

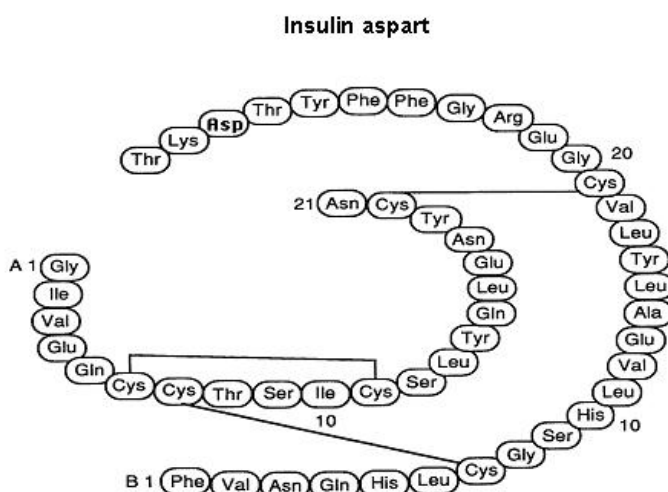
New Zealand Datasheet

Name of Medicine

NovoMix[®] 30 Penfill[®]
NovoMix[®] 30 FlexPen[®]
NovoMix[®] 50 Penfill[®]
NovoMix[®] 50 FlexPen[®]
NovoMix[®] 70 Penfill[®]
NovoMix[®] 70 FlexPen[®]

Insulin Aspart 100 Units/ml
Recombinant DNA origin: *Saccharomyces cerevisiae*

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 No.: 116094-23-6

Presentation

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

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. NovoMix 30, NovoMix 50 and NovoMix 70 should be given immediately before a meal or, when necessary, after the start of a meal.

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

Uses

Actions

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.

NovoMix 30, NovoMix 50 and NovoMix 70 are biphasic insulin preparations which contain, respectively, 30%, 50% and 70% soluble insulin aspart (rys). This has a rapid onset of action, and NovoMix products should thus be given closer to a meal than soluble human insulin. The crystalline phase in NovoMix 30, NovoMix 50 and NovoMix 70 is, respectively, 70%, 50% or 30% insulin aspart (rys) 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 1). The duration of action is up to 24 hours.

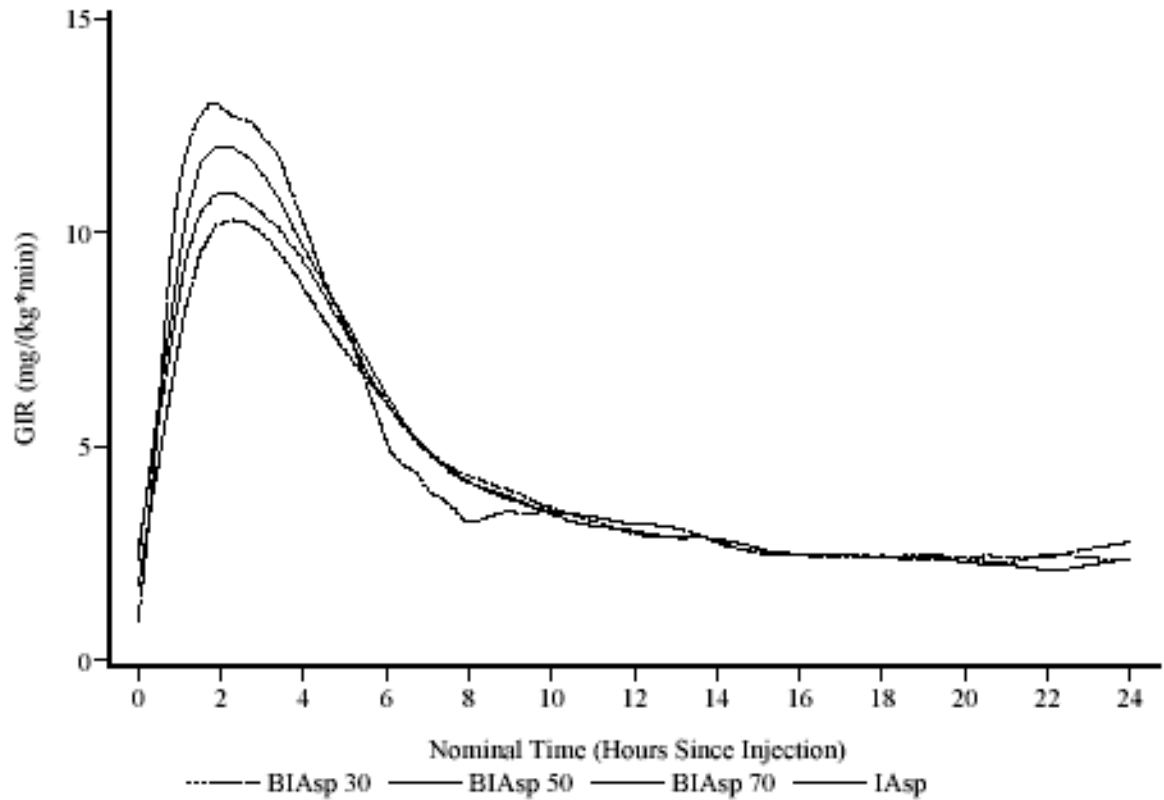
When injected immediately before a meal, NovoMix products have been demonstrated to better control postprandial hyperglycaemia than a corresponding 30/70 biphasic human insulin (Figure 2). This improvement in postprandial glycaemia is not of established clinical value.

