

New Zealand Datasheet

1 PRODUCT NAME

PENMIX[®] 30 100 IU/ml

PENMIX[®] 40 100 IU/ml

PENMIX[®] 50 100 IU/ml

MIXTARD[®] 30 100 IU/ml

PROTAPHANE[®] 100 IU/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The PENMIX and Mixtard products contain Biphasic isophane insulin injection 100 IU/ml.

The PROTAPHANE products contain Isophane (NPH) insulin suspension injection 100 IU/ml.

3 PHARMACEUTICAL FORM

PENMIX 30 is a cloudy, white, aqueous suspension containing 30% dissolved insulin and 70% isophane human insulin in 3 ml Penfill[®] cartridges made of glass, with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton.

PENMIX 40 is a cloudy, white, aqueous suspension containing 40% dissolved insulin and 60% isophane human insulin in 3 ml Penfill[®] cartridges made of glass, with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton.

PENMIX 50 is a cloudy, white, aqueous suspension containing 50% dissolved insulin and 50% isophane human insulin in 3 ml Penfill[®] cartridges made of glass, with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton.

MIXTARD 30 is a cloudy, white, aqueous suspension containing 30% dissolved insulin and 70% isophane human insulin in 10 ml glass vials closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap in a carton.

PROTAPHANE is a cloudy, white, aqueous suspension containing isophane insulin suspension in 3 ml penfill[®] cartridges made of glass, with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton or in 10 ml glass vials closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap in a carton.

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

The penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Dose and method of administration

PENMIX and MIXTARD are dual-acting insulins. They are bi-phasic formulations containing fast-acting and long-acting insulin. Premixed insulins such as PENMIX or MIXTARD are

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

PROTAPHANE is a long-acting insulin. The physician determines whether one or several daily injections of PROTAPHANE are necessary. PROTAPHANE may be used alone or mixed with a fast-acting insulin. In intensive insulin therapy PROTAPHANE may be used as basal insulin (evening and/or morning injection) with fast-acting insulin given at meals.

Dosage is individual and determined in accordance with the needs of the patient.

The individual insulin requirement is usually between 0.5 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty in the young or due to obesity) and lower in patients with residual, endogenous insulin production.

An injection of PENMIX or MIXTARD should be followed by a meal or snack containing carbohydrates within 30 minutes.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is recommended.

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 the 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 (see section 4.4).

Insulin suspensions are never to be administered intravenously.

PENMIX or MIXTARD are administered subcutaneously in the thigh or abdominal wall. If convenient the gluteal region or deltoid region may be used. A subcutaneous injection into the abdominal wall results in a faster absorption than from other injection sites.

PROTAPHANE is administered subcutaneously in the thigh. If convenient, the abdominal wall, the gluteal region or the deltoid region may also be used. Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites.

Injection into a lifted skin fold minimises the risk of intramuscular injection. Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.

Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to human insulin or any of the excipients.

4.4 Special warnings and precautions for use

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia. Usually the first symptoms of hyperglycaemia usually 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 breath. In type 1 diabetes, untreated hyperglycaemic events eventually leads to diabetic ketoacidosis which is potentially lethal.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9).

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.

Transfer from other insulin 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 (human insulin, insulin analogue) and/or method of manufacturer may result in a change in dosage. Patients transferred to PENMIX, MIXTARD or PROTAPHANE 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 when switching the patient to PENMIX, MIXTARD or PROTAPHANE, it may occur with the first dose or during the first few weeks or months.

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

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 PENMIX, MIXTARD or PROTAPHANE and other insulin products.

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 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 PENMIX, MIXTARD or PROTAPHANE.

Before travelling between different time zones, the patient should be advised to consult the doctor, 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.

Combination of thiazolidinediones and insulin 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.

PENMIX, MIXTARD and PROTAPHANE contain metacresol, which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

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

The following substances may reduce the insulin requirements:

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 insulin requirements:

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 and prolong the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no restrictions on the 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 trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values

Breast-feeding

There is no restriction on treatment with PENMIX, MIXTARD or PROTAPHANE during breast-feeding. Insulin treatment of the nursing mother involves no risk to the baby. However, the insulin dosage, diet or both may need to be adjusted.

Effects on Fertility

Not applicable.

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 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.

