Professional Information for NOVORAPID

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NovoRapid® 100 U/mL solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains insulin aspart 100 U/mL. One unit of insulin aspart corresponds to 6 nmol, 0,035 mg salt-free anhydrous insulin aspart (produced in *Saccharomyces cerevisiae* by recombinant DNA technology).

Excipients with known effect:

Preservatives: Phenol: 0,15 % *m/v* and metacresol: 0,172 % *m/v*.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Solution for injection.

NovoRapid is a clear, colourless and aqueous solution.

4. Clinical particulars

4.1 Therapeutic indications

NovoRapid® is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

4.2 Posology and method of administration

Posology

The dosage of NovoRapid® for each patient is individualised. It should normally be used in combination with intermediate-acting or long-acting insulin given at least once a day.

The individual insulin requirement is usually between 0,5 and 1,0 units/kg/day in adults and children from 1 year. In a meal-related treatment 50 – 70 % of this requirement may be provided by NovoRapid® and the remainder provided by intermediate-acting or long-acting insulin.

NovoRapid® may be used for continuous subcutaneous insulin infusion (CSII) in the pump systems (*Disetronic Pump H-TRON® plus V100 and MiniMed® 506* Pump) suitable for insulin infusion.

Patients using CSII should be comprehensively instructed in the use of the pump system. The infusion set and reservoir should be changed every 48 hours using aseptic technique.

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

Paediatric population

NovoRapid® can be used in children and adolescents aged 1 year and above in preference to soluble human insulin when a rapid onset of action might be beneficial, for example, in the timing of the injections in relation to meals.

The safety and efficacy of NovoRapid® in children below 1 year of age have not been established. No data are available.

Method of administration

NovoRapid® is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region or by infusion in the abdominal wall.

Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8). NovoRapid® may also be administered intravenously. 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. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the fast onset of action NovoRapid® should generally be given immediately before a meal. When necessary, NovoRapid® may be given immediately after the meal.

Instructions for use and handling are reflected in the attached leaflet (Use of FlexPen, and FlexTouch)

For NovoRapid® Penfill®, the leaflet carries a reference to the instructions for using the accompanying Novo Nordisk insulin delivery system.

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

NovoRapid® Penfill® cartridges are designed to be used with the Novo Nordisk insulin delivery system and NovoFine needles or NovoTwist needles.

NovoRapid® should not be used if not water-clear and colourless.

Mixing NovoRapid® with other insulins:

Mixing NovoRapid® with insulin of animal origin has not been studied.

There is inconclusive data about mixing NovoRapid® with human isophane insulin, therefore this practice cannot be recommended.

Use of NovoRapid® in ketoacidosis

No specific studies have been performed for use in ketoacidosis

4.3 Contraindications

- Hypersensitivity to insulin aspart or any of the excipients of NovoRapid® (see section 6.1).
- Hypoglycaemia.

4.4 Special warnings and precautions for use

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

Hyperglycaemia

Inadequate dosing or discontinuation of treatment may, especially in Type 1 diabetes (insulin-dependent diabetes mellitus), lead to hyperglycaemia and diabetic ketoacidosis.

Usually the first symptoms of hyperglycaemia usually develop gradually, over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased frequency of urination, thirst and loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Especially in children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose level in order to minimise the risk of hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool

pale skin, fatigue, nervousness or tremor, anxiety, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/ or convulsions and may result in temporary or permanent impairment of brain function or even death.

Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change including a less pronounced intensity of their usual warning symptoms of hypoglycaemia, and should be advised accordingly.

Since 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. Concomitant diseases in the kidney or liver can require changes in the insulin dose.

Transfer from other insulin medicines

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a change in dosage. Patients transferred to NovoRapid® from another type of insulin may require an increased number of daily injections or a change in dosage from that used with

their previous insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Combination of pioglitazone and insulin medicines:

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

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

Sodium

This medicine contains less than 1 mmoL sodium (23 mg) per 1 mL, that is to say NovoRapid® is essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

A number of medicines are known to interact with the glucose metabolism.

Possible interaction must therefore be taken into account by the doctor.

The following substances may reduce the patient’s insulin requirements:

Oral hypoglycaemic medicines, octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), salicylates, alcohol, anabolic steroids and sulphonamides.

The following substances may increase the patient’s insulin requirements:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Concomitant use of beta blockers may result in lowered blood-sugar levels and may mask the symptoms of hypoglycaemia. If a beta-adrenergic beta blocker or a MAOI is added to the patient’s treatment, adjustment of the insulin dosage may be necessary.

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

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

NovoRapid® does not cross the placental barrier and can be used in pregnancy.

Intensified blood glucose control and monitoring of pregnant women with diabetes (Type 1, Type 2 or gestational diabetes) are recommended throughout pregnancy and when contemplating pregnancy. Both hypoglycaemia and hyperglycaemia which can occur in inadequately controlled diabetes therapy may increase the risk of malformations and death in utero.

Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Breastfeeding

There are no restrictions on treatment with NovoRapid® during breastfeeding as NovoRapid® does not cross into breast milk. However, the NovoRapid® dosage may need to be adjusted.

4.7 Effects on the ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be

considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Side effects observed in patients using NovoRapid® are mainly due to the pharmacologic effect of insulin. The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control.

