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

Qualitative and quantitative composition
Insulin human, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).
1 ml contains 100 IU of insulin human.
1 cartridge contains 3 ml equivalent to 300 IU.
One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.
Mixtard® is a mixture of dissolved insulin and isophane (NPH) insulin.
Mixtard® 30 consists of 30% dissolved insulin and 70% isophane insulin.

Pharmaceutical form
Suspension for injection in cartridge.
Cloudy, white, aqueous suspension.

Therapeutic indications
Treatment of diabetes mellitus.

Posology and method of administration
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.

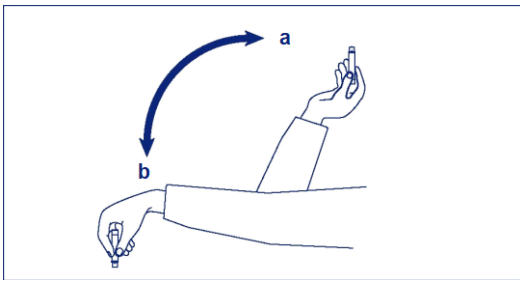
Dosage
Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.
An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

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.

Administration
For subcutaneous use. Insulin suspensions are never to be administered intravenously.
Mixtard® is administered subcutaneously by injection in the thigh or abdominal wall. If convenient, the gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.
Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.
Injection into a lifted skin fold minimises 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.
Mixtard® Penfill® is designed to be used with Novo Nordisk delivery systems and NovoFine® or NovoTwist® needles.

Resuspending the insulin
Resuspending is easier when the insulin has reached room temperature.

Before you put the Penfill® cartridge into the insulin delivery system, move it up and down between positions **a** and **b** and back (see the picture) so that the glass ball moves from one end of the cartridge to the other at least 20 times. Repeat this movement at least 10 times before each injection. The movement must always be repeated until the liquid appears uniformly white and cloudy. Complete the other stages of injection without delay.



Check there are at least 12 units of insulin left in the cartridge to allow even resuspending. If there are less than 12 units left, use a new one.

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

Special warnings and precautions for use
Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to **hyperglycaemia.**
Usually, the first symptoms of hyperglycaemia set in 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 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 a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.
Usual warning symptoms may disappear in patients with longstanding diabetes.
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 a need for a change in dosage. Patients transferred to Mixtard® from another type of insulin may require an increased number of daily injections or change in dosage from that used with their usual insulin products. If an adjustment is needed when switching the patient to Mixtard®, it may occur with the first dose or during the first few weeks or months.
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 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 Mixtard®.
Before travelling between different time zones, the patient should be advised to consult the physician, since this may mean that the patient has to take insulin and meals at different times.
Insulin suspensions are not to be used in insulin infusion pumps.

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 medicinal products
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 Mixtard® and other insulin products.

Interaction with other medicinal products and other forms of interaction
A number of medicinal products are known to interact with the glucose metabolism.
The following substances may reduce the patient's insulin requirement:
Oral anti-diabetic products, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.
The following substances may increase the patient's insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the insulin requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Pregnancy and lactation
There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.
Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero.* 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 normally return rapidly to pre-pregnancy values.

There is no restriction on treatment with Mixtard® during breast-feeding.
Insulin treatment of the nursing mother presents no risk to the baby. However, the Mixtard® dosage, diet or both 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 to avoid hypoglycaemia while 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.

Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. In clinical trials and during marketed use, the frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c 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 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.

b. Tabulated list of adverse reactions

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
	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*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Injection site reactions
	Uncommon – Oedema

* see section c
† ADR from postmarketing sources

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.

Overdose
A specific overdose of 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 an oral carbohydrate is recommended for the patient in order to prevent a relapse.

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 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® is a dual-acting insulin.
Onset of action is within ½ hour, reaches a maximum effect within 2 - 8 hours and the entire duration of action is up to 24 hours.

Pharmacokinetic properties
Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.
This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin products are therefore affected by significant intra- and inter-individual variation.

Absorption
The absorption profile is due to the product being a mixture of insulin products with fast and protracted absorption respectively. The maximum plasma concentration of the fast-acting insulin is reached within 1.5 - 2.5 hours after subcutaneous administration.

Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism
Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination
The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{½}$) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from

plasma (insulin in the blood stream has a $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ of about 5 - 10 hours.

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

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

Incompatibilities
Insulin suspensions should not be added to infusion fluids.

Special precautions for storage
Store in a refrigerator (2°C - 8°C). Keep away from the cooling element. Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.
Mixtard® must be protected from excessive heat and light.
After first opening or carried as a spare: Do not refrigerate.
The in-use shelf life is 6 weeks when stored below 30°C.

Nature and contents of container
3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton. The cartridge contains a glass ball to facilitate the resuspension.
Pack sizes of 1, 5 and 10 cartridges.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
Cartridges should only be used in combination with products that are compatible with them and allow the cartridge to function safely and effectively.
Needles and Mixtard® Penfill® must not be shared. The container must not be refilled.
Insulin preparations which have been frozen must not be used.
After removing Mixtard® Penfill® from the refrigerator, it is recommended to allow Penfill® 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.

Manufactured by:
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