

Your NovoRapid FlexPen is designed to work accurately and safely. It must be handled with care.
You can clean the exterior of your NovoRapid FlexPen with a medicinal swab. Do not soak it, wash or lubricate it as this may damage the mechanism.
Do not refill NovoRapid FlexPen.

PACKAGE LEAFLET

NovoRapid InnoLet

Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This side of the leaflet:

NovoRapid InnoLet 100 U/ml
Solution for injection in a pre-filled pen
Insulin aspart, rDNA.
The active substance is insulin aspart made by recombinant DNA technology.
1 ml contains 100 U of insulin aspart. 1 pre-filled pen contains 3 ml equivalent to 300 U.
The other ingredients are glycerol, phenol, metacresol, zinc chloride, sodium chloride, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.
The solution for injection comes as a clear, colourless, aqueous solution in packs of 1, 5 or 10 pre-filled pens of 3 ml (not all packs may be marketed).
The marketing authorisation holder is
Novo Nordisk A/S,
Novo Allé, DK-2880 Bagsværd, Denmark
and manufacturer is
Novo Nordisk A/S,
Hallas Allé, DK-4400 Kalundborg, Denmark

1. WHAT NOVORAPID IS AND WHAT IT IS USED FOR

NovoRapid is an insulin analogue to treat diabetes. It comes in a 3 ml pre-filled pen, called InnoLet – see overleaf for detailed instructions.
NovoRapid is a rapid-acting insulin for use in adults and children from 2 years of age. It will start to lower your blood sugar 10-20 minutes after you take it, a maximum effect occurs between 1 and 3 hours 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.

2. BEFORE YOU USE NOVORAPID

Do not use NovoRapid

- **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See *4 What to do in an emergency* for more about hypos
- **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see box, below left). Look out for the signs of allergy in *5 Possible side effects*.

Take special care with NovoRapid

- **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose
- **If you are drinking alcohol (also beer and wine):** watch for signs of a hypo and never drink alcohol on an empty stomach
- **If you are exercising** more than usual or if you want to change your usual diet
- **If you are ill:** carry on taking your insulin. Your need for insulin may change
- **If you have an infection, fever or an operation** you may need more insulin than usual
- **If you suffer from diarrhoea, vomiting or eat less than usual** you may also need less insulin than usual
- **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling
- **If you are planning a pregnancy or if you are pregnant or breast-feeding:** please contact your doctor for advice. There is limited clinical experience with NovoRapid in pregnancy
- **If you drive or use tools or machines:** your ability to concentrate or react may be reduced if you have a hypo. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on. You should contact your doctor about the advisability of driving if you have frequent episodes of hypos or reduced or absent warning signs of hypos.

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

There is no clinical experience with NovoRapid in children under the age of 2 years.

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

Using other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Please consult your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take:
Oral antidiabetic medicinal products, monoamine oxidase (MAO) inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and glucocorticoids (except topical administration), oral contraceptives, thiazides, thyroid hormones, sympathomimetics, danazol, octreotide and sulphonamides.

3. HOW TO USE NOVORAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
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.
Eat a meal or snack containing carbohydrates within 10 minutes of the injection to avoid hypoglycaemia. When necessary, NovoRapid may be given soon after the meal, instead of before the meal.
It is recommended that you measure your blood glucose regularly.

Injecting the insulin

See overleaf for detailed instructions.

Before using NovoRapid

► **Check the label to make sure** it is the right type of insulin.

NovoRapid should not be used

► **If the InnoLet is dropped, damaged or crushed**, there is a risk of leakage of insulin
► **If it hasn't been stored correctly** or if it has been frozen (see *6 Storing NovoRapid*)
► **If the insulin does not appear clear and colourless.**

NovoRapid is for injection under the skin (subcutaneously) or for continuous infusion in a pump system. NovoRapid may also be given intravenously by healthcare professionals under close supervision by a doctor.
Always vary the sites you inject, to avoid lumps (see *5 Possible side effects*). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

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 so as 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 alternative insulin available for injection under the skin in case of pump system failure.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo (hypoglycaemia)

A hypo means your blood sugar level is too low.
The warning signs of a hypo may come on suddenly and can include: 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.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and get medical help straight away. They must not give you any food or drink, as it could choke you.
► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death

► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of your insulin, food or exercise may need to be adjusted.

