APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

NAME OF THE MEDICINE

Protaphane HM (ge)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of bio-synthetic human isophane insulin contains 100 units of a sterile suspension of genetically engineered monocomponent isophane insulin.

Human insulin is produced in Saccharomyces cerevisiae by recombinant DNA technology.

3. PHARMACEUTICAL FORM

Suspension for injection.

A white suspension which on standing deposits a white sediment and leaves a colourless or almost colourless supernatant liquid. The sediment is readily resuspended on gentle shaking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes Mellitus

4.2 Posology and method of administration

Posology

The dosage for each patient is individualised 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.

One or several daily injections may be necessary. The preparations may be used alone or mixed with fast- or rapid acting insulin products. In intensive insulin therapy, the insulin

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suspensions may be used as basal insulin (evening and/or morning injection) with a fast- or rapid acting insulin given at meal times.

In patients with diabetes mellitus optimized metabolic control delays the onset of late diabetic complications. Close blood glucose monitoring, is therefore recommended.

Protaphane HM (ge) is administered subcutaneously in the thigh or abdominal wall. If convenient the gluteal or deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites. Injection sites should be rotated within an anatomical region in order to avoid lipodystrophy and cutaneous amyloidosis.

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

Special populations

Renal or hepatic impairment may reduce insulin requirement.

Method of administration

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 Protaphane® and other insulin products.

Use of FlexPen:

Instructions for use and handling are reflected in the Patient Information Leaflet (Use of FlexPen).

To avoid possible transmission of disease, FlexPen is for single person use only.

Injections using 10 ml vials and conventional syringes:

Instructions for use are reflected in the Patient Information Leaflet.

Protaphane HM (ge) vials are for use with insulin syringes with a corresponding unit scale.

Injections using Protaphane HM (ge) Penfill:

Protaphane HM (ge) Penfill cartridges are designed to be used with Novo Nordisk insulin delivery system and NovoFine or NovoTwist needles.

General instructions for use of Penfill (cartridges)

See patient instructions for use in the Patient Information Leaflet enclosed with the Penfill (cartridges).

Always ensure that the injection device is assembled according to manufacturer's directions.

Please refer to the instructions included with the relevant devices.

4.3 Contraindications

- Hypoglycaemia
- Hypersensitivity to human insulin or any of the excipients.

4.4 Special warnings and precautions for use

Protaphane HM (ge) is not to be administered intravenously.

Before traveling 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.

Concomitant illness, especially infections and feverish conditions, usually increases the patient’s insulin requirement.

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Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in Type 1 diabetes (insulin dependent diabetes mellitus), may lead to hyperglycaemia.

The first symptoms of hyperglycaemia usually comes on gradually, over a period of hours or days. They include 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

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.

The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiety, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

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

Transfer from other insulin products

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin, insulin analogue) and/or method of manufacture may result in a change in dosage from that used with

their usual insulins. If an adjustment is needed, it may be done 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.

Skin and subcutaneous tissue disorder

Lipodsytrophy may occur at the injection site as a consequence of failure to rotate injection sites within the same area.

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 medicines may be considered.

Combination of Protaphane with pioglitazone

Cases of congestive heart failure have been reported when pioglitazone was 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 pioglitazone 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. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicines and other forms of interaction

A number of medicines are known to interact with glucose metabolism.

The following medicines may reduce the patient's insulin requirements:

Oral hypoglycaemic agents (OHAs), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates and alcohol.

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

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

Beta blocking medicines may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Ocreotide may either decrease or increase the insulin requirements.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

Pregnancy

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier. If untreated during pregnancy, diabetes mellitus constitutes a risk in intra-uterine development. Diabetes therapy must therefore be continued during pregnancy.

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and deaths *in utero.*

Intensified blood glucose control and monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating a 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 values.

Breastfeeding

There are no restrictions on the treatment of diabetes with Protaphane HM (ge) during lactation. Insulin treatment of nursing mother presents no risk to the baby. However the dosage, diet or both 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. 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

Side effects observed in patient using Protaphane are mainly dose-dependent and due to the pharmacological effect of insulin. Hypoglycaemia is the most frequent side effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varied with the patient population and dose regimens.

(b) Tabulated list of adverse reactions

Frequencies of side effects from clinical trials, which by an overall judgment are considered related to Protaphane are listed below. The frequencies are defined as: Very Common (≥ 1/10), Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1000. Isolated spontaneous cases are presented as very rare defined as: < 1/10 000.

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System organ class	***Side effect and frequency***
Immune system disorders	*Uncommon* - Urticaria, rash
	Very rare - Anaphylactic reactions
Metabolism and nutrition disorders	*Very common* - Hypoglycaemia
Nervous system disorders	*Very rare* - Peripheral neuropathy (painful neuropathy)
Eye disorders	*Very rare* - Refraction disorders
	Uncommon - Diabetic retinopathy
Skin and subcutaneous disorders	*Uncommon* – Lipodystrophy *Not known: Cutaneous amyloidosis*†*
General disorders and administration site conditions	*Uncommon* - Injection site reactions, oedema

**see description of selected adverse reactions*
†Adverse reations from post marketing sources

(c) *Description of selected adverse reactions*

Anaphylactic reactions

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, and angio-oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting /loss of consciousness. Generalised hypersensitivity reactions are potentially life threatening.

