APPROVED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S3

PRODUCT NAME

Protaphane HM (ge); 100 IU, Suspension for Injection, human insulin

Read all of this leaflet carefully before you start using PROTAPHANE HM (ge)

- *Keep this leaflet. You may need to read it again.*
- *If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.*
- *Protaphane HM (ge) has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.*

What is in this leaflet

1. What PROTAPHANE HM (ge) is and what it is used for

Protaphane HM (ge) is a long acting human insulin preparation that is used for the treatment of diabetes mellitus (a disease where your pancreas does not produce enough insulin to control your blood sugar levels) and extra insulin is therefore needed.

2. What you need to know before you use PROTAPHANE HM (ge)

Do not use PROTAPHANE HM (ge):

- If your blood sugar is too low (hypoglycaemia).
- You are allergic to human insulin or any of the ingredients contained in Protaphane HM (ge).
- Which does not become completely homogeneous (uniform) when agitated should not be used.
- If it has not been stored correctly or if it has been frozen.

Before using PROTAPHANE HM (ge):

- Check the label to make sure it is the right type of insulin.

Warnings and precautions

Take special care with Protaphane HM (ge):

- If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid gland.
- If you are ill, carry on taking your insulin and consult your doctor
- If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travelling.
- If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.

If you are unsure as what to do, please consult your doctor, pharmacist or other healthcare professional for advice.

Other medicines and PROTAPHANE HM (ge):

Always tell your health care provider if you are taking any other medicines. (This includes all complementary or traditional medicines.)

Some medicines affect your blood sugar level, and this may mean that your insulin dose has to change.

If you take any of the below medicines your insulin requirements may be reduced

- If you are currently taking oral hypoglycaemic agents (used for treatment of Type 2 diabetes),
- Monoamine oxidase (MAO-) inhibitors (used for treatment of depression),
- Non-selective beta-blocking agents (used for treatment of certain heart conditions and high blood pressure) such as propranolol
- Angiotension converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine) and ARBS (Angiotensin Receptor Blockers)
- Salicylates (e.g. aspirin, used to relieve pain and lower fever) and alcohol your insulin requirements may decrease.

If you take any of the below medicines your insulin requirements may be increased:

If you are currently taking:

- Oral contraceptive (used for birth control)
- Thiazides (used for treatment of high blood pressure or oedema)
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation)
- Thyroid hormones (used for the treatment of a malfunctioning thyroid gland)
- Sympathomimetics (used for the treatment of asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth)
- Danazol (medicine acting on ovulation)

Beta blocking medicines (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Ocreotide (used for treatment of acromegaly) may either increase or decrease your blood sugar level.

Pioglitazone (tablets used for the treatment of type 2 diabetes)

Pioglitazone (class of oral antidiabetic medicines used for the treatment of type 2 diabetes mellitus). Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who are treated with pioglitazone in combination with insulin may develop heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

PROTAPHANE HM (ge) with alcohol

Using Protaphane HM (ge) with alcohol (including beer and wine) may lead to hypoglycaemia (low blood sugar). Therefore be careful when you drink alcohol and never drink alcohol on an empty stomach. Careful monitoring is recommended.

Pregnancy and breast-feeding

- There is limited clinical experience with Protaphane HM (ge) in pregnancy. If you are planning a pregnancy, or if you are pregnant while using this medicine, please contact your doctor, pharmacist or other healthcare professional for advice. Your insulin dosage and diet may need to be adjusted during pregnancy and after delivery. Therefore it is important to consult your doctor immediately to discuss your insulin needs in order to control your diabetes and thereby avoid hyperglycaemia (high blood sugar) and hypoglycaemia (low blood sugar) as these conditions could harm your baby.
- Breastfeeding your baby whilst using insulin does not put your baby at risk, therefore there are no restrictions on treatment with Protaphane HM (ge) during breast-feeding.

