APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Actraphane® HM (ge)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of biphasic bio-synthetic human insulin contains a sterile suspension of 100 units of genetically engineered monocomponent insulin, (30 % soluble insulin and 70 % isophane insulin).

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

For full list of excipients, see section 6.1

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 re-suspended 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. 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.

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

Special populations

Renal and hepatic impairment

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 Actraphane® HM (ge) and other insulin products.

Actraphane® 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 result in 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.

Injections using 10 ml vials and conventional syringes.

Instructions for use are reflected in the Patient Information Leaflet.

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

Use of FlexPen

Instructions for use and handling are reflected in the Patient Information Leaflet (Use of FlexPen®). See patient instruction leaflet enclosed in FlexPen® packaging.

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

Injections using Actraphane® HM (ge) Penfill® (cartridge)

Actraphane® 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 enclosed with Penfill ®(cartridge).

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Actraphane® HM (ge) is not to be administered intravenously.

Before travelling between time zones, the patient should seek the doctor’s advice, since this may mean that the patient has to take insulin and meals at different times.

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 analogue) and/or method of manufacture may result in a change in dosage from that used

with their previous insulin. 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 the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

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 come on 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 usually lead to diabetic ketoacidosis which is potentially lethal.

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

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.

Severe hypoglycaemia may lead to unconsciousness and /or convulsion 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, 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 convulsion and may result in temporary or permanent impairment of brain function or even death.

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.

Skin and subcutaneous tissue disorder

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 pioglitazone with Actraphane® HM (ge)

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 medicines (OHAs), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking medicines, 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.

Octreotide may both decrease and increase 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.

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

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

Breast-feeding

There are no restrictions on treatment of diabetes with insulin during breastfeeding, as insulin does not pass into breast milk.

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, 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.

4.8 Undesirable effects

(a) Summary of the safety profile

Side effects observed in patients using Actraphane® HM (ge) 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 therefore no specific frequency can be presented.

(b) Tabulated list of adverse reactions

Frequencies of other side effects from clinical trials, which by an overall judgement are considered related to Actraphane® HM (ge) are listed below. The frequencies are defined as:

Very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥ 1/0 000, <1/1000). Isolated spontaneous cases are presented as very rare, defined as: <1/10 000.

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

† ADR from postmarketing sources

c. Description of selected adverse reactions

Anaphylactic reactions

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic 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. This reaction is usually of transitory nature

Eye disorders

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.

Refraction disorders

Refraction anomalies may occur upon initiation of Actraphane.

These symptoms are usually of transitory nature.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohyperthrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site as a consequence of failure to rotate injection sites within the same area. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Oedema

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product 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 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 some sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0,5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or glucose given intravenously by a medical 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- or long-acting combined with fast-acting, insulin (human). ATC code: A10AD01.

(A 21.1 Insulin preparations)

Mechanism of action and pharmacodynamic effects

The insulin in Actraphane® HM (ge) has a rapid onset of action and an intermediate duration. 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.

The effect of biphasic insulin begins after approximately ½ hour, is maximal between 2 - 8 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 absorption profile is due to the product being a mixture of insulins 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol (0,15 % (mv) preservative)

Phenol (0,065 % (mv) preservative)

Zinc chloride,

Glycerol,

Sodium phosphate dihydrate,

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Protamine sulphate

Water for injection

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

6.2 Incompatibilities

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

6.3 Shelf life

Before opening

Actraphane® HM (ge) FlexPen®, Penfill® and vial stored at in a refrigerator (2 °C – 8 °C) for 30 months

After first opening

Actraphane® HM (ge) FlexPen®, Penfill® and vial in use may be kept at room temperature (max. 25 °C) for one month.

6.4 Special precautions for storage

Do not freeze.

Keep out of sunlight

Insulin FlexPen®, Penfill® and vials not in use to be stored between 2°C and 8°C (in a refrigerator). Actraphane® HM (ge) FlexPen®, Penfill® and vial in use may be kept at room temperature (max. 25 °C) for one month. They must not be exposed to sunlight or temperatures above 37 ºC.

Do not store FlexPen® and Penfill in use in the refrigerator.

6.5 Nature and contents of container

Actraphane® HM (ge) vial:

10 ml vial made of glass (type 1). The vial is closed with a rubber closure and packed in a carton.

Actraphane HM (ge) Penfill®:

3 ml cartridge is made of glass (Type 1), containing a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. The cartridge contains a glass ball to facilitate re-suspension.

5 x 3 ml Actraphane® HM (ge) FlexPen® packed in a carton.

Actraphane® HM (ge) FlexPen®:

FlexPen® is a pre-filled (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/polyisoprene rubber stopper. The cartridge contains a glass ball to facilitate re-suspension.

5 x 3 ml Actraphane® HM (ge) FlexPen® packed in a carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Actraphane® HM (ge) which does not become completely homogeneous (uniform) when agitated should not be used. Never use insulin after expiry date.

Actraphane HM (ge) which has been frozen must not be used.

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.

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/21.1/287

9. DATE OF FIRST 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:

20 August 2021