AUSTRALIAN PRODUCT INFORMATION

NovoRapid® (insulin aspart (rys))
NovoMix® (soluble insulin aspart (rys)/insulin aspart (rys) crystalised with protamine)

1. NAME OF THE MEDICINE

NovoRapid® (insulin aspart (rys)) 100 U/mL solution for injection 10mL Vial
NovoRapid® Penfill® (insulin aspart (rys)) 100 U/mL solution for inejction 3mL cartridge
NovoRapid® FlexPen® (insulin aspart (rys)) 100 U/mL solution for injection 3mL cartridge
NovoRapid® FlexTouch® (insulin aspart (rys)) 100 U/mL solution for inejction 3mL cartridge
NovoMix® 30 Penfill® (30% soluble insulin aspart (rys) and 70% insulin aspart (rys) crystallised with protamine) 100 U/mL suspension for inejction 3mL cartridge
NovoMix® 30 FlexPen® (30% soluble insulin aspart (rys) and 70% insulin aspart (rys) crystallised with protamine) 100 U/mL suspension for injection 3mL cartridge
NovoMix® 50 FlexPen® (50% soluble insulin aspart (rys) and 50% insulin aspart (rys) crystallised with protamine)100 U/mL suspension for injection 3mL cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart is a rapid-acting analogue of human insulin that rapidly lowers blood glucose. Insulin aspart is homologous with human insulin with the exception of a substitution of the amino acid proline by aspartic acid at position 28 on the B-chain. The unique structure of insulin aspart increases the rate of absorption from a subcutaneous injection site, giving a faster onset of action, an earlier peak effect and a shorter duration of action than soluble human insulin. Insulin aspart should be given immediately before a meal or, when necessary, after the start of a meal.

Insulin aspart is produced by recombinant DNA technology using Saccharomyces cerevisiae. One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.

3. PHARMACEUTICAL FORM

NovoRapid is a sterile, clear, colourless, aqueous, neutral solution of insulin aspart (B28 Asp) 100 U/mL. NovoRapid is a solution for injection.

NovoMix 30 and NovoMix 50 are white suspensions for subcutaneous injection consisting, respectively, of 30% soluble insulin aspart and 70% protamine-crystallised insulin aspart, and 50% soluble insulin aspart and 50% protamine-crystallised insulin aspart. These are biphasic insulin preparations (NovoMix 30 and NovoMix 50) which produce insulin plasma profiles similar to premixed biphasic human insulin, apart from the initial faster absorption of the soluble component.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of diabetes mellitus.

4.2 Dose and Method of Administration

Dosage

NovoRapid has a faster onset and a shorter duration of action than soluble human insulin. Similarly, NovoMix products have a faster onset of action than biphasic human insulin. Due to the faster onset of

action, insulin aspart products should generally be given immediately before a meal or when necessary, soon after the start of a meal.

The dosage of insulin aspart is determined by the physician according to the patient's individual needs. The individual insulin requirement is usually between 0.5 and 1.0 Units/kg/day in adults and children. In a meal-related treatment 50-70% of this requirement may be provided by NovoRapid and the remainder provided by an intermediate-acting or long-acting insulin given at least once a day. Alternatively, the daily insulin requirement may be fully or partially supplied with NovoMix products.

The recommended starting dose of NovoMix products in combination with metformin is 0.2 Units/kg/day and should be adjusted depending on individual requirements based on blood glucose response.

Method of Administration

NovoRapid 10mL Vial may be used for continuous subcutaneous insulin infusion ('CSII') in pump systems suitable for insulin infusion (see section 5.1 Pharmacodynamic Properties - Clinical Trials). When used in external insulin infusion pumps the initial programming of the pump should be based on the total daily insulin dose on the previous regimen. Approximately 50% of the total dose is to be given as the basal rate, and the remainder is to be divided between breakfast, lunch, dinner and snacks. The usual individual daily insulin requirement of between 0.5 and 1.0 U/kg/day also applies when NovoRapid is used in CSII.

When used in an insulin infusion pump NovoRapid should not be mixed with any other medicinal products. Patients using CSII should be comprehensively instructed in the use of the pump system. The infusion and reservoir set should be changed every 48 hours using aseptic technique. Patients administering NovoRapid by CSII must always carry a spare vial of NovoRapid and a U100 syringe, or an alternative insulin delivery system, in case of pump system failure.

Insulin aspart products are administered by subcutaneous injection in the abdominal wall, the thigh, the deltoid region or the gluteal region. NovoRapid may also be administered by subcutaneous infusion in the abdominal wall. Injection and infusion sites should be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable Effects)). When injected subcutaneously into the abdominal wall, the onset of action for insulin aspart products, will occur within 10-20 minutes of injection. For NovoRapid, the maximum effect is exerted between 1 and 3 hours after the injection, and the duration of action is 3 to 5 hours. The duration of action of NovoMix 30 is up to 24 hours. The duration of action of NovoMix 50 is up to 16 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. Based on studies of soluble insulin aspart and soluble human insulin, subcutaneous injection in the abdominal wall is expected to result in a faster absorption than from other injection sites. However, the faster onset of action of insulin aspart products compared to their respective human insulin products is expected to be maintained regardless of injection site. Formal studies on the bioavailability of NovoRapid administered by subcutaneous injection in the gluteal region have not been conducted.

NovoRapid may be administered intravenously under medical supervision. For emergency use with Penfill®/FlexPen®/FlexTouch® the NovoRapid must first be withdrawn into a syringe. Discard Penfill/FlexPen/FlexTouch cartridge/pen after emergency use. NovoRapid has been used intravenously (see section 5.1 Pharmacodynamic Properties - Clinical Trials). No studies have been conducted in critically ill people with diabetes who are likely to require intravenous administration. There is no pharmacokinetic or pharmacodynamic advantage in using NovoRapid over soluble human insulin when these insulins are given intravenously.

NovoMix products should never be administered intravenously. Intramuscular administration should be avoided.

Dosage Adjustment

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

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

As with all insulins, in elderly patients and patients with hepatic or renal impairment glucose monitoring should be intensified and dosage adjusted on an individual basis.