When combined with once-daily (dinnertime) NovoMix 30, twice-daily (breakfast and lunch) NovoMix 50 and NovoMix 70 are both 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.

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

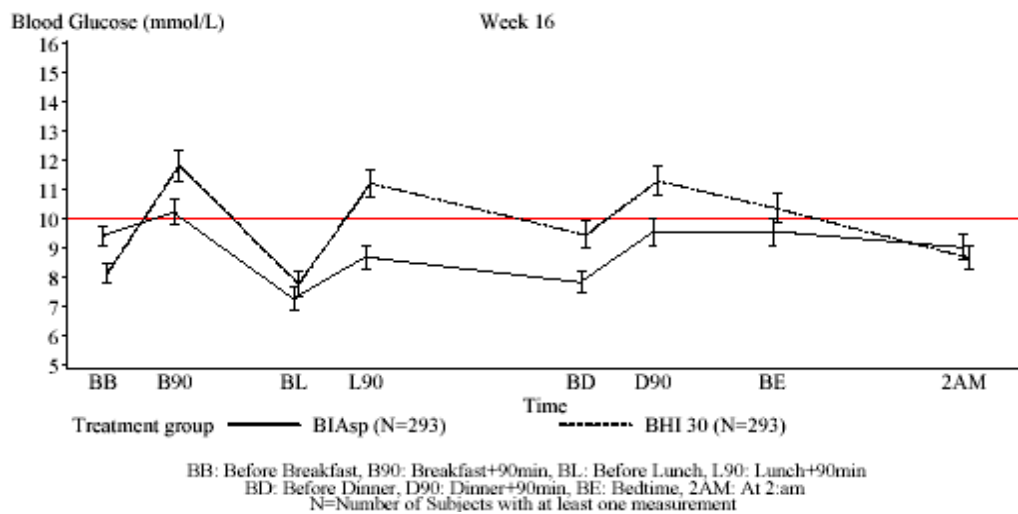
Insulin aspart (rys) is equipotent to human insulin on a molar basis.

Figure 1* 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.

Figure 2* Self monitored blood glucose (mean \pm 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.

Pharmacokinetics

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.

The insulin aspart (rys) in the soluble phases of NovoMix 30, NovoMix 50 and NovoMix 70 comprise, respectively, 30%, 50% and 70% 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%, 50% or 30% (respectively) is in crystalline form as insulin aspart (rys) protamine; this has a similar prolonged absorption profile to human NPH (isophane or protamine-crystallised) 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 ($t_{1/2}$) 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.

NovoMix 70

In healthy volunteers a C_{max} of 645 ± 185 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 75 minutes after dosing. In type 1 patients a mean maximum serum concentration of 721 ± 184 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.30 U/kg body weight.

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 C_{max} is maintained with soluble insulin aspart. As in younger subjects with type 2 diabetes, t_{max} 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 t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in subjects with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function. 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, C_{max} 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.

Indications

Treatment of diabetes mellitus.

Dosage and Administration

Dosage of NovoMix products is individual and determined in accordance with the needs of the patient. NovoMix products have a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix products may be given soon after the start of a meal.

Individual insulin requirements are usually between 0.5 and 1.0 Units/kg/day and this may be fully or partially supplied with NovoMix products. 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 or change their usual diet. 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.

NovoMix products are administered by subcutaneous injection in the abdominal wall or the thigh. If convenient, the gluteal or deltoid region may be used. Injection sites should be rotated within the same region. The duration of action of NovoMix 30 is up to 24 hours. The duration of action of NovoMix 50 and NovoMix 70 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 monocomponent 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 NovoMix products compared to biphasic human insulin is expected to be maintained regardless of injection site.

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.

NovoMix products should never be administered intravenously.

Transfer of patients to NovoMix products

NovoMix products differ from human insulin by their faster onset. Because of the fast onset of action, the injection of NovoMix products should immediately be followed by a meal.

Biphasic insulin aspart is equipotent to biphasic human insulin with respect to hypoglycaemic effect, receptor affinity and effect on lipogenesis. Patients currently treated with human insulin can be transferred to 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.

Contraindications

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

Warnings and Precautions

Inadequate dosing or discontinuation of treatment may 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 as acetone breath. Untreated hyperglycaemic events may be life threatening.

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.

NovoMix 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 and feverish conditions, especially infections, 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.

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

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

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 may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of NovoMix products.

NovoMix products contain metacresol, which may cause allergic reactions.

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.

Carcinogenicity

Lifetime carcinogenicity studies of insulin aspart (rys) 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 (rys), 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 (rys) does not differ from that observed with human insulin.

