Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Humulin M3 KwikPen (mixture 3) 100 IU/ml Suspension for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 IU insulin human (produced in E. coli by recombinant DNA technology).

One pre-filled pen contains 3 ml equivalent to 300 IU of biphasic isophane insulin – 30 % soluble insulin / 70 % isophane insulin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A suspension for injection in a pre-filled pen.

Humulin M3 is a sterile suspension of human insulin in the proportion of 30 % soluble insulin to 70 % isophane insulin.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis.

4.2 Posology and method of administration

Posology
The dosage should be determined by the physician, according to the requirement of the patient.

Paediatric population No data are available Method of administration
Humulin M3 in pre-filled pen is only suitable for subcutaneous injections. This formulation should not be administered intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Care should be taken when injecting any Humulin insulin preparations to ensure that a blood vessel has not been entered. After any insulin injection, the injection site should not be massaged. Patients must be educated to use proper injection techniques.
Humulin Mixture formulation is a ready-made defined mixture of soluble and isophane insulin designed to avoid the need for the patient to mix insulin preparations. A patient's treatment regimen should be based on their individual metabolic requirements.

Each pack contains a patient information leaflet with instructions on how to inject insulin.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, unless used as part of a desensitisation programme.

Under no circumstances should any Humulin formulation other than Humulin S (Soluble) be given intravenously.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (soluble, isophane, mixture), species (animal, human, human insulin analogue), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Some patients taking human insulin may require a change in dosage from that used with animal- source insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

A few patients who experienced hypoglycaemic reactions after transfer to human insulin have reported that the early warning symptoms were less pronounced or different from those experienced with their previous animal insulin. Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly. Other conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, diabetic nerve disease, or medications such as beta blockers. Uncorrected hypoglycaemic and hyperglycaemic reactions can cause loss of consciousness, coma or death.

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin- dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Treatment with human insulin may cause formation of antibodies, but titres of antibodies are lower than those to purified animal insulin.

Insulin requirements may change significantly in diseases of the adrenal, pituitary or thyroid glands and in the presence of renal or hepatic impairment.

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of insulin dosage may also be necessary if patients change their level of physical activity or change their usual diet.

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, and dose adjustment of antidiabetic medications may be considered.

Combination of human insulin with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind, if treatment with the combination of pioglitazone and human insulin is considered. If the
combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

Instructions for use and handling
To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions

A number of medicinal products are known to interact with glucose metabolism and therefore the physician should be consulted when using other medications in addition to human insulin (see section 4.4). The physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

Insulin requirements may be increased by substances with hyperglycaemic activity, such as glucocorticoids, thyroid hormones, growth hormone, danazol, beta$_2$- sympatomimetics (such as ritodrine, salbutamol, terbutaline), thiazides.

Insulin requirements may be reduced in the presence of substances with hypoglycaemic activity, such as oral hypoglycaemics (OHA), salicylates (for example, acetylsalicylic acid), certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme (ACE) inhibitors (captopril, enalapril), angiotensin II receptor blockers, non-selective beta-blocking agents and alcohol.

Somatostatin analogues (octreotide, lanreotide) may both decrease or increase insulin dose requirements.

4.6 Fertility, pregnancy and lactation

It is essential to maintain good control of the insulin treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy.

Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

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

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise.

Local allergy in patients is common (≥ 1/100 to < 1/10). Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, local reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy, which is very rare (< 1/10,000) but potentially more serious, is a generalised allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalised allergy may be life-threatening. In the rare event of a severe allergy to Humulin, treatment is required immediately. A change of insulin or desensitisation may be required.

Lipodystrophy at the injection site is uncommon (≥ 1/1,000 to < 1/100).

Skin and subcutaneous tissue disorders: Frequency "unknown": Cutaneous amyloidosis

<u>Skin and subcutaneous tissue disorders:</u>
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (See section 4.4).

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

Reportingof 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 **Ireland:** HPRA Pharmacovigilance**,** Website: www.hpra.ie.