Transfer of patients to insulin aspart products

NovoRapid differs from human insulin by its rapid onset and shorter duration of action. NovoMix products also differ from human insulin by their faster onset. Because of the rapid onset of action, the injection of insulin aspart products should immediately be followed by a meal.

Insulin aspart products are equipotent to their respective human insulin products, in regards to hypoglycaemic effect, receptor affinity and effect on lipogenesis. Patients currently treated with human insulin can be transferred to NovoRapid or NovoMix products on a unit for unit basis when administered just before a meal. Although no change in dose is anticipated other than the routine adjustments made in order to maintain stable diabetic control, any change to insulin therapy should be made under medical supervision and blood glucose should be monitored.

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.

Instructions for use and handling

10mL vials

NovoRapid vials are for use with U100 insulin syringes and for use with an infusion pump system. The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling.

Penfill 3mL cartridges

The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. The leaflet refers to the instructions for using the accompanying Novo Nordisk insulin delivery system.

The suspension contained within NovoMix Penfill products must be resuspended after removal from the refrigerator and immediately before use so that it appears uniformly white and cloudy. It is recommended to allow the insulin to reach room temperature before resuspending. *The necessity to resuspend immediately before use is to be stressed to the patient.*

Insulin aspart Penfill products are for use by one person only. The cartridges must not be refilled.

Insulin aspart Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine® needles.

Failure to change the needle may result in needle blockage. The patient should be advised to discard the needle after each injection.

FlexPen 3mL

The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. Please note that insulin is not delivered if the patient reverse dials the insulin pen by returning the dose selector to zero after inserting the needle. Patients should be instructed that insulin injection only occurs when the pushbutton is depressed.

The suspension contained within NovoMix FlexPen products must be resuspended after removal from the refrigerator and immediately before use so that it appears uniformly white and cloudy. It is recommended to allow the insulin to reach room temperature before resuspending. *The necessity to resuspend immediately before use is to be stressed to the patient.*

Insulin aspart FlexPen products are for use by one person only. The cartridge inside the pen must not be refilled.

NovoFine needles up to a length of 8 mm are designed to be used with insulin aspart FlexPen products.

Failure to change the needle may result in needle blockage.The patient should be advised to discard the needle after each injection.

FlexTouch 3mL
The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling.

NovoRapid FlexTouch is for use by one person only. The cartridge inside the pen must not be refilled.

NovoFine needles up to a length of 8 mm are designed to be used with NovoRapid FlexTouch.

Failure to change the needle may result in needle blockage. The patient should be advised to discard the needle after each injection.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

Avoidance of accidental mix-ups/medication errors
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoRapid or NovoMix and other insulins.

Hyperglycaemia
Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. 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 breath. Untreated hyperglycaemic events may be life threatening.

Hypoglycaemia
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia (see section 4.8 Adverse Effects (Undesirable Effects) and section 4.9 Overdose).

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

Insulin aspart products should be administered immediately before a meal or, when necessary, after the start of a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements.

Renal or hepatic impairment, or concomitant diseases in the kidney or liver or affecting the adrenal, pituitary or thyroid gland, can require changes in the insulin dose.

Care should be taken, especially in children, to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose levels in order to minimise the risk of hypoglycaemia.

Injection site reactions
As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, bruising, swelling and inflammation. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of insulin aspart products.

Insulin aspart products contain metacresol which on rare occasions may cause allergic reactions.

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.

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

Transfer of patients between insulin types
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (human insulin, insulin analogue) and/or method of manufacture may result in the need for a change in dosage. Patients transferred to insulin aspart from another type of insulin may require an increased number of daily injections or a change in dosage from that used with their usual insulin products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

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

General
NovoMix products are not to be used in insulin infusion pumps.

Paediatric use
Safety and effectiveness of NovoMix products in children and adolescents under the age of 18 have not been assessed due to limited clinical experience.

Use in the elderly
See section 5.2 Pharmacokinetic Properties.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Form of Interactions

A number of drugs are known to interact with glucose metabolism. Possible interactions must therefore be taken into account by the physician.

The following substances may reduce the patient's insulin requirements:
Oral hypoglycaemic agents (OHAs), monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulfonamides.

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

Beta blockers may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

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

Alcohol may intensify and prolong, or reduce, the hypoglycaemic effect of insulin.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
In reproductive toxicity studies, insulin aspart did not affect the fertility of male and female rats but caused a slight increase in pre-implantation loss at subcutaneous doses greater than 10U/kg/day. Similar effects were seen with human insulin.

Use in pregnancy
Pregnancy Category: A
Insulin aspart can be used in pregnancy. Data from two randomised controlled clinical trials with NovoRapid (157 + 14 insulin aspart-exposed pregnancies, respectively) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1 Pharmacodynamic Properties - Clinical Trials).

There are no clinical trials with biphasic insulin aspart in pregnancy.

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

Use in lactation
Although no clinical trial data are available with insulin aspart products during lactation, there are no restrictions on treatment with these medicines during lactation. Insulin treatment of the nursing mother should not affect the baby. However, the dosage of insulin aspart 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 to avoid hypoglycaemia while driving or operating a machine. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving or operating a machine should be considered in these circumstances.

4.8 Adverse Effects (Undesirable Effects)

Summary of the safety profile

The safety profile of insulin aspart products observed in clinical trials is similar to the safety profile reported for the respective Novo Nordisk human insulin products.

Adverse drug reactions observed in patients using insulin aspart products are mainly dose-dependent and due to the pharmacological effect of insulin. As for other insulin products, hypoglycaemia in general is the most frequently occurring undesirable effect. In clinical trials and during marketed use the frequency varies with patient population, dose regimens and level of glycaemic control. Therefore no specific frequency can be presented, see 'Description of selected adverse reactions' below.

