Summary of Product Characteristics for Pharmaceutical Products

1. NAME OF THE MEDICINAL PRODUCT

Mixtard® 30 100 IU/ml Suspension for injection in vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin human, rDNA (produced by recombinant DNA technology in Saccharomyces cerevisiae).

1 ml contains 100 IU of human insulin.

1 vial contains 10 ml equivalent to 1,000 IU.

One International Unit (IU) corresponds to 0.035 mg of anhydrous human insulin.

Mixtard® 30 is a premixed insulin containing 30% soluble (dissolved) insulin and 70% isophane (NPH) insulin.

Excipients with known effect: zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, protamine sulphate, sodium hydroxide/hydrochloric acid (for pH adjustment) and water for injections.

3. PHARMACEUTICAL FORM

Suspension for injection in vial.

Cloudy, white, aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus requiring insulin therapy.

4.2 Posology and method of administration

Posology

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. Daily insulin requirements may be higher in patients with insulin resistance (e.g., during puberty or due to obesity) and lower in patients with residual endogenous insulin production.

Mixtard® 30 contains both rapid-acting and intermediate-acting insulin components. Premixed insulin products are generally administered once or

twice daily when a rapid initial effect combined with a more prolonged effect is desired. An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

Special populations
Dose adjustments may be required in concomitant illness (infections, fever), renal or hepatic impairment, changes in physical activity or diet, and when transferring patients from other insulin preparations.

Paediatric use
Individual dose titration is required. Refer to clinical guidance for use in children and adolescents.

Method of administration
For subcutaneous use. Insulin suspensions must never be administered intravenously.
Mixtard® is administered by subcutaneous injection in the thigh or abdominal wall. If necessary, the gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region to reduce the risk of lipodystrophy and cutaneous amyloidosis. Subcutaneous injection into the abdominal wall gives faster absorption than other sites. Injection into a lifted skin fold reduces the risk of unintended intramuscular injection. After injection, the needle should remain under the skin for at least 6 seconds to ensure the full dose is delivered.

Mixtard® vials are intended for use with insulin syringes with an appropriate unit scale.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia. Usual early symptoms of hyperglycaemia include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite and acetone odour of breath. Untreated hyperglycaemia in type 1 diabetes may lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved (e.g., by intensified insulin therapy) may experience changes in their usual warning symptoms of hypoglycaemia; usual warning symptoms may disappear in long-standing diabetes.

Transferring a patient to another type or brand of insulin should be done under medical supervision. Changes in strength, brand, type, origin (human insulin, insulin analogue) and/or manufacturing method may require dosage changes. Patients switched to Mixtard® from another insulin may require an increased number of daily injections or dose modifications; adjustments may occur at the first dose or over the first weeks to months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. These reactions are usually transient and resolve within days to weeks; in rare cases they may require discontinuation of Mixtard®. Continuous rotation of injection sites within a given area may help reduce the risk.

Skin and subcutaneous tissue disorders

Perform continuous rotation of injection sites to reduce the risk of lipodystrophy and cutaneous amyloidosis. These reactions may delay local insulin absorption and affect glycaemic control. A sudden change from an affected to an unaffected injection area has been reported to result in hypoglycaemia; blood glucose monitoring is recommended after such changes and consideration should be given to dose adjustment of antidiabetic medications.

Use in insulin pumps

Insulin suspensions must not be used in insulin infusion pumps.

Thiazolidinediones

Cases of congestive heart failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for congestive heart failure. If the combination is used, patients should be monitored for signs and symptoms of congestive heart failure, weight gain

and oedema. Thiazolidinediones should be discontinued if cardiac symptoms worsen.

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® and other insulin products.

Driving and using machines
Mixtard® may impair the patient's ability to concentrate and react as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving, operating machinery). Patients should take precautions to avoid hypoglycaemia while driving, especially those with reduced awareness of hypoglycaemia or frequent hypoglycaemic episodes.

4.5 Interaction with other medicinal products and other forms of interaction
A number of medicinal products are known to interact with glucose metabolism.

The following may reduce insulin requirement: oral antidiabetic agents, monoamine oxidase inhibitors (MAOI), non-selective beta-blockers, ACE inhibitors, salicylates, anabolic steroids and sulphonamides.

The following may increase insulin requirement: oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia and delay recovery. Octreotide and lanreotide may increase or decrease insulin requirement. Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation
There are no restrictions on the use of insulin during pregnancy since insulin does not cross the placental barrier. Both hypoglycaemia and hyperglycaemia in inadequately controlled diabetes increase the risk of malformations and intrauterine death. Intensified blood glucose control and moni-

toring are recommended throughout pregnancy and when planning pregnancy. Insulin requirements typically fall in the first trimester and increase during the second and third trimesters; after delivery requirements usually return rapidly to pre-pregnancy values.

Mixtard® may be used during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby, though Mixtard® dosage, diet or both may need adjustment.

4.7 Effects on ability to drive and use machines

See section 4.4. Hypoglycaemia can impair concentration and reactions; patients should take precautions when driving or operating machinery.

