APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF MEDICINE

NovoMix® 30

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains soluble insulin aspart/protamine-crystallised insulin aspart 100 U/ml in the ratio of 30/70 (recombinant DNA origin, *Saccharomyces cerevisiae*).

One unit of insulin aspart corresponds to 6 nmol, 0,035 mg salt-free anhydrous insulin aspart.

For full list of excipients, *see section 6.1*

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is sterile and white. The resuspended liquid must appear uniformly white and cloudy after agitation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NovoMix® 30 is indicated for the treatment of insulin requiring patients with diabetes mellitus.

4.2 Posology and method of administration

Posology

NovoMix 30 should not be administered intravenously (*see contraindications*)

The dosage of NovoMix® 30 for each patient is individualised.

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

Type 1 diabetes

In patients with type 1 diabetes the individual insulin requirement is usually between 0,5 and 1,0 Units/kg/day. NovoMix® 30 may fully or partially meet this requirement.

Type 2 diabetes

In patients with type 2 diabetes, NovoMix® 30 can be given as monotherapy if oral antidiabetic medicines cannot be tolerated or are contraindicated or in combination with oral antidiabetic medicines, when the blood glucose is inadequately controlled with oral antidiabetic medicines alone.

For patients with type 2 diabetes, the recommended starting dose of NovoMix® 30 is 6 U at breakfast and 6 U at dinner (evening meal).

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

When using NovoMix® 30 once daily, it is generally recommended to move to twice-daily subcutaneous injections when reaching 30 units by splitting the dose into equal breakfast and dinner doses. Dose titration should continue as needed. A NovoMix® 30 thrice-daily regimen can be safely initiated from a twice-daily regimen by splitting the morning dose

into equal morning and lunch doses. Further adjustments to a thrice-daily regimen should be made based on the recommended titration guideline below.

The following titration guideline is recommended for dose adjustments:
The lowest of three previous days' pre-meal levels should be used. The dose should not be increased if hypoglycaemia occurred within these days. Dose adjustments can be made once a week until target HbA_{1c} is reached. Pre-meal blood glucose levels should be used to evaluate the adequacy of the preceding dose as illustrated in the following table:

Pre-meal blood glucose level *(mmol/l)*	NovoMix® 30 dose adjustment *(U)*
< 4,4	- 2
4,4 – 6,1	0
6,2 – 7,8	+ 2
7,9 – 10	+ 4
> 10	+ 6

The daily insulin requirement may be higher in patients with insulin resistance (e.g. due to obesity) and lower in patients with residual endogenous insulin production.

In patients with diabetes mellitus optimised metabolic control delays the onset and slows the progression of diabetic late complications. Optimised metabolic control, including HbA_{1c} and glucose monitoring, is therefore recommended.

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.

Special populations

Renal and hepatic impairment

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

Paediatric population

Novomix® 30 can be used in adolescents and children aged 10 years and above when premixed insulin is preferred. Limited clinical data exists for children aged 6 to 9 years.

Method of administration

Avoidance of accidental mix-ups/medicine errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix® 30 and other insulin products.

NovoMix® 30 should be administered in immediate relation to a meal.
The fast onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

NovoMix® 30 is administered subcutaneously in the thigh or in the abdominal wall. If convenient, the gluteal or deltoid region may be used. Injection sites should be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (*see sections 4.4 and 4.8*).

The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Subcutaneous injection in the abdominal wall results in a faster absorption than from other injection sites. However, the faster onset of action of NovoMix® 30 is maintained regardless of injection site.

The necessity of resuspending the NovoMix® 30 suspension immediately before use is to be stressed to the patient. The resuspended liquid must appear uniformly white and cloudy.

FlexPen®: Instructions for use and handling are reflected in the patient information leaflet (Use of FlexPen®)

To avoid possible transmission of disease, FlexPen® is for single person use only.

Penfill®: Instructions for use and handling are reflected in the patient information leaflet (Use of Penfill®)

NovoMix® 30 Penfill® cartridges are designed to be used with the Novo Nordisk insulin delivery system and NovoFine® or NovoTwist® needles.