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

Tabulated list of adverse reactions

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: very common (≥ 1/10), 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 - Generalised hypersensitivity reactions*
Metabolism and nutrition disorders	Very common - Hypoglycaemia*
Nervous system disorders	Rare - Peripheral neuropathy
Eye disorders	Uncommon - Refraction disorders
	Uncommon - Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon - Lipodystrophy*
General disorders and administration site conditions	Uncommon - Injection site reactions
	Uncommon - Oedema

*see 'Description of selected adverse reactions'

Adverse reactions listed below are based on post-marketing source data and classified according to MedDRA System Organ Class.

Skin and subcutaneous tissue disorders	Not known – Cutaneous amyloidosis*

*see 'Description of selected adverse reactions'

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product 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 at http://www.tga.gov.au/reporting-problems.

Description of selected adverse reactions

Generalised hypersensitivity reactions
Symptoms 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.

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

During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared with human insulin.

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the particular area may help to reduce or prevent these reactions (see section 4.4 Special Warnings and Precautions for Use).

Antibody production
In a Phase III study of NovoMix 30, the level of antibodies cross-reactive to human insulin and insulin aspart showed an increase during the first 3 months which persisted at a lower level after 12 and 24 months. After 24 months of treatment a correlation was found between absolute antibody level and absolute insulin dose; no correlation, however, was found between the increase in antibody formation and the increase in insulin dose. There was no significant correlation with glycaemic control attained or adverse event reporting. The long-term clinical significance of insulin antibodies is uncertain. Antibodies were not extensively investigated during the NovoMix 50 development programme since immunogenicity and assay methodology for NovoMix 30 can be applied to NovoMix 50.

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the person with diabetes always carry products containing sugar with them.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or with glucose given intravenously by a medical professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, oral administration of carbohydrate is recommended for the patient in order to prevent relapse.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action
Insulin lowers blood glucose levels by binding to insulin receptors to increase glucose uptake and inhibit hepatic glucose output.

As with all insulins in clinical practice, the duration of action of insulin aspart will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

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

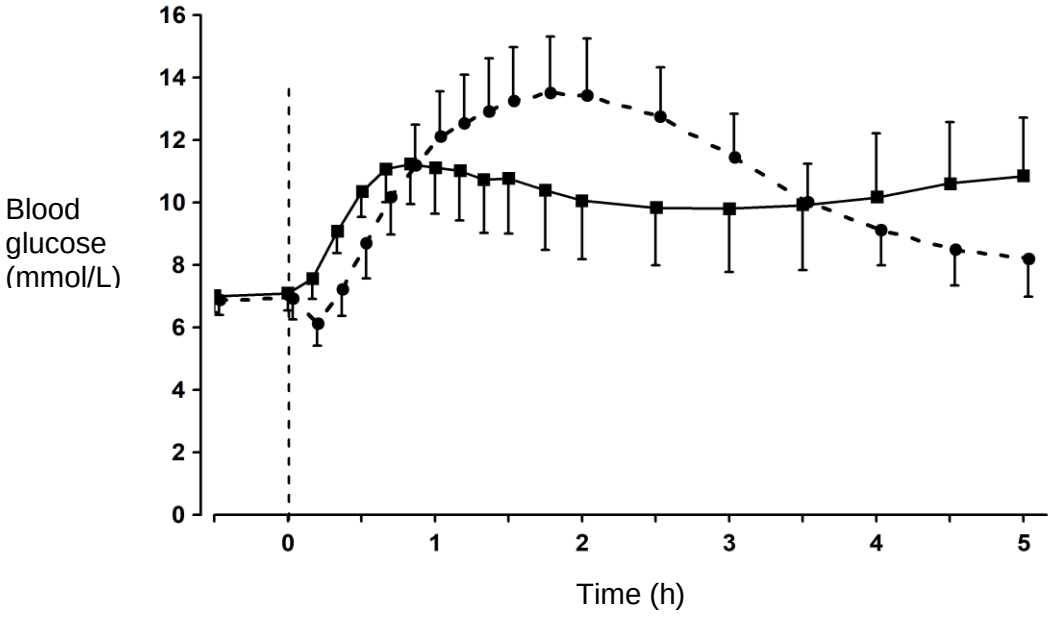
NovoRapid
NovoRapid produces a more rapid and pronounced blood glucose lowering effect than soluble human insulin, due to the faster onset of action.

NovoRapid has a shorter duration of action compared to soluble human insulin after subcutaneous injection (Fig.1).

When administered immediately before a meal, the effect of NovoRapid more closely mimics normal physiological postprandial insulin release than soluble human insulin.

The onset of action of NovoRapid occurs within 10-20 minutes of subcutaneous injection. The maximum effect is exerted between 1 and 3 hours after injection. The duration of action is 3 to 5 hours. NovoRapid has a more predictable time to peak effect within subjects than soluble human insulin.

Fig. 1: Blood glucose concentrations* (mean +/- 2SEM) following a single pre-meal dose (0.15 U/kg) of NovoRapid injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (dashed curve) in patients with type 1 diabetes mellitus.



* Data from Trial 024/UK, a randomised, double-blind, crossover trial involving 24 subjectspatients.