Driving and using machines

Your ability to concentrate and react may be reduced if you have hypoglycaemia (too low blood sugar). Please keep this possible problem in mind in all situations where you might put yourself and other people at risk (e.g. when driving a car or operating machinery). You must contact your doctor about the advisability of driving if you have frequent episodes of hypoglycaemia or have reduced or absent awareness of warning signs of hypoglycaemia.

PROTAPHANE HM (ge) contains sodium

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

3. How to use PROTAPHANE HM (ge)

Do not share medicines prescribed for you with any other person.
Always use your PROTAPHANE HM (ge) exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you have the impression that the effect of Protaphane HM (ge) is too strong or too weak, tell your doctor or pharmacist.

Protaphane HM (ge) should be generally administered immediately 30 minutes before a meal.
Dosage of Protaphane HM (ge) is individualised and determined on the basis of the doctor’s advice in accordance with the needs of the patient.

You must never stop using your insulin even if you are ill, as you may need to have more insulin than normally. This may be especially the case if you have an infection, have fever, eat less than usual or vomit. If you get certain problem with your kidneys or your liver your doctor may lower your insulin dosage.

The injection can be administered subcutaneously by injection in the abdominal wall, the thigh or the deltoid region, or the gluteal region.

Injection sites should be rotated within the same region.

When injected subcutaneously into the abdominal wall, the onset of action will occur within 1½ hours of injection.

The maximum effect is exerted between 2 - 14 hours after the injection. The duration of action is 24 hours. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Do not use Protaphane HM (ge) in insulin infusion pumps.

If you inject more PROTAPHANE HM (ge) than you should:

Hypoglycaemia symptoms may develop over sequential stages:

mild hypoglycaemia which can be treated by oral administration of glucose or sugary products, it is therefore recommended that you always carry products containing sugar and *severe* hypoglycaemia where by you become unconscious and can be treated by administration of glucagon intramuscularly or intravenously by a trained person, or by administration of glucose intravenously by a healthcare professional. After regaining conscious, oral administration of any sugar containing products is recommended to avoid any relapse.

In the event of overdosage, please consult your doctor or pharmacist. If neither is available, contact nearest hospital or poison center.

If you forget to inject PROTAPHANE HM (ge) or you inject inadequate dose of Protaphane *HM (ge),* especially if you are Type 1 Diabetes (insulin-dependant diabetes), you may experience hyperglycaemia and diabetic ketoacidosis. The symptoms of hyperglycaemia develop gradually over a period of hours or days and include the following:

- Thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite, odour of acetone when you breathe. If hyperglycaemia is not treated, it will lead to diabetic ketoacidosis which is potentially dangerous and lethal.

Diabetic ketoacidosis means a condition in which the blood sugar is usually very high. This is a very serious condition, which may develop if you take less insulin than you need. This may be due to increased insulin demand during illness or infection, neglect of diet, omission of insulin doses or the injection of a smaller insulin dose than that prescribed by your doctor.

A developing ketoacidosis will be revealed by urine tests which show large amounts of sugar and ketones. The symptoms of thirst, large urine volumes, loss of appetite, fatigue, dry skin and deep and rapid breathing come on gradually, usually over a period of some hours or days. If you recognize these symptoms, consult your doctor immediately. If such symptoms are not treated, they can cause diabetic coma and death.

Do not inject a double dose of Protaphane HM (ge) to make up for forgotten individual doses.

If you stop using PROTAPHANE HM (ge):

You must never stop using your Protaphane HM (ge) discontinuation of treatment may lead to hyperglycaemia especially in type 1 diabetes.

3. POSSIBLE SIDE EFFECT

Protaphane HM (ge) can have side effects.

The side effects most frequent reported include:

Hypoglycaemia is the most frequent side effect. It may occur if the insulin dose is too high in relation to that 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. *Please refer to section*

"If you inject more Protaphane HM (ge) than you should"

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.

The following side effects are less frequently reported:

- Oedema (swollen joints):

  When you start taking Protaphane, water retention may cause swelling around your ankles and other joints. Usually this soon disappears.
- Injection site reactions (redness, swelling and itching at the injection site):

  These symptoms usually disappear after a few weeks of taking Protaphane HM (ge). If they do not disappear please consult your doctor or pharmacist.
- Diabetic retinopathy (eye disease related to diabetes which can lead to loss of vision):

  If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

- Changes at injection site (lipodystrophy):

  The fatty tissue under the skin at injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area.

  Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell

your doctor or other healthcare professionals. These reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

The other side effects reported include:

- Vision problems:

  When you start your Protaphane treatment, it may disturb your vision, but the disturbance is usually temporary.

- Allergic side effects have been reported.

  They include generalised skin rash, itching, sweating, gastrointestinal upset, difficulty in breathing, palpitation (rapid heartbeat). These side effects are potentially life threatening and immediate medical attention should be sought.

- Painful neuropathy (pain due to nerve damage):

  If your blood sugar level improves very fast, you may get nerve related pain, this is called acute painful neuropathy and is usually transient.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Not all side effects reported for Protaphane HM (ge) are included in this leaflet. Should your general health worsen while using Protaphane HM (ge), please consult your doctor, pharmacist or other healthcare professional for advice.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found on line under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of Protaphane® HM (ge).

5. How to store PROTAPHANE® HM (ge)

Before opening:

PROTAPHANE® HM (ge) vials, FlexPen® and Penfill® not in use to be stored between 2 °C and 8 °C (in a refrigerator) for 30 months.

Keep away from the cooling element.

Do not freeze

During use or when carried as a spare:

PROTAPHANE® HM (ge) vial, FlexPen® and Penfill® in use may be kept at room temperature (maximum 25 °C) for one month. Discard any unused portion after one month,

Always keep the vial in the outer carton when you are not using it, in order to protect from light.

Protaphane HM (ge) Penfill cartridges can be used in, e.g. the NovoPen, or carried with you as a spare for up to one month.

Do not store cartridges in use in the refrigerator.

Do not expose PROTAPHANE® HM (ge) to excessive heat or sunlight.

Do not use PROTAPHANE® HM (ge) after the expiry date stated on the label and carton.

The expiry date refers to the last day of that month.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What PROTAPHANE® HM (ge) contains

The active ingredient of Protaphane HM (ge) is bio-synthetic human isophane insulin.

Each ml contains 100 IU of bio-synthetic human isophane insulin.

The other ingredients are:

Glycerol

Disodium phosphate dihydrate

Metacresol

Phenol

Zinc chloride

Protamine Sulphate

Sodium hydroxide

Hydrochloric acid

Water for injections

What PROTAPHANE HM (ge) looks like and contents of the pack

Protaphane HM (ge) is a white suspension which on standing deposits white sediment and leaves a colourless or almost colourless supernatant liquid. The sediment is readily resuspended on gentle shaking.

- Protaphane HM (ge) vial:

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

- Protaphane HM (ge) Penfill:

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

- Protaphane HM (ge) FlexPen:

  5 x 3 ml Protaphane HM (ge) FlexPen packed into carton boxes. 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.

Holder of Certificate of Registration

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W/21.1/290

Appendix 1

Vial instructions for use

How to inject Protaphane HM (ge) on its own or to mix with fast-acting insulin

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin.

This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

► Make sure you have the correct syringe with the corresponding unit scale for insulin injections.

- Clean the skin. Wipe the rubber disc on the vial with alcohol.
- Draw the piston of the syringe out to a distance corresponding to the quantity of insulin required.
- Gently agitate the vial of insulin.

► Just before injecting this insulin, roll the vial between your hands until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.

- Then pierce the rubber disc with the needle, then push the piston home, and turn the vial upside down.
- Draw the required amount of insulin into the syringe. Avoid air in the syringe and needle by working the piston slightly up and down.

► Follow the instructions given by your healthcare professional.

► Use the injection technique advised by your doctor or other healthcare professional.

- Make the injection at a suitable depth under the skin (subcutaneously). It is important that the injection is made with a syringe which is marked for use with an insulin preparation containing 100 units per ml. Failure to use the correct syringe, can lead to dosage errors.

► Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered.