Using glucagon

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:
- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).
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.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5. POSSIBLE SIDE EFFECTS

Like all medicines, NovoRapid can have side effects.
The most common side effect is low blood sugar (hypoglycaemia). See the advice in *4 What to do in an emergency.*

Side effects reported uncommonly

(less than 1 in 100)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes of the injection site. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same region.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid or one of its ingredients (called a systemic allergic reaction). See also the warning in *2 Before you use NovoRapid*.

Diabetic retinopathy. If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Side effects reported rarely

(less than 1 in 1,000)

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Painful neuropathy. If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If you notice any side effects also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING NOVORAPID

Keep out of the reach and sight of children.
NovoRapid InnoLet that is not being used is to be stored at 2°C – 8°C in the refrigerator, away from the freezer compartment. Do not freeze.
NovoRapid InnoLet that is being used or about to be used is not to be kept in the refrigerator.
You can carry them with you and keep them at room temperature (not above 30°C) for up to 4 weeks.
Always keep the pen cap on your InnoLet when you're not using it in order to protect it from light.
NovoRapid must be protected from excessive heat and sunlight. Do not use NovoRapid after the expiry date stated on the label and carton.

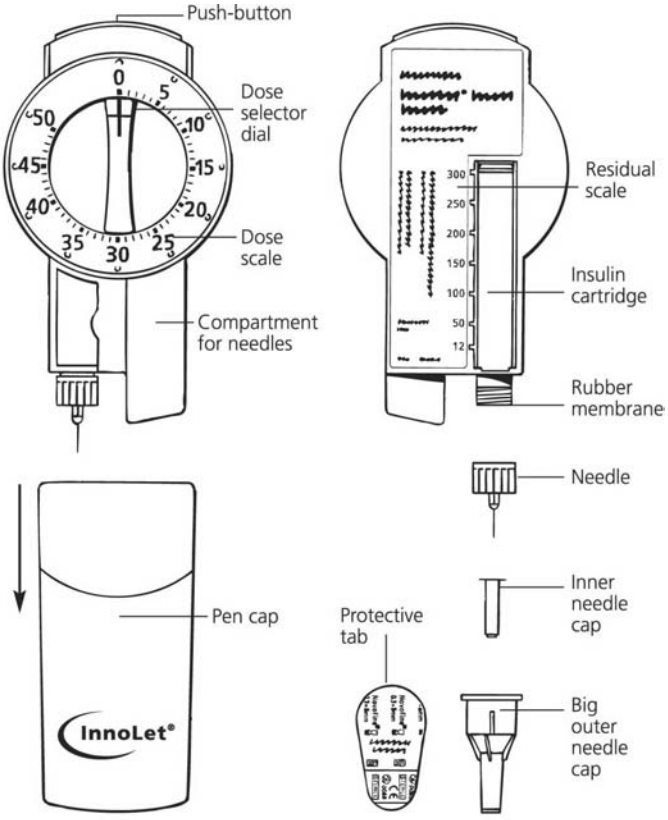
Now turn for information on how to use your InnoLet.

This leaflet was last approved

Please read the following instructions carefully before using your NovoRapid InnoLet

Introduction

NovoRapid InnoLet is a simple, compact pre-filled pen able to deliver 1 to 50 units in increments of 1 unit. NovoRapid InnoLet is designed to be used with NovoFine **S** needles of 8 mm or shorter in length. Look for an **S** on the needle box. The **S** stands for short cap.
As a precautionary measure, always carry a spare insulin delivery device in case your InnoLet is lost or damaged.

