SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Mixtard® 30 FlexPen®

2. Qualitative and quantitative composition

Each ml contains: 100 IU corresponds to 0.035 mg of anhydrous human insulin produced by recombinant DNA technology in Saccharomyces cerevisiae.

1 pre-filled pen contains 3 ml equivalent to 300 IU.

Mixtard® 30 is a mixture of dissolved insulin and isophane (NPH) insulin.

Mixtard® 30 consists of 30% dissolved insulin and 70% isophane insulin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Suspension for injection in pre-filled pen.

The suspension is cloudy, white and aqueous.

4. Clinical particulars

4.1 Therapeutic indications

Mixtard® 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

4.2 Posology and method of administration

Posology

Mixtard® is a dual-acting insulin. It is a biphasic formulation containing both fast-acting and long-acting insulin.

Premixed insulin products are usually given once or twice daily when a rapid initial effect together with a more prolonged effect is desired.

Dosage adjustment

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose. Adjustment of dosage may also be

necessary if patients change physical activity or their usual diet. Dosage adjustment may be necessary when transferring patients from one insulin preparation to another

Method of administration

For subcutaneous use. Insulin suspensions are never to be administered intravenously.

Mixtard® is administered subcutaneously in the thigh or abdominal wall. If convenient, the gluteal region or the deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites. For detailed user instructions, please refer to the package leaflet.

Mixtard® 30 Penfill

Administration with an insulin delivery system

Mixtard® 30 Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. Mixtard® 30 Penfill is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

Mixtard® 30 FlexPen

Administration with FlexPen

Mixtard® 30 FlexPen is a pre-filled pen (colour-coded) designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1-60 units in increments of 1 unit. Mixtard® 30 FlexPen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

Injection into a lifted skin fold minimizes the risk of unintended intramuscular injection. The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Mixtard® 30 must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. Mixtard® 30 is not to be used in insulin infusion pumps.

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

Hyperglycaemia

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

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, Mixtard® 30 must not be injected. After stabilization of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.2, 4.8 and 4.9).

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

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

Tighter control of glucose levels can increase the potential for hypoglycaemic episodes and therefore require special attention during dose intensification as outlined in section 4.2.

Since Mixtard® 30 should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

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

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal insulin, human

insulin or insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to Mixtard® 30 from another type of insulin may require an increased number of daily injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. 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 Mixtard® 30.

Combination with thiazolidinedione

Cases of cardiac failure have been reported when thiazolidinedione was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of thiazolidinedione and Mixtard is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinedione 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 Mixtard® 30 and other insulin products.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

<u>The following substances may reduce the patient's insulin requirements:</u>

Oral antidiabetic medicinal products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

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

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

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with insulin in pregnancy.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Breast-feeding

There are no restrictions on treatment with Mixtard® 30 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the Mixtard® 30 dose 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 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. 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, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders	Uncommon – Urticaria, rash, eruptions
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site conditions	Uncommon – Oedema
	Uncommon – Injection site reactions

* see Description of selected adverse reactions

Description of selected adverse reactions

Anaphylactic reactions:

The occurrence of generalized hypersensitivity reactions (including generalized skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be 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 concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Lipodystrophy:

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular area reduces the risk of developing these reactions.

Paediatric population

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

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medical products is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via TMDA ADR reporting tool; website: *https://imis.tmda.go.tz/arrt* or search for TMDA adverse reactions reporting tool in the google play store.

4.9 Overdose

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

• Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.

• 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 healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting.

ATC code: A10AD05.

Mixtard® 30 is a biphasic suspension of 30% soluble insulin aspart (rapid-acting human insulin analogue) and 70% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue).

Mechanism of action and Pharmacodynamic effects

The blood glucose lowering effect of insulin aspart is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Mixtard® 30 is a biphasic insulin, which contains 30% soluble insulin aspart. This has a rapid onset of action, thus allowing it to be given closer to a meal (within zero to 10 minutes of the meal) when compared to soluble human insulin. The crystalline phase (70%) consists of protamine-crystallised insulin aspart, which has an activity profile similar to that of human NPH insulin.