Appendix 2

Penfill® instructions for use

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin.

This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

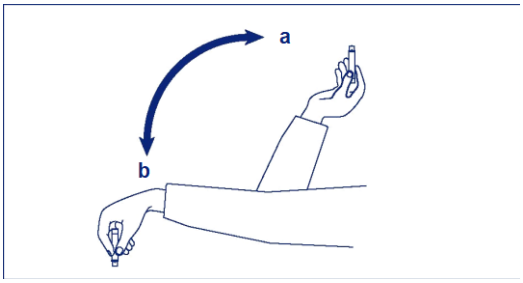
Resuspending the insulin

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.

How to inject this insulin

► Inject the insulin under the skin. Use the injection technique advised by your doctor or other healthcare professional and as described in your delivery system manual.

► Keep the needle under your skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.

► After each injection be sure to remove and discard the needle and store

Protaphane® without the needle attached. Otherwise the liquid may leak out which can cause inaccurate dosing.

Do not refill Protaphane® HM (ge) Penfill®.

Penfill® cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine® or NovoTwist® needles.

If you are treated with Protaphane® Penfill® and another insulin Penfill® cartridge, you should use two insulin delivery systems, one for each type of insulin.

As a precautionary measure, always carry a spare insulin delivery device in case your Penfill® is lost or damaged.

Delivery of dosage using NovoPen:

Use the injection technique advised by the healthcare practitioner.

With NovoPen it is possible to select a dose larger than the number of units remaining in the Penfill. For your convenience the cartridge holder has marks which show the approximate dose remaining in the Penfill.

Do not dial up more than what is available.

Do not initiate injection if the rubber piston can be seen in the small inspection windows as the glass ball needs room to resuspend the insulin.

When a dosage greater than that remaining in the cartridge is required, the following options can be exercised:

i) The dosage remaining in the current Penfill can be administered. A new Penfill is then inserted according to the manufacturer's instructions, and the balance of the required dosage is administered from the new Penfill

or

ii) The current Penfill can be discarded. A new Penfill is then inserted according to the manufacturer's instructions and the full dosage is administered from the new Penfill.

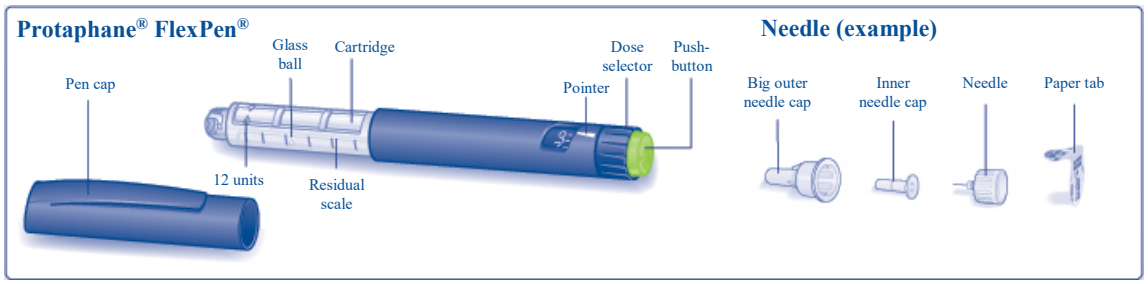
To avoid possible transmission of disease, Penfill is for single person use only.

Appendix 3

Instructions on how to use Protaphane® HM (ge) suspension for injection in pre-filled FlexPen®

Read the following instructions carefully before using your FlexPen®. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your Protaphane® HM (ge) FlexPen® is a pre-filled dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. The FlexPen® is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm. As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen® is lost or damaged.



Caring for your pen

Your Protaphane® HM (ge) FlexPen® must be handled with care.

If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

You can clean the exterior of your FlexPen® by wiping it with a medicinal swab.

Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your Protaphane® HM (ge) FlexPen®.

Preparing your Protaphane® HM (ge) FlexPen®

A

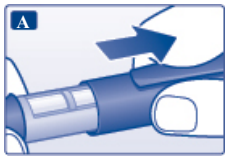
Check the name and coloured label of your pen to make sure that it contains

the correct type of insulin.

