New Zealand Datasheet

1 PRODUCT NAME
NovoMix® 30 FlexPen® 3ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Insulin Aspart 100 Units/ml
Recombinant DNA origin: *Saccharomyces cerevisiae*

3 PHARMACEUTICAL FORM
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.

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 is a white suspension for subcutaneous injection consisting of 30% soluble insulin aspart (rys) and 70% protamine-crystallised insulin aspart (rys). This biphasic insulin preparation (NovoMix 30) produces an insulin plasma profile 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
NovoMix 30 has a faster onset of action than biphasic human insulin. Due to the faster onset of action, NovoMix 30 should generally be given immediately before a meal or when necessary, soon after the start of a meal.

The dosage of NovoMix 30 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 a meal-related treatment the daily insulin requirement may be fully or partially supplied with NovoMix 30.

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.

NovoMix 30 is administered by subcutaneous injection in the abdominal wall, the thigh, the deltoid region or the gluteal region. 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). When injected subcutaneously into the abdominal wall, the onset of action for NovoMix 30 will occur within 10-20 minutes of injection. The duration of action of NovoMix 30 is up to 24 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. The influence of different injection sites on the absorption of NovoMix 30 has not been investigated. 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.

NovoMix 30 should never be administered intravenously. Intramuscular administration should be avoided.

The recommended starting dose of NovoMix 30 in combination with metformin is 0.2 Units/kg/day and should be adjusted depending on individual requirements based on blood glucose response.

Transfer of patients to insulin aspart products
NovoMix 30 differs from human insulin by its faster onset. Because of the rapid onset of action, the injection of NovoMix 30 should immediately be followed by a meal.

NovoMix 30 is equipotent to its 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 NovoMix 30 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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 30 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.

Safety and effectiveness of NovoMix 30 in children and adolescents under the age of 18 have not been assessed due to limited clinical experience.

NovoMix 30 is 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 30.

NovoMix 30 contains metacresol which on rare occasions 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 NovoMix 30 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.

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

Combination of 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.

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 NovoMix 30 and other insulins.

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.

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.

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

4.5 Interaction with other medicines and other forms of interaction
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), 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 sulphonamides.

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 '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 pre-pregnancy levels.

Use in Lactation
Although no clinical trial data are available with NovoMix 30 during lactation, there are no restrictions on treatment with this medicine during lactation. Insulin treatment of the nursing mother should not affect the baby. However, the dosage of NovoMix 30 may need to be adjusted.

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

Patients should be advised to take precautions in order to avoid hypoglycaemia whilst driving 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 Undesirable effects
a. 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 NovoMix 30 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 section c 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.

b. 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 section c

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

Skin and subcutaneous tissue disorders	Not known – Cutaneous amyloidosis*

* see section c. Description of selected adverse reactions

c. 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

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

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.

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 medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

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:

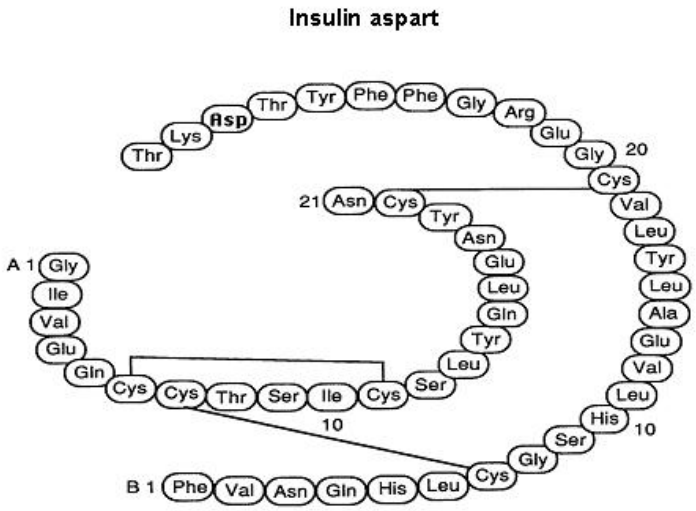
- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the person with diabetes always carry products containing sugar with them.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with 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 Poison Information Centre on 0800 764766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