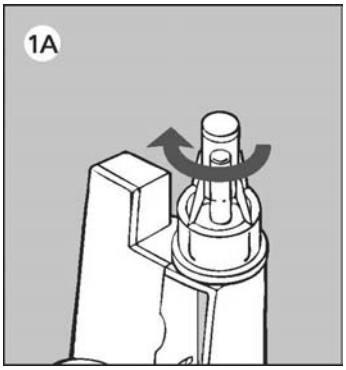


Preparing for injection

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

Attaching the needle

- **Disinfect the rubber membrane** with a medicinal swab
- **Remove the protective tab** from a NovoFine **S** short cap needle
- **Screw the needle straight and tightly** onto NovoRapid InnoLet (picture **1A**)
- **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.

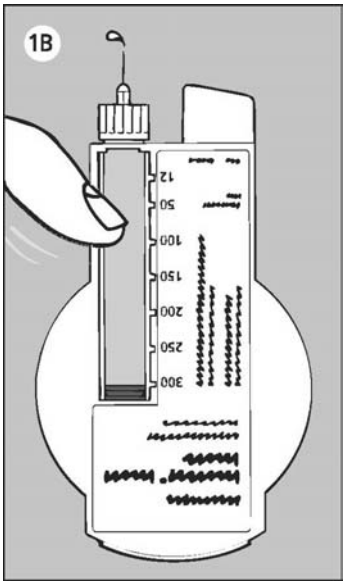


Priming to expel air

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 NovoRapid InnoLet with the needle upwards and tap the cartridge gently** with your finger a few times 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 zero
- **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.

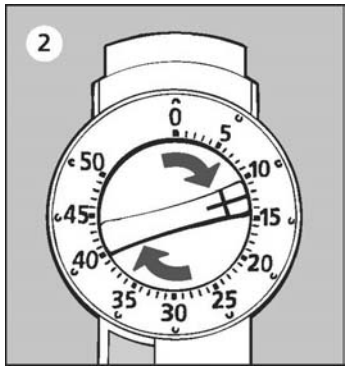
If a drop of insulin still does not appear, the device is defective and must not be used.



Setting the dose

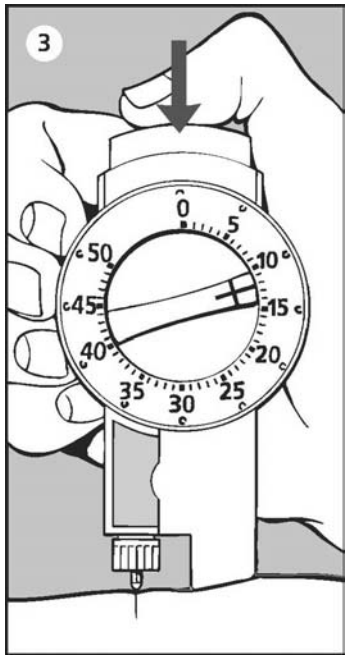
- **Always check that the push-button is fully depressed and the dose selector is set to zero**
- **Dial the number of units required** by turning the dose selector clockwise (picture **2**). Do not use the residual scale to measure your dose of insulin
- **You will hear a click for every single unit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

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



Injecting the insulin

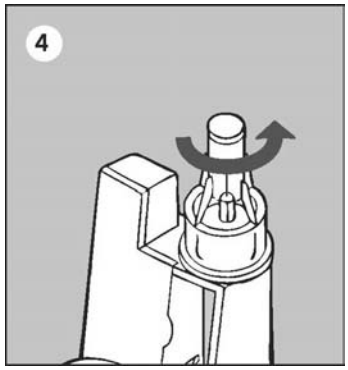
- **Insert the needle into your skin.** Use the injection technique advised by your doctor
- **Deliver the dose by pressing the push-button fully down** (picture **3**). You will hear clicks as the dose selector returns to zero
- **After the injection, the needle must remain under the skin for at least 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 zero 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 the needle after each injection. Otherwise, the liquid may leak out when the temperature changes.
Health care professionals, relatives and other carers must follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Dispose of your used NovoRapid InnoLet carefully without the needle attached.



Maintenance

Your NovoRapid InnoLet is designed to work accurately and safely. It must be handled with care. You can clean your NovoRapid InnoLet with a medicinal swab. Do not soak it, wash or lubricate it as this may damage the mechanism.
Do not refill NovoRapid InnoLet.