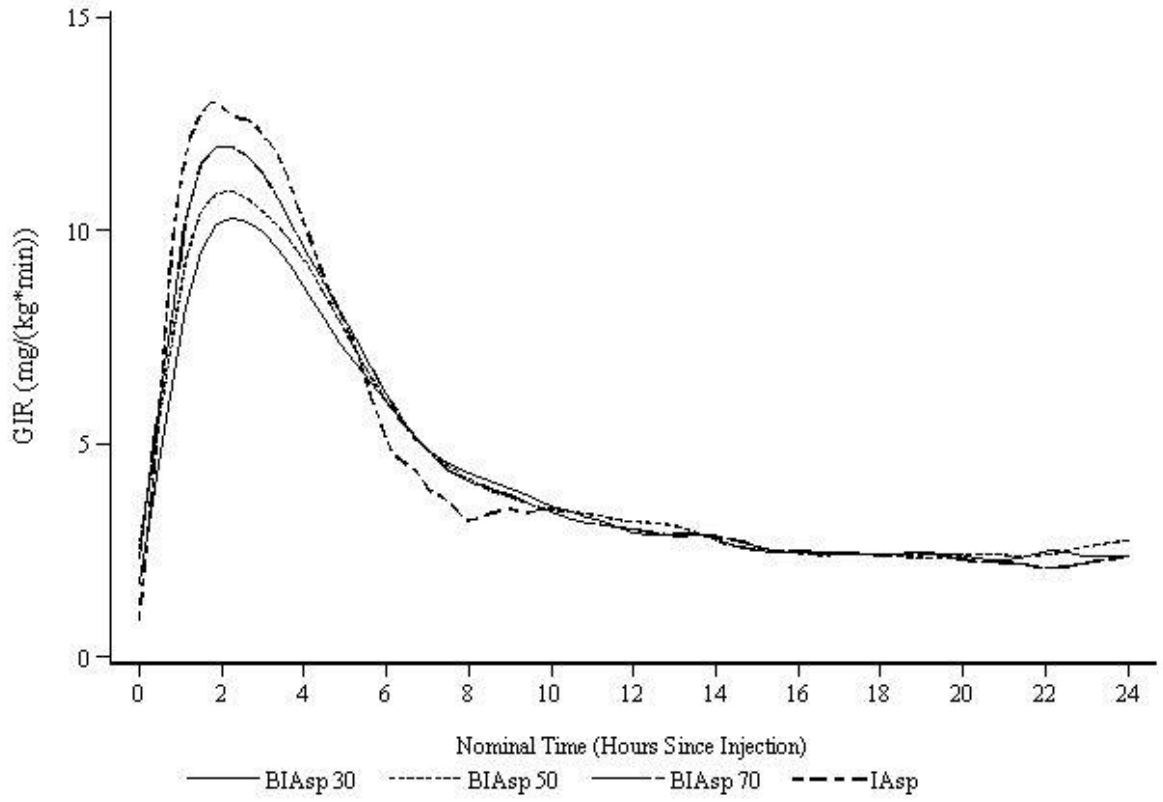
NovoMix products
NovoMix 30 and NovoMix 50 are biphasic insulins which contain, respectively, 30% and 50% soluble insulin aspart. This has a rapid onset of action, and NovoMix products should thus be given closer to a meal than biphasic human insulin. The crystalline phase in NovoMix 30 and NovoMix 50 is, respectively, 70% or 50% insulin aspart protamine, which has an activity profile similar to that of human isophane (NPH) insulin.

The onset of action of NovoMix products occurs within 10-20 minutes of subcutaneous injection. The maximum effect is exerted between 1 and 4 hours after injection (Figure 2). The duration of action of NovoMix 30 is up to 24 hours. The duration of action of NovoMix 50 is up to 16 hours.

When injected immediately before a meal, NovoMix products have been demonstrated to better control postprandial hyperglycaemia than a corresponding 30/70 biphasic human insulin (Figure 3). This improvement in postprandial glycaemia is not of established clinical value.

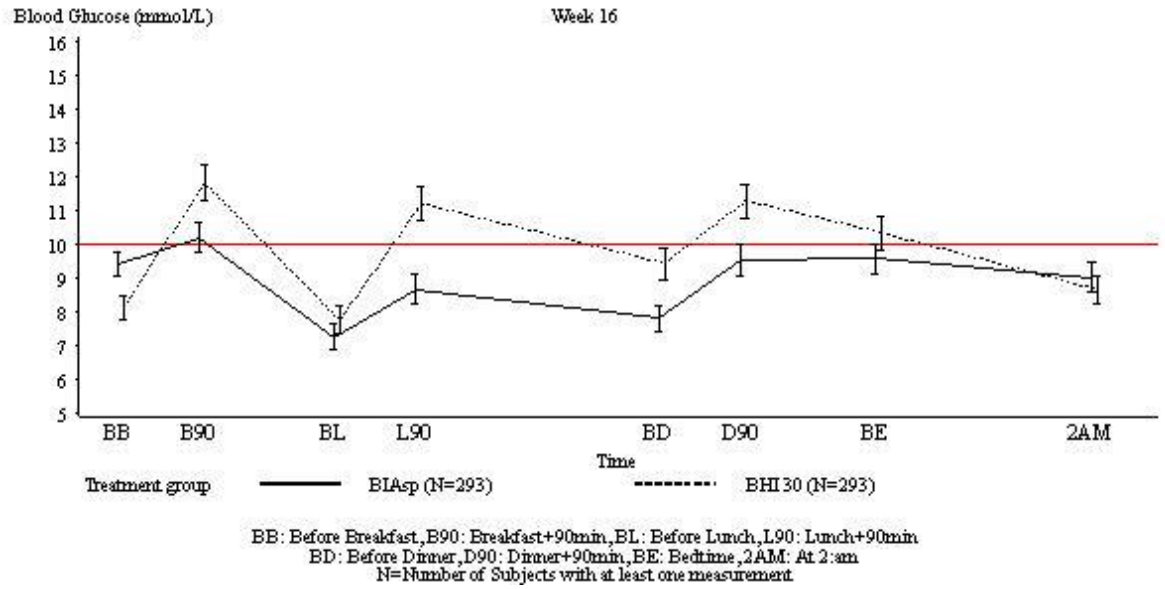
When combined with once-daily (dinnertime) NovoMix 30, twice-daily (breakfast and lunch) NovoMix 50 is able to provide glycaemic control that is non-inferior to that obtained with four daily (basal bolus) treatment with insulin aspart plus NPH, in type 2 diabetes.

Fig. 2. Smoothed mean glucose infusion rate curves after 0.3 U/kg doses of BIAsp 30, 50 and 70, and soluble insulin aspart.



*Data from trial BIAsp-1086, a randomised, phase I PK/PD (euglycaemic clamp) study in 34 healthy subjects.

Fig. 3. Self monitored blood glucose (mean ± 2SEM) in patients with diabetes treated with thrice-daily BIAsp (NovoMix 50 or NovoMix 70 t.i.d.; NovoMix 30 at dinner where required) or biphasic human insulin 30/70.



*Data from trial BIAsp-1075 --- a 16 week, multicentre, open-labelled, randomised, parallel-group Phase III study.