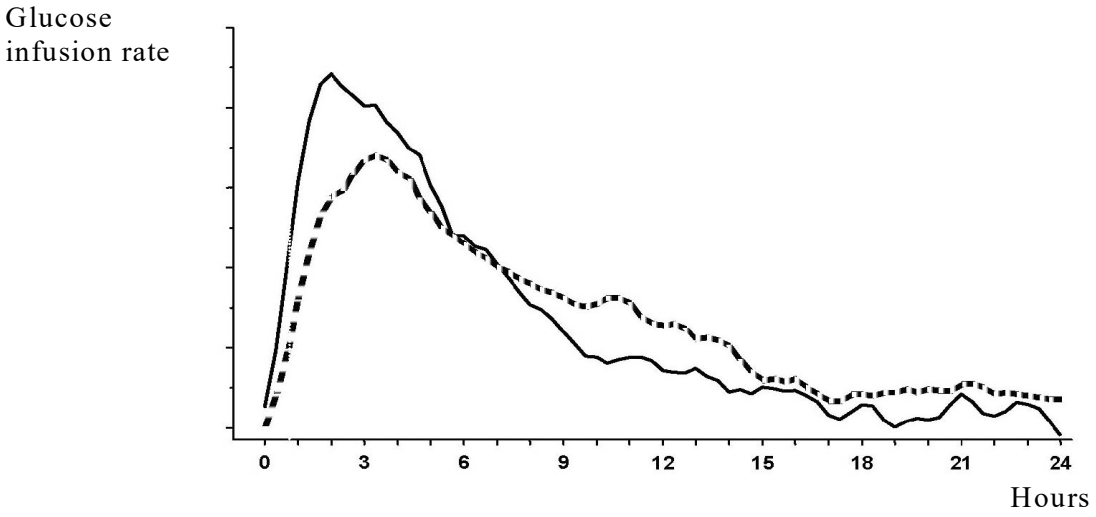
Insulin aspart is equipotent to soluble human insulin on a molar basis.

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

The onset of action of NovoMix 30 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 of NovoMix 30 is up to 24 hours.

When injected immediately before a meal, NovoMix 30 has 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.

Figure 1: Activity profile of NovoMix® 30 (___) and biphasic human insulin 30 (---) in healthy subjects.



Clinical Safety and Efficacy

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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**				
	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.

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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).

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.

The insulin aspart (rys) in the soluble phase of NovoMix 30 comprises 30% 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% is in crystalline form as insulin aspart (rys) protamine; this has a similar prolonged absorption profile to human NPH (isophane or protamine-crystallised) insulin.

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.

Special patient populations

Children: The pharmacokinetics of NovoMix 30 have not been investigated in children. However, 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.

Elderly: The pharmacokinetics of NovoMix 30 have not been investigated in the elderly. However, 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.

Hepatic impairment: The pharmacokinetics of NovoMix 30 have not been investigated in this population.

Renal impairment: The pharmacokinetics of NovoMix 30 have not been investigated in this population.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

In *in vitro* tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NovoMix 30 contains 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.

6.2 Incompatibilities

In general, NovoMix 30 should only be added to compounds with which it has known compatibility. Drugs added to the insulin may cause degradation of the insulin, e.g. if the drugs contain thiols or sulphites.

NovoMix 30 should not be added to infusion fluids.

6.3 Shelf life

The in-use time is 4 weeks.

The shelf-life is 24 months when stored between 2°C and 8°C.

6.4 Special precautions for storage

NovoMix 30 should be stored between 2°C and 8°C. Do not freeze. NovoMix 30 which has been frozen must not be used.

NovoMix 30 FlexPen pens 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. Do not refrigerate. They should not be exposed to excessive heat or sunlight. Keep the cap on when not in use, to protect them from light.

It is recommended that NovoMix 30 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

NovoMix 30 FlexPen penscontain biphasic insulin aspart 100 U/ml. The following presentation is available:

NovoMix® 30 FlexPen® 3ml

NovoMix 30 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 bromobutyl/polyisoprene rubber disc. The cartridges contained within NovoMix 30 FlexPen also contain a glass ball to facilitate resuspension. The pen injector is made of plastic (polypropylene). Five FlexPen are packed in a carton.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

NovoMix 30 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. 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.*

NovoMix 30 FlexPen 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 NovoMix 30 FlexPen pens.

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

7 MEDICINE SCHEDULE
Prescription Medicine

8 SPONSOR
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9 DATE OF FIRST APPROVAL
14 June 2001.

10 DATE OF REVISION OF THE TEXT
14 July 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Warning on cutaneous amyloidosis added
4.4	Warning on lipodystrophy and cutaneous amyloidosis added
4.8	Skin and subcutaneous tissue disorders - Cutaneous amyloidosis added