When Mixtard® 30 is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours (Figure 1).

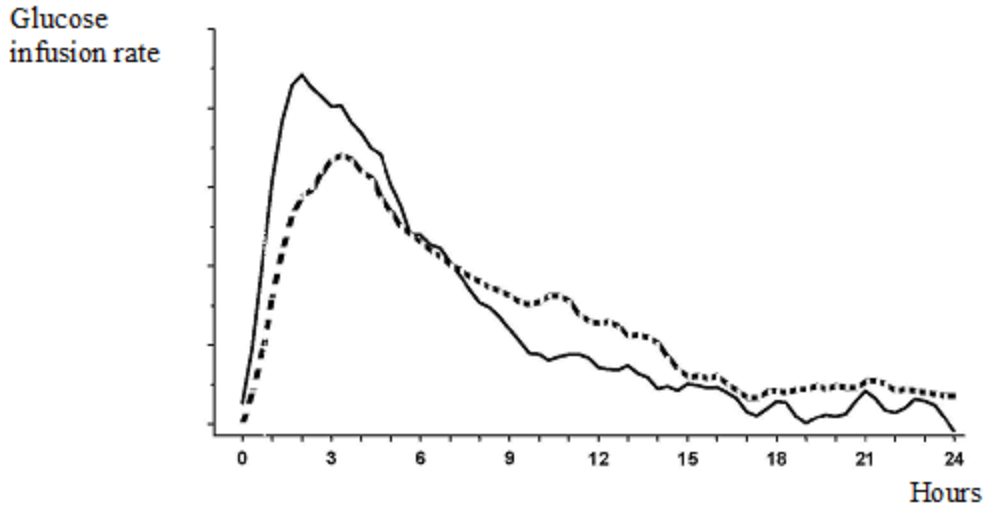

Figure 1: Activity profile of Mixtard® 30 (—) and biphasic human insulin 30 (---) in healthy subjects.

Clinical efficacy and safety

In a 3 month trial in patients with type 1 and type 2 diabetes, Mixtard® 30 showed equal control of glycosylated haemoglobin compared to treatment with biphasic human insulin 30. Insulin aspart is equipotent to human insulin on a molar basis. Compared to biphasic human insulin 30, administration of Mixtard® 30 before breakfast and dinner resulted in lower postprandial blood glucose after both meals (breakfast and dinner).

A meta-analysis including nine trials in patients with type 1 and type 2 diabetes showed that fasting blood glucose was higher in patients treated with Mixtard® 30 , than in patients treated with biphasic human insulin 30.

In one study, 341 patients with type 2 diabetes were randomised to treatment with Mixtard® 30 either alone or in combination with metformin, or to metformin together with sulfonylurea. The primary efficacy variable - HbA_{1c} after 16 weeks of treatment - did not differ between patients with Mixtard® 30 combined with metformin and patients with metformin plus sulfonylurea. In this trial, 57% of the patients had baseline HbA_{1c} above 9%; in these patients, treatment with Mixtard® 30 in combination with metformin resulted in significantly lower HbA_{1c} than metformin in combination with sulfonylurea.

In one study, patients with type 2 diabetes, insufficiently controlled on oral hypoglycaemic agents alone, were randomised to treatment with twice daily Mixtard® 30 (117 patients) or once daily insulin glargine (116 patients). After 28 weeks of treatment following the dosing guideline outlined in section 4.2, the mean reduction in HbA_{1c} was 2.8% with Mixtard® 30 (mean at baseline = 9.7%). With Mixtard® 30 , 66% and 42% of the patients reached HbA_{1c} levels below 7% and 6.5%, respectively, and mean FPG was reduced by about 7 mmol/l (from 14.0 mmol/l at baseline to 7.1 mmol/l).