Clinical trials

NovoRapid
Adults: Clinical trials with NovoRapid have demonstrated an improved postprandial blood glucose control compared to soluble human insulin. In long-term trials, NovoRapid has shown a small but statistically significant improvement in glycosylated haemoglobin with no increase in hypoglycaemic events compared to soluble human insulin. In the pivotal trials, NovoRapid has shown a statistically significant reduction in the number of patients experiencing major nocturnal hypoglycaemia compared to soluble human insulin. Hypoglycaemic events with insulin aspart were seen at 2-4 hours post dose compared to 2-7 hours with soluble human insulin. There were no safety issues with NovoRapid and no evidence of increased immunogenicity with NovoRapid compared with soluble human insulin.

There were four adequate and well-controlled clinical trials in the insulin aspart clinical development program: one phase II trial in men with type I diabetes (025/UK), and three phase III trials - two in adults with type 1 diabetes (035/EU and 036/USA), and one in adults with type 2 diabetes (037/USA). In all pivotal efficacy trials, NovoRapid was administered immediately before meals, and soluble human insulin was dosed 30 minutes before meals. The phase III trials involved a wide variety of people (aged 18 - 77 years) with type 1 and 2 diabetes.

Elderly: A randomised, double-blind cross-over PK/PD (ANA-1416) trial comparing insulin aspart with soluble human insulin was performed in elderly subjects with type 2 diabetes (19 patients aged 65-83 years, mean age 70 years). The relative differences in the pharmacodynamic properties between insulin aspart and soluble human insulin in elderly were consistent with those seen in healthy patients and in younger subjects with diabetes. No safety issues were raised, but careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients.

Children and adolescents: Limited data suggest that when given to children NovoRapid showed similar glucose control compared to soluble human insulin. A clinical trial (ANA-1415) comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (26 patients aged 2 to 6 years), and a single dose PK/PD trial (043/UK) 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. Long term data in children, including the effects on growth and development, are not available.

Continuous subcutaneous insulin infusion ('CSII'): Compatibility with NovoRapid was investigated in MiniMed 506 and Disetronic H-TRON pIus V-100 infusion pumps, and in MiniMed Polyfin (MMT-106) and Sof-set (MMT-111) and Disetronic Classic and Tender infusion sets. The infusion sets used in compatibility testing employed the same materials as the MiniMed systems registered in Australia. Two clinical trials (ANA-2018/US and ANA-2024/US) were conducted to evaluate the safety and efficacy of NovoRapid when administered by continuous subcutaneous insulin infusion (`CSII'). Clinical use was investigated in MiniMed 506, 507, 507c and Disetronic H-TRON plus V-100 insulin infusion pumps; of these, Disetronic H-TRON plus V-100, MiniMed 507 and 507c are registered in Australia.

025/UK, 035EU, 036/USA and 037/USA
The pivotal phase II and III trials, were multi-centre, randomised, active-controlled studies of 1 month (025/UK) or 6 months (035/EU, 036/USA and 037/USA) duration, designed to evaluate short- and long term efficacy and safety of NovoRapid compared to soluble human insulin in type 1 and type 2 diabetes.

In the short term study, the NovoRapid glucose profiles were lower after meals and higher during the night than soluble human insulin. Overall 24-hour glucose control, as assessed by the excursion of glucose level outside the range 4.0 – 7.0 mmol/L, was significantly improved with NovoRapid. The number of major hypoglycaemic events was significantly lower with NovoRapid than soluble human insulin. The minor hypoglycaemic event rate with NovoRapid was the same as, if not lower than, the soluble human insulin but with fewer events during the night.

In the 6 month phase III studies, treatment with NovoRapid significantly improved HbA_{1c} in patients with type 1 diabetes. A similar improvement in HbA_{1c} was observed in type 2 patients, but was not significant due to the lower number of patients (Table 1).

Table 1: HbA_{1c} after 6 Months Treatment - Phase III Trials (ITT Population)

	NovoRapid		Soluble human insulin				
Trial	n	Mean (SEM)	n	Mean (SEM)	Difference in Mean	95% C.I.	P
Type 1 Diabetes							
036/USA	585	7.78(0.03)	278	7.93(0.05)	-0.15	[-0.26 to -0.05]	0.0048
035/EU	694	7.88(0.03)	346	8.00(0.04)	-0.12	[-0.22 to -0.03]	0.0137
Type 2 Diabetes							
037/USA	90	7.70(0.09)	86	7.82(0.10)	-0.12	[-0.38 to 0.14]	0.3684

Postprandial glucose levels and mean prandial glucose increments were significantly lower in the NovoRapid treated than in the soluble human insulin treated type 1 patients.

Overall, the relative risk of major hypoglycaemic events was 19% lower with NovoRapid compared to soluble human insulin. The number of mild hypoglycaemic events was similar between insulin groups. Treatment with NovoRapid led to higher glucose levels at night compared to human insulin, resulting in a lower incidence of nocturnal, major hypoglycaemic events. Specifically, compared to soluble human insulin, there was a 50% lower risk of experiencing a major nocturnal hypoglycaemic event with NovoRapid (p=0.013) in the 036/USA trial and, similarly, a 30% lower risk with NovoRapid (p=0.076) in the 035/EU trial.

ANA-2024/US
This was a multi-centre, open-label, parallel-group, phase IIIb study in which 146 adults with type 1 diabetes were randomised 2:2:1 to receive NovoRapid, buffered regular insulin or insulin lispro by CSII over a 4-week dose adjustment period and 12-week maintenance periods. All subjects had been on other

forms of CSII for at least 3 months prior to study entry. The primary efficacy outcome measure was a comparison against baseline of HbA_{1c} values at 16 weeks. The major endpoints for the safety analysis were comparisons of the numbers of adverse events and hypoglycaemic episodes.

Change-from-baseline values of HbA_{1c}, blood glucose variability, average daily insulin use or body weight were not significantly different between treatment groups at any time point. The adverse event profile of NovoRapid was similar to that of buffered regular insulin and insulin lispro, and the three treatment groups had similar rates of hypoglycaemia. When administered as continuous subcutaneous insulin infusion in a pump, NovoRapid was shown to be as safe and effective as buffered regular human insulin.