This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Every time you use a new pen

Let the insulin reach room temperature before you use it. This makes it easier to resuspend. Pull off the pen cap (see A).



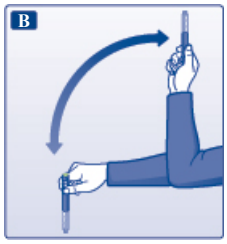
B

Before your first injection with a new pen, you must resuspend the insulin:

Move the pen up and down twenty times between the two positions as shown, so the glass ball moves from one end of the cartridge to the other. Repeat until the liquid appears uniformly white and cloudy.

For every following injection, move the pen up and down between the two positions at least 10 times until the liquid appears uniformly white and cloudy.

Always make sure that you have resuspended the insulin prior to each injection. This reduces the risk of too high or too low blood sugar level. After you have resuspended the insulin, complete all the following steps of injection without delay.



- Always check there are at least 12 units of insulin left in the cartridge to allow resuspension. If there are less than 12 units left, use a new pen.

Attaching a needle

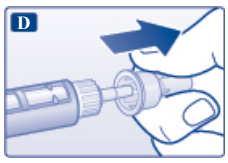
C

Remove the paper tab from a new disposable needle.

Screw the needle straight and tightly onto your Protaphane® HM (ge) FlexPen®.

D

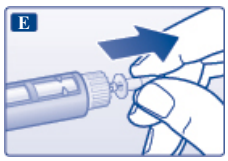
Pull off the big outer needle cap and keep it for later.



E

Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



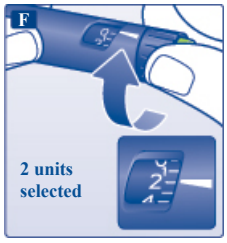
- Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- Be careful not to bend or damage the needle before use.

Checking the insulin flow

F

Prior to each injection, small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:

Turn the dose selector to select 2 units.



G

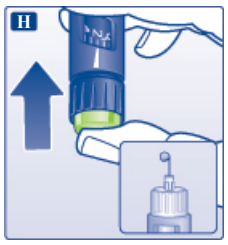
Hold your FlexPen® with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.

H

Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If a drop of insulin still does not appear, the pen is defective, and you must use a new one.



- Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.
- Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Selecting your dose

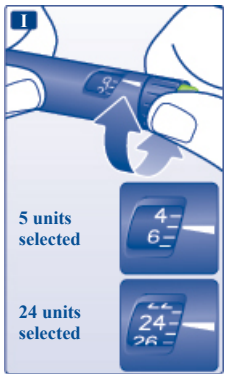
I

Check that the dose selector is set at 0.

Turn the dose selector to select the number of units you need to inject.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.



- Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
- Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Making the injection

J

Insert the needle into your skin. Use the injection technique shown by your doctor or other healthcare professional.

Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer.

Be careful only to push the push-button when injecting.

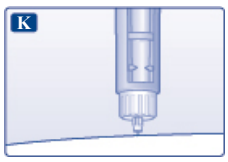
Turning the dose selector will not inject insulin.

K

Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose.

Withdraw the needle from the skin, then release the pressure on the push-button.

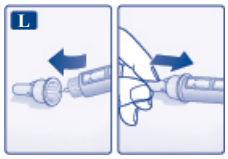
Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



L

Lead the needle into the big outer needle cap without touching it. When the needle is covered, carefully push the big outer needle cap completely on and then unscrew the needle.

Dispose of it carefully and put the pen cap back on.



- ⚠ Always remove the needle after each injection and store your Protaphane® HM (ge) FlexPen® without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

- ⚠ Caregivers must be very careful when handling used needles – to reduce the risk of needle sticks and cross-infection.
- ⚠ Dispose of your used FlexPen® carefully without the needle attached.
- ⚠ Never share your pen or your needles with other people. It might lead to cross-infection. Never share your pen with other people. Your medicine might be harmful to their health. Always keep your pen and needles out of sight and reach of others, especially children.