APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

Actrapid® HM (ge)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of bio-synthetic human soluble insulin contains 100 units of a sterile solution of genetically engineered monocomponent neutral insulin.

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

For full list of excipients, *see section 6.1*

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is colourless liquid free from turbidity and foreign matter.

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 optimised metabolic control delays the onset of late diabetic complications. Close blood glucose monitoring including monitoring of Hb_{A1c}, is therefore recommended.

Special populations

Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

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.

Method of administration

Actrapid® 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 results in a faster absorption than from other injection sites.

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

Actrapid® HM (ge) may also be administered intravenously, which should only be carried out by healthcare professionals.

Actrapid® HM (ge) is not recommended for use in infusion pumps for continuous subcutaneous insulin infusion due to the risk of precipitation in some pump catheters.

Injections using 10 ml vials and conventional syringes.

Instructions for use are reflected in the Patient Information Leaflet.

Actrapid 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 Actrapid HM (ge) Penfill:

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

Always ensure that the injection device is assembled according to manufacturer's directions. Please refer to the instructions included with the device.

4.3 Contra-indications

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

4.4 Special warnings and precautions for use

Self administering patients must not use the intravenous route.

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.

Hyperglycaemia

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

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.

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.

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

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 Actrapid® HM (ge) 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.

Avoidance of accidental mix-ups/medicine errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Actrapid HM (ge) and other insulin products.

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 agents,
- Angiotensin converting enzyme (ACE) inhibitors,
- Angiotensin receptor blockers (ARBs),
- 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 agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.
- Octreotide may either decrease or increase insulin requirements.
- Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Fertility, 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 are 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 normally return rapidly to pre-pregnancy values.

Breastfeeding

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 should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those patients 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 patients using Actrapid® HM (ge) are mainly dose dependent and due to the pharmacological effect of insulin. Hypoglycaemia is the most common side effect. It may occur if the insulin dose is too high in relation to insulin requirement.

(b) Tabulated summary of adverse reactions

Frequencies of other side effects from clinical trials, which by an overall judgment are considered related to Actrapid® 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 (≥ 1/10 000, < 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: Refraction disorders
	Very rare: 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

**Adverse reactions based on post-marketing source data*

(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.

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 palpitations.

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

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohyperthrophy, lipotrophy) 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.

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, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Refraction disorders

Refraction anomalies may occur upon initiation of Actrapid HM (ge). These symptoms are usually of transitory nature.

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 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 sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0,5 to 1,0 mg) given intramuscularly or subcutaneously by a trained person who has received appropriate instruction, or 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: Insulins and analogues for injection, fast-acting, insulin (human).

ATC code: A10AB01 (A 21.1 Insulin preparations)

Mechanism of action and pharmacodynamic effects

The insulin in Actrapid® HM (ge) is a fast acting soluble insulin.

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 soluble insulin after subcutaneous administration begins after approximately 30 minutes, reaches maximal effect between 1,5 and 3,5 hours and the entire duration of action is approximately 7 - 8 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 soluble 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

Glycerol

metacresol (preserved with 0,3 % m-cresol)

zinc chloride

sodium hydroxide *(pH adjustment*),

hydrochloric acid *(pH adjustment*)

and water for injection

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

6.2 Incompatibilities

In the absence of compatibility studies, Actrapid HM (ge) must not be mixed with other medicines

6.3 Shelf life

Before opening:

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

After first opening:

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

6.4 Special precautions for storage

Do not freeze.

Keep out of sunlight.

Keep out of reach of children.

Before opening:

Insulin vials, FlexPen® and Penfill® 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, Actrapid® 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:

Actrapid® HM (ge) vial, FlexPen® and Penfill® in use may be kept at room temperature at or below 30 ˚C) for 6 weeks (42 days).

Please record the beginning of use on the product carton.

6.5 Nature and contents of container

- Actrapid® HM (ge) vial: 10 mL vial made of glass (type 1). The vial is closed with a rubber closure and packed in a carton (1 x 10 mL).
- Actrapid® 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. 5 x 3 mL Actrapid® HM (ge) FlexPen® packed in a carton.
- Actrapid® HM (ge) Penfill: 3 mL Penfill cartridge. The cartridge is made of glass (Type 1), containing a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. 5 x 3 mL Actrapid® HM (ge) Penfill packed in a carton.

6.6 Special precautions for disposal and other handling

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.

Actrapid® HM (ge) should not be used if not water-clear and colourless.

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

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

Never use insulin after expiry date.

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 NUMBERS

W/21.1/288

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: 17 June 2021