4.8 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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), PENMIX, MIXTARD
	Very rare – Peripheral neuropathy (Painful neuropathy), PROTAPHANE
Eye disorders	Very rare – 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

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.

Lipodystrophy

Lipodystrophy is reported as uncommon. Lipodystrophy may occur at the injection site.

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 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 also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness administration of oral carbohydrate is recommended for the patient in order to prevent a relapse.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate-acting, insulin (human). ATC code A10AC01 or 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.

For PENMIX and MIXTARD the absorption profile is caused by the product being a mixture of insulins with protracted and fast absorption respectively.

An average action profile for PENMIX and MIXTARD after subcutaneous injection indicates:

Onset: within ½ hour
Maximum: 2 - 8 hours
Duration: up to 24 hours

For PROTAPHANE the protracted absorption is caused by the product being a suspension.

An average action profile for PROTAPHANE after subcutaneous injection indicates:

Onset: 1.5 hours
Maximum: 4 - 12 hours
Duration: up to 24 hours

5.2 Pharmacokinetic properties

Insulin in the bloodstream has a half-life of only 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), which is why considerable intra- and inter-patient variations are seen.

Absorption

The absorption profile is due to the product being a mixture of insulin products with fast and protracted absorption respectively. In PENMIX and MIXTARD the maximum plasma concentration of the fast-acting insulin is reached within 1.5-2.5 hours after subcutaneous administration. In PROTAPHANE the maximum plasma concentration of the insulin is reached within 2-18 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 ($t_{1/2}$) 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 $t_{1/2}$ of a few minutes). Trials have indicated a $t_{1/2}$ of about 5-10 hours.

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, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Disodium phosphate dihydrate
Metacresol
Phenol
Zinc chloride
Protamine sulphate
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In general terms, insulin should only be added to compounds with which it has known compatibility. Insulin suspensions should not be added to infusion fluids.

Instructions for Use/Handling

The carton contains a package leaflet with instructions for use and handling. The necessity of re-suspending the insulin suspension immediately before use is to be stressed to the patient. The re-suspended liquid shall appear uniformly white and cloudy.

PENMIX and PROTAPHANE Penfill is accompanied by a package leaflet with detailed instructions for use to be followed.

MIXTARD and PROTAPHANE vials are for use with insulin syringes with the corresponding unit scale. When two types of insulin are mixed, draw the amount of fast-acting insulin first, followed by the amount of long-acting insulin.

PENMIX and PROTAPHANE Penfill are for single person use only. The container must not be refilled.

PENMIX and PROTAPHANE Penfill are designed to be used with Novo Nordisk insulin delivery systems and NovoFine® needles.

6.3 Shelf life

The shelf-life is 30 months. The in-use time is 6 weeks.

6.4 Special precautions for storage

Insulin preparations should be stored between 2°C and 8°C, (in a refrigerator), not in or near a freezing compartment. Insulin preparations which have been frozen must not be used. Insulin preparations should be protected from excessive heat or sunlight.

After first use MIXTARD and PROTAPHANE vials may be kept at room temperature (up to 25°C) for 6 weeks. PENMIX and PROTAPHANE Penfill may be used or carried as a spare (below 25°C) for 6 weeks.

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

6.5 Nature and contents of container

PENMIX 30, 40 and 50 are available as a Penfill® of 3 ml in cartons of five.

MIXTARD 30 is available in glass vials of 10 ml.

PROTAPHANE is available as a Penfill® of 3 ml in cartons of five, or in glass vials of 10 ml.

6.6 Special precautions for disposal

Penfills must not be shared. The container must not be refilled. 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

PENMIX 30 Penfill 28 April 1989.

PENMIX 40 Penfill 28 August 1989

PENMIX 50 Penfill 28 August 1989

MIXTARD 30 10 ml 9 June 1993

PROTAPHANE Penfill 5 August 1988

PROTAPHANE 10 ml 16 September 1983

10 DATE OF REVISION OF THE TEXT

27 March 2019

Mixtard CCDS version 14.0, 20 December 2019.

Protaphane CCDS version 15.0, 20 December 2018.

PenMix, Protaphane, Mixtard, Penfill and NovoFine are trademarks owned by Novo Nordisk A/S, Denmark

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Avoidance of accidental mix-ups/medication errors added