Frequencies of other adverse reactions listed below are based on clinical trial data and the frequencies are defined as: Very common (≥1/10); common (≥1/100 to < 1/10; uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data):

System organ class	Side effect and frequency	
Immune system disorders	*Uncommon:*	Urticaria, rash, eruptions
	Very rare:	Anaphylactic reactions*
Metabolism and nutrition disorders	*Very common:*	Hypoglycaemia*
Nervous system disorders	*Rare:*	Peripheral neuropathy (painful neuropathy): Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible.
	Uncommon:	Refraction (blurred vision):

Eye disorders		Refraction anomalies may occur upon institution of insulin therapy and are usually of transitory nature.
	Uncommon:	Diabetic retinopathy: Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.
Skin and subcutaneous tissue disorders	*Uncommon:*	Lipodystrophy*: Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection site within an area.
	Not known:	Cutaneous amyloidosis*†
General disorders and administration site conditions	*Uncommon:*	Injection site reactions: Injection site reactions (pain, redness, swelling, bruising and itching at the injection site) may occur during treatment with NovoRapid®. These reactions are usually transitory and normally disappear during continued treatment.
	Uncommon:	Oedema: Oedema may occur upon institution of NovoRapid® therapy and is usually of transitory nature.

* See section 4.8, Description of selected adverse reactions.

† ADR from post marketing sources.

Description of selected adverse reactions

Anaphylactic reactions

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

Skin and subcutaneous tissue disorders:

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NovoRapid® is important. It allows continued monitoring of the benefit/risk balance of NovoRapid®. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carry some sugar lumps or sugar containing products, e.g. a few biscuits.
- 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

Category and class: A 21.1 Insulin preparations

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, fast-acting.

ATC code: A10AB05.

The insulin aspart is a fast-acting human insulin analogue.

When insulin aspart is injected subcutaneously the onset of action will occur within 10 – 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.

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

Special populations

Paediatric population

The pharmacokinetic and pharmacodynamic properties of insulin aspart 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 insulin aspart.

The efficacy and safety of insulin aspart given as bolus insulin in combination with either insulin detemir or insulin degludec as basal insulin has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children aged 1 to less than 18 years (n = 712). The trials included 167 children aged 1 – 5 years, 260 aged 6 – 11 and 285 aged 12 – 17. The observed improvements in HbA1c and the safety profiles were comparable between all age groups.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

Substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers which enhances the absorption from subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin and was, in different studies, reached after 40 to 50 minutes with insulin aspart compared to 80 to 120 minutes for soluble human insulin.

The return to baseline insulin levels is faster for NovoRapid® than for soluble human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Phenol (preservative)

Metacresol (preservative)

Zinc chloride

Disodium phosphate dihydrate

Sodium chloride

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injections.

6.2 Incompatibilities

Substances added to NovoRapid® may cause degradation of insulin aspart.

This medicine must not be diluted or mixed with other medicines.

6.3 Shelf life

NovoRapid® vial/NovoRapid® Penfill®/NovoRapid® FlexPen® /NovoRapid® FlexTouch®

Before opening: 30 months. Store in a refrigerator (between 2 ºC and 8 ºC). Do not freeze.

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

6.4 Special precautions for storage

For storage conditions of the medicine, see section 6.3.

In-use storage

NovoRapid® Penfill®/ NovoRapid® Vials

During use or when carried as a spare: Store at or below 30 ºC for up to 4 weeks. Do not expose to heat and sunlight. Do not store cartridges/Penfill®, in use in the refrigerator (between 2 ºC and 8 ºC).

Vials: Discard any unused portion after 4 weeks of use.

NovoRapid® FlexPen® and NovoRapid® FlexTouch®

During use or when carried as a spare: Store at or below 30 ºC for up to 4 weeks. Do not expose to heat and sunlight. Can be stored in the refrigerator (2 ºC – 8 ºC) for up to 4 weeks.

Note: Never use insulin after expiry date.

6.5 Nature and contents of container

NovoRapid® single vial:

10 mL solution in a colourless type 1 glass vial, closed with a rubber disc and protective tamper-proof plastic cap.

Pack size: 1 vial in an outer carton.

NovoRapid® 3 mL Penfill®:

3 mL solution in colourless type I glass Penfill® cartridges with a plunger (bromobutyl) and a rubber closure.

Pack size: 5 x 3 mL cartridges in an outer carton.

NovoRapid® 3 mL FlexPen®:

3 mL solution in colourless type I glass Penfill® cartridges with a plunger (bromobutyl) and a rubber closure contained in a disposable pen.

Pack size: 5 x 3 mL pre-filled pens in an outer carton.

NovoRapid® 3 mL FlexTouch®:

3 mL solution in colourless type I glass Penfill® cartridges with a plunger (bromobutyl) and a rubber closure contained in a disposable pen.

Pack size: 5 x 3 mL pre-filled pens in an outer carton.

6.6 Special precautions for disposal and other handling

Do not use NovoRapid® if you notice that the solution is not clear, colourless and aqueous.

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

Needles, syringes, cartridges, pre-filled pens and infusion sets must not be shared

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2196

8. REGISTRATION NUMBER

34/21.1/0160

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2001

10. DATE OF REVISION OF THE TEXT

05 December 2024