ANA/DCD/066
This phase IIIb, double-blind, randomized, cross-over, multi-centre trial compared the frequency of major hypoglycaemic episodes after 16 weeks treatment with NovoRapid versus 16 weeks treatment with soluble human insulin in 139 adults with well-controlled type 1 diabetes treated on a basal bolus regimen. Frequency of major hypoglycaemic episodes during the treatment periods was the primary endpoint.

A statistically non-significant (p=0.119) NovoRapid/soluble human insulin relative risk for major hypoglycaemia of 0.72 (95% CI: 0.47-1.09) was found. A secondary finding was that subjects treated with NovoRapid experienced a significantly (p=0.001) lower rate of major hypoglycaemic episodes during the night (midnight-6am). The estimated NovoRapid/soluble human insulin relative risk was 0.28 (95% CI: 0.13-0.59). This was not a predefined endpoint in the study protocol and this result represents a post hoc analysis. A statistically significant (p=0.048) reduction in the frequency of minor hypoglycaemic episodes was found with NovoRapid treatment (N=1590) compared to human soluble insulin (N=1752), with the estimated NovoRapid/soluble human insulin relative risk being 0.93 (95% CI: 0.87-1.00). No significant differences between insulin aspart and human soluble insulin were found for the investigated glycaemic control parameters or in the domain scores of the Quality of Life questionnaires. The statistical testing was not adjusted for the multiple variables examined.

028/UK
This phase II trial was conducted in 16 subjects with well controlled type 1 diabetes who did not require intravenous therapy. Both NovoRapid and human soluble insulin were given intravenously to determine the blood glucose threshold for autonomic activation during hypoglycaemia. There were no statistically significant differences between NovoRapid and soluble human insulin. No advantage is expected in giving NovoRapid intravenously over soluble human insulin intravenously.

ANA-1415
A clinical trial investigated the safety and efficacy of insulin aspart (N = 26) vs. soluble human insulin (N = 26) in children with type 1 diabetes aged 2 – 6 years. Human NPH insulin was used as the basal insulin in both groups. Similar results for the two primary safety and efficacy endpoints (frequency of hypoglycaemic episodes and postprandial glucose increment, respectively), as well as the secondary endpoints, were observed with both regimens.

ANA-1474 and -2067
A clinical trial comparing safety and efficacy of insulin aspart vs. soluble human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies: insulin aspart, N = 157; human insulin, N = 165) did not detect any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn. Efficacy when measured by HbA_{1c} was observed to be comparable to insulin aspart versus soluble human insulin, whilst mean prandial glucose increments were significantly improved for insulin aspart during the first and third trimesters. In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. soluble human insulin (insulin aspart, N = 14; soluble human insulin, N = 13) showed similar safety profiles between treatments.

NovoMix products

038

In a 3 month, multicentre, open-labelled, randomised, parallel group Phase III study, NovoMix 30 was as effective as biphasic human insulin (BHI) in overall glycaemic control (Table 2).

Table 2: Glycaemic control of NovoMix 30 versus BHI as measured by HbA_{1c} (%) and prandial increment over the three meals (mmol/L) in people with type 1 or type 2 diabetes

	Biphasic Insulin Aspart		**Biphasic Human Insulin 30/70**				
	N	**Mean (SEM)**	**N**	**Mean (SEM)**	**Difference in Mean**	**95%C.I.**	**P**
HbA_{1c}	132	8.14 (0.06)	143	8.15 (0.06)	-0.01	-0.14 to 0.12	NS
prandial increments	128	1.66 (0.20)	141	2.34 (0.19)	-0.68	-1.20 to –0.16	<0.02

There were no safety issues with NovoMix 30 compared with human insulin.

1241

This was a multinational, open-label, parallel-group trial in 329 subjects with type 2 diabetes. The primary objective of the trial was to compare glycaemic control between the existing 'gold standard' metformin plus add-on treatment with sulphonylurea (glibenclamide), against metformin plus add-on treatment with NovoMix 30 b.i.d., and against NovoMix 30 b.i.d. monotherapy, in patients inadequately controlled on current metformin monotherapy. Subjects were randomised to receive as add-on therapy with metformin either NovoMix 30 b.i.d. (108 subjects exposed), or glibenclamide (114 subjects exposed), or to receive NovoMix 30 b.i.d. monotherapy (107 subjects exposed). After 16 weeks of treatment decreases in mean HbA_{1c} levels relative to baseline of at least 1.5% were observed for all three treatment groups. The mean level of HbA_{1c} at end of trial was statistically significantly lower for the NovoMix 30+Met group than for the NovoMix 30 Mono group (by 0.39%, p=0.0074).

1075

The primary analysis of the 1075 trial (a 16 week, multicentre, open-labelled, randomised, parallel group Phase III study) confirmed that the thrice-daily 'BIAsp' treatment regimen (NovoMix 50 or NovoMix 70 t.i.d.; NovoMix 30 at dinner where required) resulted in a lower level of HbA_{1c} at study end than the twice-daily regimen with BHI (estimated mean difference: -0.32%, p = 0.0001; Table 3). The initial total daily dose of BIAsp (t.i.d.) was increased by 10% as compared with the initial total daily dose of BHI (b.i.d.) The relative risk of minor hypoglycaemia was higher in the BIAsp group. Most episodes were observed during daytime (85% of all events of minor hypoglycaemia with BIAsp occurred between 8 a.m. and 10 p.m.)