In patients with type 2 diabetes, a meta-analysis showed a reduced risk of overall nocturnal hypoglycaemic episodes and major hypoglycaemia with Mixtard® 30 compared to biphasic human insulin 30. The risk of overall daytime hypoglycaemic episodes was increased in patients treated with Mixtard® 30.

Paediatric population

A 16-week clinical trial comparing postprandial glycaemic control of meal-related Mixtard® 30 with meal-related human insulin/biphasic human insulin 30 and bedtime NPH insulin was performed in 167 patients aged 10 to 18 years. Mean HbA_{1c} remained similar to baseline throughout the trial in both treatment groups, and there was no difference in hypoglycaemia rate with Mixtard® 30 or biphasic human insulin 30.

In a smaller (54 patients) and younger (age range 6 to 12 years) population, treated in a double-blind, cross-over trial (12 weeks on each treatment), the rate of hypoglycaemic episodes and the postprandial glucose increase were significantly lower with Mixtard® 30 compared to biphasic human insulin 30. Final HbA_{1c} was significantly lower in the biphasic human insulin 30 treated group compared with Mixtard® 30.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In insulin aspart, substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. The insulin aspart in the soluble phase of Mixtard® 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 protamine-crystallised insulin aspart; this has a prolonged absorption profile similar to human NPH insulin.

The maximum serum insulin concentration is, on average, 50% higher with Mixtard® 30 than with biphasic human insulin 30. The time to maximum concentration is, on average, half of that for biphasic human insulin 30. In healthy volunteers, a mean maximum serum concentration of 140 ± 32 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.20 unit/kg body weight. The mean half life ($t_{½}$) of Mixtard® 30 , reflecting the absorption rate of the protamine bound fraction, was about 8-9 hours. Serum insulin levels returned to baseline 15-18 hours after a subcutaneous dose. In type 2 diabetic patients, the maximum concentration was reached about 95 minutes after dosing, and concentrations well above zero for not less than 14 hours post-dosing were measured.

Special populations

The pharmacokinetics of Mixtard® 30 have not been investigated in elderly patients or in patients with renal or hepatic impairment.

Paediatric population

The pharmacokinetics of Mixtard® 30 have not been investigated in children or adolescents. However, the pharmacokinetic and pharmacodynamic properties of soluble insulin aspart have been investigated in children (6–12 years) and adolescents (13–17 years) with type 1 diabetes. Insulin aspart was rapidly absorbed in both age groups, with similar t_{max} as in adults. However, C_{max} differed between the age groups, stressing the importance of the individual titration of insulin aspart.

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 and development.

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

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Protamine sulfate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening:

30 months.

During use

The product can be stored for a maximum of 6 weeks.

6.4 Special precautions for storage

Before opening:

Store in a refrigerator (2°C–8°C). Keep away from the cooling element. Do not freeze.

During use

Store below 30°C. Do not refrigerate. Do not freeze.

Keep the pen cap on FlexPen® in order to protect from light.

6.5 Nature and contents of container

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene in a carton. The cartridge contains a glass ball to facilitate the resuspension.

Pack sizes of 1 x 3ml pre-filled pen.

6.6 Special precautions for disposal and other handling

Pens should only be used in combination with products that are compatible with them and allow the pen to function safely and effectively. Needles and Mixtard® FlexPen® must not be shared.

The container must not be refilled. Insulin preparations which have been frozen must not be used.

After removing Mixtard® FlexPen® from the refrigerator, it is recommended to allow FlexPen® to reach room temperature before resuspending the insulin as instructed for first time use.

Insulin suspensions should not be used if they do not appear uniformly white and cloudy after resuspension.

The patient should be advised to discard the needle after each injection

7. Marketing authorization holder and manufacturing site

7.1 Marketing authorization holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

7.2 manufacturing site

Novo Nordisk
Novo Alle Dk-2880
Post Box 2000
Bagsvaerd
Denmark

8. Registration number

TZ 17 H 0229

9. Date of first registration

11/9/2017

10. Date of revision of the text
June 2020