4.8 Undesirable effects

a) Summary of safety profile

The most frequently reported adverse reaction is hypoglycaemia. Frequency varies with patient population, dosing regimens and degree of glycaemic control.

b) *Tabulated list of adverse reactions*

Tabulated list of adverse reactions	Immune system disorders
- Uncommon: urticaria, rash	- Very rare: anaphylactic reactions
	Metabolism and nutrition disorders
- Very common: hypoglycaemia	
Nervous system disorders	- Uncommon: peripheral neuropathy (painful neuropathy)
	Eye disorders
- Very rare: refraction disorders	- Uncommon: diabetic retinopathy
	Skin and subcutaneous tissue disorders
- Uncommon: lipodystrophy (including lipohypertrophy, lipoatrophy)	- Frequency not known: cutaneous amyloidosis (post-marketing)
	General disorders and administration site conditions
- Uncommon: injection site reactions	- Uncommon: oedema
	Description of selected adverse reactions

Anaphylactic reactions: Generalised hypersensitivity reactions are very rare but can be life-threatening.	
Hypoglycaemia: May occur if insulin dose is too high. Severe hypoglycaemia can lead to unconsciousness, convulsions, and brain damage or death. Symptoms typically appear suddenly and may include cold sweat, pale cool skin, fatigue, nervousness or tremor, anxiety, unusual tiredness, confusion, difficulty concentrating, drowsiness, excessive hunger, visual disturbances, headache, nausea and palpitations.	
Skin and subcutaneous tissue disorders: Lipodystrophy and cutaneous amyloidosis at injection sites may delay absorption and affect glycaemic control. Continuous rotation of injection sites is recommended.	

c) Description of selected adverse reactions

Anaphylactic reactions

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness) 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 concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

d. Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems- PvERS: the Pharmacovigilance Electronic Reporting System: Users

4.9 Overdose

A specific overdose for insulins is not defined. Hypoglycaemia may progress through stages if insulin doses exceed requirements.

Mild hypoglycaemia: treat with oral glucose or sugary products — patients should carry such products.

Severe hypoglycaemia with unconsciousness: treat with intramuscular or subcutaneous glucagon (0.5–1 mg) by a trained person, or intravenous glucose by medical personnel. If no response to glucagon within 10–15 minutes, administer intravenous glucose. Once conscious, give oral carbohydrates to prevent 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 insulin (human). ATC code: A10AD01.

The blood glucose lowering effect of insulin is due to facilitated uptake of glucose by binding of insulin to receptors on muscle and fat cells and simultaneous inhibition of hepatic glucose output.

Mixtard® 30 is a biphasic (premixed) insulin formulation containing fast-acting and prolonged-acting components. Onset of action is within 30 minutes after injection; maximum effect occurs between 2 and 8 hours; duration of action can reach up to 24 hours.

5.2 Pharmacokinetic properties

Insulin in the bloodstream has a half-life of a few minutes; the time-action profile is determined by absorption characteristics. Absorption is influenced

by dose, route and site of injection, subcutaneous fat thickness and type of diabetes, causing intra- and inter-individual variability.

Absorption: The maximum plasma concentration of the fast-acting component is reached approximately 1.5–2.5 hours after subcutaneous administration.

Distribution: No significant binding to plasma proteins except circulating anti-insulin antibodies if present.

Metabolism: Human insulin is degraded by insulin proteases and insulin-degrading enzymes and possibly protein disulfide isomerase. Metabolites formed are inactive.

Elimination: Terminal half-life is determined by absorption rate from subcutaneous tissue; reported terminal half-life approximately 5–10 hours.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide/hydrochloric acid (for pH adjustment), protamine sulphate and water for injections.

6.2 Incompatibilities

Insulin suspensions should not be added to infusion fluids. Insulin preparations which have been frozen must not be used.

6.3 Shelf life

The shelf life is as per product labelling. After first opening or when carried as a spare: do not refrigerate. In-use shelf life: 6 weeks when stored below 25°C or 5 weeks when stored below 30°C (refer to vial product information).

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Keep away from the cooling element. Do not freeze. Keep the vial in the outer carton to protect from light. Mixtard® must be protected from excessive heat and light. After first opening or when carried as a spare: do not refrigerate. In-use shelf life: 6 weeks when stored below 25°C or 5 weeks when stored below 30°C (refer to vial product information).

6.5 Nature and contents of container

10 ml suspension in vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene) rubber and a protective tamper-proof plastic cap in a carton.

Pack sizes: 1 and 5 vials (not all pack sizes may be marketed).

6.6 Special precautions for disposal and other handling

Insulin preparations which have been frozen must not be used. After removing the vial from the refrigerator, allow it to reach room temperature before resuspending the insulin as instructed for first use. Insulin suspensions should not be used if they do not appear uniformly white and cloudy after resuspension. Dispose of needles and syringes safely. Do not share vials or syringes.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

5892

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

21 Oct 1997

10. DATE OF REVISION OF THE TEXT

26/03/2026