Table 3: Glycaemic control of BIAsp versus BHI as measured by HbA_{1c} (%) in people with type 1 or type 2 diabetes

	BIAsp (biphasic insulin aspart)		**BHI (biphasic human insulin)**		**BIAsp - BHI**		
	N	**Mean (SEM)**	**N**	**Mean (SEM)**	**Est. mean difference**	**95%C.I.**	**P**
All subjects	296	8.35 (0.06)	291	8.67 (0.06)	-0.32	[-0.48 ; -0.16]	0.0001
Type 2	224	8.29 (0.07)	207	8.68 (0.07)	-0.38	[-0.57 ; -0.19]	0.0001
Type 1	72	8.54 (0.11)	84	8.66 (0.10)	-0.12	[-0.41 ; 0.17]	0.4105

1486
A 16 week, non-treat-to-target, randomized, open-label parallel group trial compared basal bolus treatment with insulin aspart at mealtimes and NPH at bedtime versus NovoMix 50 with breakfast and lunch and NovoMix 30 with dinner, and versus NovoMix 70 with breakfast and lunch and NovoMix 30 with dinner, in subjects with type 2 diabetes. Three daily injections with the NovoMix insulins (split approx. 30%, 20% and 50% of total daily dose before breakfast, lunch and dinner, respectively) provided glycaemic control (as measured by HbA_{1c}) that was non-inferior to that obtained by four daily injections in basal bolus treatment with insulin aspart plus NPH.

Table 4: NovoMix 50 and NovoMix70 versus IAsp+NPH in type 2 diabetes - glycemic parameters at the end of treatment [mean ± (SD)]

	NovoMix 50*	***IAsp + NPH***	***NovoMix 70****	***IAsp + NPH***
Body mass index	> 30		<= 30	
Baseline	N=94	N=89	N=102	N=109
HbA_{1c} (%)	9.1 ± 0.7	9.0 ± 0.7	9.1 ± 0.7	9.2 ± 0.7
End-of-Study	N=88	N=84	N=94	N= 103
HbA_{1c} (%)	7.8 ± 1.1	7.8 ± 1.0	7.8 ± 0.9	7.8 ± 1.0

From study BIAsp 1486.
*b.i.d. (breakfast and lunch) + NovoMix 30 (dinner)

5.2 Pharmacokinetic Properties

Human insulin molecules self-associate to form hexamers. The substitution of proline by aspartic acid at position B28 in insulin aspart produces an intermolecular repulsion which reduces the tendency of the insulin molecules to self-associate. This increases the rate of dissociation of hexamers into dimers and monomers in the subcutaneous layer.

NovoRapid is more rapidly absorbed from the subcutaneous layer than soluble human insulin. The insulin aspart in the soluble phases of NovoMix 30 and NovoMix 50 comprise, respectively, 30%, and50% of the total insulin: this is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 70% or 50% (respectively) is in crystalline form as insulin aspart protamine; this has a similar prolonged absorption profile to human NPH (isophane or protamine-crystallised) insulin.

NovoRapid
The t_{max} is on average half of that for soluble human insulin. In different studies, the t_{max} was reached after 40-50 minutes with NovoRapid compared to 80-120 minutes for soluble human insulin. The intra-individual variability in t_{max} is significantly less for NovoRapid than for soluble human insulin.

The C_{max} is on average at least twice as high with NovoRapid than with soluble human insulin. In one study in subjects with type 1 diabetes, the mean C_{max} was 492 pmol/L with NovoRapid and 216 pmol/L with soluble human insulin (administered at a dose of 0.15 U/kg bodyweight). The return to baseline insulin levels is faster with NovoRapid than soluble human insulin.

In a clinical study in healthy subjects, the pharmacokinetic differences between NovoRapid and soluble human insulin, were maintained independent of the injection site (abdomen, thigh or deltoid).

Insulin aspart has a low binding to plasma proteins, 0-9%. After subcutaneous administration, insulin aspart was more rapidly eliminated than soluble human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for soluble human insulin.

NovoMix 30
The C_{max} is, on average, 50% higher with NovoMix 30 than with biphasic human insulin 30/70. The T_{max} is, on average, half of that for biphasic human insulin 30/70. 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 NovoMix 30 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.

NovoMix® 50
In healthy volunteers a C_{max} of 445 ± 135 pmol/L was reached about 60 minutes after a subcutaneous dose of **0.30 U/kg** body weight. In type 2 patients, the maximum concentration was reached about 95 minutes after dosing.

Special patient populations
Children: The pharmacokinetic and pharmacodynamic properties of soluble insulin aspart were investigated in children (6-12 years) and adolescents (13-17 years) with type 1 diabetes. The relative difference in pharmacokinetics and pharmacodynamics in children and adolescents with type 1 diabetes between soluble insulin aspart and soluble human insulin correlated well with those in healthy adult subjects and adults with type 1 diabetes. The pharmacokinetics of biphasic insulin aspart have not been investigated in children.

Elderly: The relative differences in pharmacokinetic properties between soluble insulin aspart and soluble human insulin in elderly subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes; i.e. the significantly earlier and higher Cmax is maintained with soluble insulin aspart. As in younger subjects with type 2 diabetes, tmax of soluble insulin aspart may be slightly delayed in elderly subjects with type 2 diabetes, though still significantly earlier than for human insulin. The pharmacokinetics of biphasic insulin aspart have not been investigated in the elderly.

Hepatic impairment: A single dose pharmacokinetic study of soluble insulin aspart was performed in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment absorption rate was decreased and more variable, resulting in delayed tmax from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, Cmax and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function. The pharmacokinetics of biphasic insulin aspart have not been investigated in this population.

Renal impairment: A single dose pharmacokinetic study of soluble insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, Cmax and CL of soluble insulin aspart was found. The PK in subjects with renal failure necessitating dialysis treatment was not investigated. Special precautions should be taken in these patients as insulin clearance may be reduced. The pharmacokinetics of biphasic insulin aspart have not been investigated in this population.

5.3 Preclinical Safety Data

Genotoxicity
Insulin aspart did not cause gene mutations, chromosomal damage or DNA damage in a range of genotoxicity tests.