Always ensure that the injection device is assembled according to the manufacturer's directions. Please refer to the instructions included with the relevant device.

Before use, check that the Penfill® cartridge is intact (i.e. no fissures).

Do not use Penfill® if any damage is seen.

Always expel air, with the needle pointing upwards, before injection.

The needle should be removed immediately after each injection and discarded.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to insulin aspart or any of the excipients
- Intravenous injection

4.4 Special warnings and precautions for use

NovoMix® 30 should never be administered intravenously (see contraindications).

Do not use NovoMix® 30 in insulin pumps.

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

Hyperglycaemia

Inadequate dosing or discontinuation of treatment may, especially in Type 1 diabetes (insulin-dependent diabetes mellitus), lead to hyperglycaemia and diabetic ketoacidosis. The first symptoms of hyperglycaemia usually come on gradually, over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well an acetone breath. Untreated hyperglycaemic events are potentially lethal.

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. 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 may result in temporary or permanent impairment of brain function or even death.

Compared with biphasic human insulin, NovoMix® 30 may have a more pronounced glucose lowering effect up to 6 hours after injection. This may have to be compensated for in the individual patient, through adjustment of insulin dose and/or food intake.

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

Tighter control of glucose levels can increase the potential for hypoglycaemic episodes and therefore require special attention during dose intensification as outlined under the section of *Dosage and directions for use*.

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

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

Transfer from other insulin medicines

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type species, human, insulin analogue, and/or method of manufacture may result in the need for a change in dosage. Patients taking NovoMix® 30 may need a change in dosage from that used with their previous insulin. If adjustment is needed, it may be done with the first dose or during the first few weeks or months.

Injection site reactions

At the beginning of the insulin treatment injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at injection site) may occur. These reactions are usually of transitory nature.

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 medicines may be considered

Combination of pioglitazone with NovoMix 30

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 NovoMix 30 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.

NovoMix 30 is not to be used in insulin infusion pumps.

Insulin antibodies

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

4.5 Interaction with other medicines and other forms of interaction

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

The following medicines may reduce the patient's insulin requirements:

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

The following medicines may increase the patient's insulin requirements:

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

Beta-blocking medicines may mask the symptoms of hypoglycaemia and inhibit the body's response to hypoglycaemia.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

Pregnancy

Intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

After delivery, insulin requirements normally return to pre-pregnancy values.

Breastfeeding

There are no restrictions on treatment with NovoMix® 30 during lactation or for women breastfeeding their infants. However, the NovoMix® 30 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 while driving. This is particularly important in those patients who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

(a) Summary of the safety profile

Hypoglycaemia is the most common occurring adverse reactions reported during treatment.

(b) Tabulated summary of adverse reactions

The adverse reactions listed below are based on clinical trial data. The frequency categories are defined according to the following convention:

Very common (≥ 1/10); common (≥1/100 to < 1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very rare (< 1/10 000).

System Organ Class	*Side effect and frequency*
Metabolism and nutrition disorders	Very common • Hypoglycaemia
Immune system disorders:	Uncommon • Urticaria, rash, eruptions Very rare • Anaphylactic reactions
Eye disorders:	Uncommon • Refraction disorders • Diabetic retinopathy

Skin and subcutaneous tissue disorders:	Uncommon • Lipodystrophy may occur at injection site • *Not known:* Cutaneous amyloidosis†
General disorders and administration site conditions:	Uncommon • Oedema • Injection site reactions
Nervous system disorders:	Rare • Peripheral neuropathy (painful neuropathy)

† ADR from post-marketing sources

(c) Description of selected adverse reactions

Anaphylactic reactions

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

Refraction disorders

Refraction anomalies may occur at the beginning of the insulin treatment and are usually of transitory nature

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.

Peripheral neuropathy (painful neuropathy)

Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible.

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 4.3*)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications *https://www.sahpra.org.za/Publications/Index/8*

4.9 Overdose

Insulin has no specific overdose definitions, but hypoglycaemia may develop over sequential stages.