Peripheral neuropathy (*painful neuropathy*)

Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy” which is usually reversible.

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Skin and subcutaneous tissue disorders

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

Injection site reactions

Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Oedema

Oedema may occur upon initiation of insulin treatment. These symptoms are usually of transitory nature.

Eye disorders

Refraction disorders:

Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Diabetic retinopathy

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

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 medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug

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Reactions Reporting Form", found online under SAHPRA's publications

https://www.sahpra.org.za/Publications/Index/8

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 requirements are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries sugary 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 carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicines used in diabetes. Insulins and analogues for injection, intermediate-acting, insulin (human). ATC code: A10AC01. (A 21.1 Insulin preparations)

Mechanism of action and pharmacodynamic effects

Protaphane HM (ge) is a long acting insulin.

Replaces the insufficiency of insulin secretion by the beta-cells of the pancreas.

The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells – and simultaneously inhibit the output of glucose from the liver.

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The effect of Protaphane HM (ge) begins after approximately 1½ hours, is maximal between 4 - 12 hours and terminates after approximately 24 hours.

5.2 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). The pharmacokinetics of insulins is therefore affected by significant intra- and inter-individual variation.

Absorption

The maximum plasma concentration of 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 ($t_{½}$) is therefore a measure of the terminal absorption rather than of the elimination *per se* of insulin from the plasma (insulin in the blood stream has a $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ is about 5 – 10 hours.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate

Metacresol (preservative; 0,15 % m/v)

Phenol (preservative; 0,065 % m/v)

Zinc chloride

Glycerol

Disodium phosphate

Sodium hydroxide (*pH adjustment*)

Hydrochloric acid (*pH adjustment*)

Water for injection

Protaphane HM (ge) contains less than 1 mmol (23 mg) sodium per dose, i.e. Protaphane HM (ge) is essentially ‘sodium-free’.

6.2 Incompatibilities

Protaphane HM (ge) should not be used in insulin infusion pumps.

6.3 Shelf life

Before opening:

30 months when stored between 2 °C and 8 °C.

After first opening:

Protaphane HM (ge) FlexPen® and Penfill® in use or carried as a spare may be kept at room temperature at or below 30 °C) for 42 days (6 weeks).

Protaphane HM (ge) vial, in use or carried as a spare may be kept at room temperature at or below 30 °C for 28 days (4 weeks).

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6.4 Special precautions for storage

Avoid freezing.

Keep out of sunlight.

Before opening:

Protaphane FlexPen®, Penfill® (cartridges) and vials not in use are to be stored between 2 °C and 8 °C.

Optional additional storage by patient

If there are 6 months or more until the expiry date, Protaphane HM (ge) may be stored outside of the refrigerator (at or below 30 ˚C) for a maximum of 4 weeks before it is taken into use or carried as a spare. After storage outside of the refrigerator, the product must not be returned to the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

After first opening:

The FlexPen® and Penfill (cartridges) in use may be kept at room temperature at or below 30 ˚C) for 42 days (6 weeks).

The 10 ml vials in use may be kept at room temperature at or below 30 ˚C for 28 days (4 weeks).

Do not store FlexPen®, Penfill® (cartridges) and vials in use in the refrigerator.

Protaphane® HM (ge), Penfill® (cartridges) can be used in, e.g. the NovoPen®, or carried with you as a spare for up to 42 days (6 weeks). They must not be exposed to sunlight or temperatures above 37 °C. Do not store cartridges in use in the refrigerator.

6.5 Nature and contents of container

- 5 x 3 mL Protaphane® HM (ge) – FlexPen®:

  FlexPen® packed into carton boxes, The FlexPen® is a pre-filled pen (multidose disposable pen) in which a Penfill® cartridge of 3 mL is inserted. The cartridge is made of glass (Type 1), containing a bromobutyl rubber plunger and a bromobutyl/polysisoprene rubber stopper. The cartridge contains a glass ball to facilitate the re-suspension.

  - Protaphane® HM (ge) - vial:

    10 ml vial is made of glass (type 1). The vial is closed with a bromobutyl/polyisoprene rubber stopper and tamper-proof plastic cap. The vial is packed in a carton.

  - Protaphane® HM (ge) - Penfill®:

    3 ml cartridge is made of glass (type 1), containing a rubber closure shaped as a plunger and closed with a rubber closure. The cartridge contains a glass ball to facilitate the re-suspension. 5 x 3 mL cartridges are packed in a carton.

6.6 Special precautions for disposal and other handling

The necessity of resuspending the Protaphane® HM (ge) suspension immediately before use is to be stressed to the patient.

The re-suspended liquid must appear uniformly white and cloudy.

Note: Protaphane® HM (ge) which does not become completely homogeneous (uniform) when agitated should not be used.

Never use insulin after expiry date.

Snap-off caps:

The insulin vials are packed and shipped with a protective, colour coded, tamper-proof plastic cap. In order to withdraw insulin from a new vial, the cap must be removed. If the cap is not securely fastened to a newly purchased vial, return the vial to the pharmacy.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg
2196

8. REGISTRATION NUMBER

W/21.1/290

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on the registration certificate of the medicine: 28/06/1989

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA:

07 Feb 2022

Type IB, implemented: 20 Oct 2023 – Storage conditions

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