Carcinogenicity
Lifetime carcinogenicity studies of insulin aspart have not been performed in animals. In 52-week repeat dose toxicity studies in Sprague-Dawley rats at doses up to 50 U/kg/d SC, the only significant toxicity findings were related to hypoglycaemia. At a higher dose of 200 U/kg/d SC in female Sprague-Dawley rats, insulin aspart, like human insulin, caused induction of mammary tumours. The clinical relevance of these findings is not known. Neither clinical nor epidemiological studies conducted to date have

shown an association between insulin use and carcinogenesis but the available evidence is considered too limited to be conclusive at this time. *In vitro* studies showed that the mitogenic activity of insulin aspart does not differ from that observed with human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

NovoRapid contains the following inactive ingredients: glycerol, phenol, metacresol, zinc chloride, dibasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

NovoMix 30 and NovoMix 50 contain the following inactive ingredients: protamine sulfate (a fish product), glycerol, phenol, metacresol, zinc chloride, dibasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

6.2 Incompatibilities

In general, insulin aspart products should only be added to compounds with which they have known compatibility. Drugs added to the insulin may cause degradation of the insulin, e.g. if the drugs contain thiols or sulphites.

NovoMix products should not be added to infusion fluids.

6.3 Shelf Life

The shelf-life is 30 months for NovoRapid and 24 months for NovoMix products when stored between 2ºC and 8ºC. After first opening or carried as a spare: A maximum of 4 weeks, any remainder must then be discarded.

6.4 Special Precautions for Storage

Insulin aspart products should be stored between 2ºC and 8°C. Do not freeze. Insulin aspart products which have been frozen must not be used.

NovoRapid FlexPen/FlexTouch: After first opening or carried as a spare:Can be kept at ambient temperature (below 30ºC) or stored in a refrigerator (2°C – 8°C). .

NovoRapid Vial/Penfill: After first opening or carried as a spare: Do not refrigerate. Store below 30°C.

NovoMix FlexPen/Penfill: After first opening or carried as a spare: Do not refrigerate. Store below 30°C.

Insulin aspart products should not be exposed to excessive heat or sunlight. Keep the product in the carton (vial, Penfill) or keep the cap on (FlexPen, FlexTouch) when not in use, to protect it from light.

It is recommended that NovoMix products in use or carried as spares be resuspended after removal from the refrigerator and immediately before use. It is recommended to allow the insulin to reach room temperature before resuspending.

6.5 Nature and Contents of Container

NovoRapid contains insulin aspart 100 U/mL. NovoMix 30 and NovoMix 50 products contain biphasic insulin aspart 100 U/mL. The following presentations are available:

10mL Vial

The 10mL glass vial is closed with a latex-free bromobutyl/polyisoprene rubber disc and a protective tamper-proof plastic cap. One 10mL vial is packed in a carton.

NovoRapid 10mL vial

Penfill 3mL
Penfill cartridge is made of glass, contains a bromobutyl rubber piston and is closed with a latex-free bromobutyl/polyisoprene rubber disc. NovoMix 30 Penfill also contain a glass ball within the cartridge to facilitate resuspension. Five 3mL Penfill cartridges are packed in a carton.

NovoRapid Penfill, NovoMix 30 Penfill.

FlexPen 3mL
FlexPen is a pre-filled, multidose, disposable pen consisting of a pen injector and a 3mL cartridge. The cartridge is made of glass, contains a bromobutyl rubber piston and is closed with a latex-free rubber bromobutyl/polyisoprene disc. The cartridges contained within NovoMix FlexPen products also contain a glass ball to facilitate resuspension. The pen injector is made of plastic (polypropylene). Five FlexPen are packed in a carton.

NovoRapid FlexPen, NovoMix 30 FlexPen, NovoMix 50 FlexPen.

FlexTouch 3mL
FlexTouch is a pre-filled, multidose, disposable pen consisting of a pen injector and a 3mL cartridge. The cartridge is made of glass, contains a bromobutyl rubber piston and is closed with a latex-free bromobutyl/polyisoprene rubber disc. The pen injector is made of plastic (polypropylene). FlexTouch are packed in cartons of 1, 5 or 10.

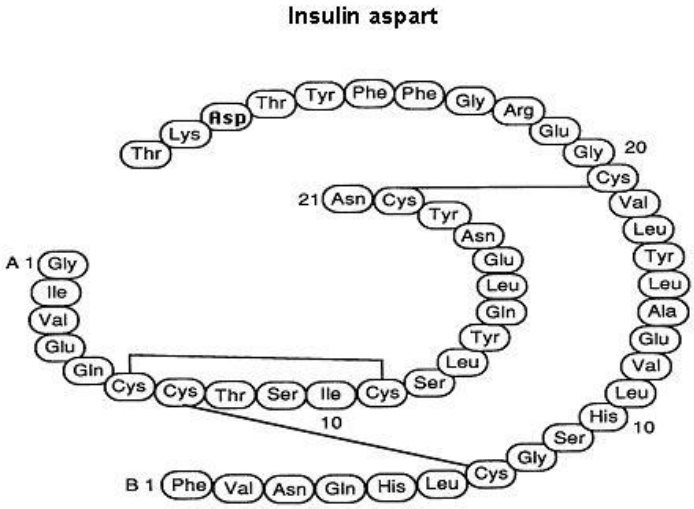
NovoRapid FlexTouch

*Not all presentations or pack sizes may be available.

6.6 Special Precautions for Disposal
In Australia, any unused medicine or waste material should be disposed of by takin it to your local pharmacy.

6.7 Physicochemical Properties

Chemical structure
Insulin aspart (rys) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.



CAS number
CAS No.: 116094-23-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
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Baulkham Hills NSW 2153

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9. DATE OF FIRST APPROVAL

NovoRapid (FlexPen, Penfill, vial)	21 December 2006
NovoRapid (FlexTouch)	07 August 2012
NovoMix 30 (FlexPen, Penfill)	05 June 2008
NovoMix 50 (FlexPen)	10 May 2007

10. DATE OF REVISION

16 April 2021

Summary table of changes

Section changed	Summary of new information
Name of the Medicine, Pharmaceutical Form, Adverse Effects (Undesirable Effects), Pharmacological Properties, Pharmaceutical Particulars	Deletion of references to deregistered therapeutic goods (NovoRapid InnoLet, NovoMix 50 Penfill, NovoMix 70 Penfill, NovoMix 70 FlexPen).
Various	Correction and addition of subheadings to fully align with TGA approved PI template.