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps or a source of sugar, e.g. biscuits.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0,5 to 1,0 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 for injection, intermediate or long-acting combined with fast-acting. ATC code: A10AD05 (A 21.1 Insulin preparations)

Mechanism of action and pharmacodynamic effects

Biphasic insulin aspart has a rapid onset of action and an intermediate duration.

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.

Biphasic insulin, formulation contains 30 % soluble insulin aspart – which has a rapid onset of action. The crystalline phase of this biphasic insulin is 70 % insulin aspart protamine, which has an activity profile.

When it is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In insulin aspart, substitution of the amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers in the soluble fraction of insulin.

The insulin aspart in the soluble phase of the formulation comprises 30 % of the total insulin.

The remaining 70 % is in the crystalline form as insulin aspart protamine; this has a prolonged absorption profile.

A mean maximum serum concentration of 140 ± 32 pmol/L was reached after 60 minutes (interquartile range 45 to 70 minutes) after a subcutaneous dose of 0,20 U/kg body weight in healthy volunteers.

The mean half-life ($t_{½}$) of biphasic insulin aspart was about 8 – 9 hours (interquartile range 6,5 – 17,5 hours). Serum insulin levels returned to baseline 15 – 18 hours after a subcutaneous dose.

Special populations

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

Paediatric population

Children and adolescents: 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following preservatives are included: Phenol 0,15 % m/v and metacresol 0,172 % m/v.

Other excipients:

Glycerol, zinc chloride, disodium phosphate dihydrate, sodium chloride, protamine sulphate, hydrochloric acid, sodium hydroxide and water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine should not be mixed with other medicines.

6.3 Shelf life

Before opening:

24 months (2 years) when stored, in the refrigerator (between 2 °C and 8 °C)

During use or when carried as a spare:

4 weeks when stored at room temperature (at or below 30 °C).

6.4 Special precautions for storage

Before opening:

Unopened packs of FlexPen® / Penfill® should be stored in the carton box, in the refrigerator (between 2 °C and 8 °C), protected from light. Do not freeze.

During use or when carried as a spare:

FlexPen® / Penfill® in use or carried as spare should be kept at room temperature (at or below 30 °C) for up to 4 weeks, but should not be exposed to heat and sunlight.

Keep the Penfill in the outer carton in order to protect it from light.

keep the cap on FlexPen in order to protect from light.

Do not store FlexPen®/ Penfill® in use in the refrigerator (between 2 °C and 8 °C)

6.5 Nature and contents of container

FlexPen

NovoMix® 30, 3 ml FlexPen®, disposable pen (5 x 3 ml) is packed into carton boxes.

FlexPen® is a multi-dose disposable pre-filled syringe made of Polypropylene/Polyacetal and Polypropylene/Polyethylene in which a Penfill® cartridge of 3 ml is inserted.

Penfill®

NovoMix® 30, 3 ml Penfill® cartridges (5 x 3 ml) are made of colourless glass, containing a rubber piston and closed with a rubber disc. The cartridges contain a glass bead which helps to facilitate the re-suspension of the NovoMix® 30.

The cartridges are packed into carton boxes.

Keep out of reach of children.

6.6 Special precautions for disposal and other handling

The necessity of resuspending the NovoMix® 30 suspension immediately before use is to be stressed to the patient. The resuspended liquid must appear uniformly white and cloudy.

Before use, check that the Penfill® cartridge is intact (i.e. no fissures).

Do not use Penfill® if any damage is seen.

Always expel air, with the needle pointing upwards, before injection.

The needle should be removed immediately after each injection and discarded.

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

NovoMix 30 which has been frozen must not be used.

The Penfill cartridge must not be refilled.

Never use insulin after expiry date.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2146

8. REGISTRATION NUMBERS

35/21.1/0031

9. DATE OF FIRST AUTHORISATION

Date on the registration certificate of the medicine: 26 March 2002

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised package insert as approved by SAHPRA:

12 July 2023