Genotoxicity

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

Effects on Fertility

In reproductive toxicity studies, insulin aspart (rys) did not affect the fertility of male and female rats but caused a slight increase in pre-implantation loss at subcutaneous doses greater than 10 U/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 'Clinical Trials').

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

Intensified treatment of pregnant women with diabetes is recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Use in Lactation

Although no clinical experience is available with NovoMix 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 NovoMix 30, NovoMix 50 or NovoMix 70 dosage may need to be adjusted.

Effects on Ability to Drive and Use Machines

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

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

Adverse Effects

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. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use the frequency varies with patient population and dose regimens and therefore no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared with human insulin.

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

Immune system disorders

Uncommon – Urticaria, rash, eruptions

Very rare - 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.

Nervous system disorders

Rare – Peripheral neuropathy

Rapid improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders

Uncommon – Refraction disorder

Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of a transitory nature.

Uncommon – Diabetic retinopathy

Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy, which is usually reversible. 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 the injection site within an area.

Uncommon – Local hypersensitivity

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

General disorders and administration site conditions

Uncommon - Oedema

Oedema may occur upon initiation of insulin therapy. These symptoms are usually transitory in nature.

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 and NovoMix 70 development programme since immunogenicity and assay methodology for NovoMix 30 can be applied to NovoMix 50 and NovoMix 70.

Interactions

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia (see Adverse Effects and Overdosage).

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), octreotide, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulphonamides.

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

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

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Overdosage

Insulins have no specific overdose definitions. 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 person with diabetes always carry products containing sugar with them.
- 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, oral administration of carbohydrate is recommended for the patient in order to prevent relapse.

Pharmaceutical Precautions

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 30 Penfill® must be resuspended after removal from the refrigerator and immediately before use so that it appears uniformly white and cloudy. *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 30 FlexPen[®] must be resuspended after removal from the refrigerator and immediately before use so that it appears uniformly white and cloudy. *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.

Special precautions for storage

NovoMix products should be stored between 2°C and 8°C. Do not freeze. NovoMix products which have been frozen must not be used. Keep the product in the carton (Penfill) or keep the cap on (FlexPen) when not in use, to protect it from light.

The in-use time is 4 weeks.

NovoMix products in use or carried as spares can be kept at ambient temperature (below 30°C) for up to 4 weeks, but any remainder must then be discarded. They should not be exposed to excessive heat or sunlight.

It is recommended that NovoMix products in use or carried as spares be resuspended after removal from the refrigerator and immediately before use.

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.

Medicine Classification

Prescription Medicine

Package Quantities

NovoMix 30, NovoMix 50 and NovoMix 70 products contain biphasic insulin aspart 100 U/ml. The following presentations are available:

Penfill

Penfill cartridges are made of glass, contain a rubber piston and are closed with a latex-free rubber disc. The cartridge contains a glass ball to facilitate resuspension. Five 3ml cartridges are packed in a carton.

NovoMix 30 Penfill, NovoMix 50 Penfill, NovoMix 70 Penfill.

FlexPen

FlexPen is a pre-filled, multidose, disposable syringe consisting of a pen injector and a 3ml cartridge. The cartridge is made of glass, contains a rubber piston and is closed with a latex-free rubber disc. The cartridge also contains a glass ball to facilitate resuspension. The pen injector is made of plastic. Five FlexPen are packed in a carton.

NovoMix 30 FlexPen, NovoMix 50 FlexPen, NovoMix 70 FlexPen.

Further Information

Instructions for use and handling

Penfill 3ml cartridges

The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. 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. The necessity to resuspend immediately before use is to be stressed to the patient.

NovoMix Penfill products are for use by one person only. The cartridges must not be refilled. NovoMix 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. The necessity to resuspend immediately before use is to be stressed to the patient.

NovoMix FlexPen products are for use by one person only. The cartridge inside the pre-filled syringe must not be refilled. NovoMix FlexPen products are designed to be used with NovoFine S needles.

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

Clinical Trials

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 1).

Table 1 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		Difference in Mean	95%C.I.	P
	N	Mean (SEM)	N	Mean (SEM)			
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 2). 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 2 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		P
	N	Mean (SEM)	N	Mean (SEM)	Est. mean difference	95%C.I.	
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 3 NovoMix 50 and NovoMix 70 versus IAsp+NPH in type 2 diabetes - glycemic parameters at the end of treatment [mean ± (SD)]

	<i>NovoMix 50*</i>	<i>IAsp + NPH</i>	<i>NovoMix 70*</i>	<i>IAsp + NPH</i>
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)

List of Excipients

NovoMix 30, NovoMix 50 and NovoMix 70 contain the following inactive ingredients: protamine sulfate, glycerol, phenol, meta-cresol, zinc chloride, dibasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

Trademarks

NovoMix, Penfill, FlexPen and NovoFine are registered trademarks owned by Novo Nordisk A/S

Name and Address

Novo Nordisk Pharmaceuticals Ltd

PO Box 51-268

Pakuranga

Auckland

Tel: (09) 916 5590

Fax: (09) 916 5595

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