4.9 Overdose

Insulin has no specific overdose definitions, because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin relative to food intake and energy expenditure.

Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycaemic episodes will respond to oral administration of glucose or sugar products.

Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously, if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may occur after apparent clinical recovery.

5 PHARMACOLOGICAL PROPERTIES

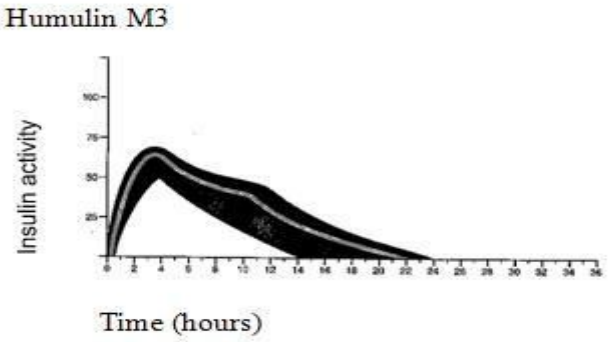
5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Insulins and analogues for injection, intermediate acting combined with fast acting.ATC code: A10A D01. Humulin M3 is a premixed suspension of rapid and intermediate acting insulin.

The prime activity of insulin is the regulation of glucose metabolism.

In addition insulin has several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

The typical activity profile (glucose utilisation curve) following subcutaneous injection is illustrated below by the heavy line. Variations that a patient may experience in timing and/or intensity of insulin activity are illustrated by the shaded area. Individual variability will depend on factors such as size of dose, site of injection temperature and physical activity of the patient.



5.2 Pharmacokinetic properties

The pharmacokinetics of insulin do not reflect the metabolic action of that hormone. Therefore, it is more appropriate to examine glucose utilisation curves (as discussed above) when considering the activity of insulin.

5.3 Preclinical safety data

Humulin is human insulin produced by recombinant technology. No serious events have been reported in subchronic toxicology studies. Human insulin was not mutagenic in a series of *in vitro* and *in vivo* genetic toxicity assays.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

m-cresol
glycerol
phenol
protamine sulfate
dibasic sodium phosphate $7H_2O$
zinc oxide
water for injections.

The following may be used to adjust pH; hydrochloric acid and/or sodium hydroxide.

6.2 Incompatibilities

Humulin preparations should not be mixed with insulins produced by other manufacturers or with animal insulin preparations.

6.3 Shelf life

Unused pre-filled pens
3 years.

After first use
28 days.

6.4 Special precautions for storage

Unused pre-filled pens

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Do not expose to excessive heat or direct sunlight.

After first use

Store below 30°C. Do not refrigerate. The pre-filled pen should not be stored with the needle attached.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type I glass) with a plunger head at the bottom (rubber) and disc seal at the top (rubber) in a pre-filled pen. Pack size of 5.

6.6 Special precautions for disposal and other handling

Do not reuse needles. Dispose of the needle in a responsible manner. Needles and pens must not be shared. Humulin M3 KwikPen can be used until empty, then properly discard. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instruction for use and handling
To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

A suspension for injection in a pre-filled / disposable pen injector containing a 3ml cartridge. Humulin M3 KwikPen delivers up to 60 units per dose in single unit increments.

a) Preparing a dose

Humulin KwikPen containing Humulin M3 formulation should be rolled in the palms of the hands ten times and inverted 180^0 ten times immediately before use to resuspend the insulin until it appears uniformly cloudy or milky. If not, repeat the above procedure until contents are mixed. Cartridges contain a small glass bead to assist mixing. Do not shake vigorously as this may cause frothing, which may interfere with the correct measurement of the dose.

The cartridges should be examined frequently and should not be used if clumps of material are present or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance.

The cartridges are not designed to allow any other insulin to be mixed in the cartridge. Cartridges are not designed to be refilled.

Follow the instructions with Humulin M3 KwikPen for attaching the needle and administering the insulin injection.

For Humulin M3 KwikPen, a needle must always be attached before priming, dialing and injecting an insulin dose. Humulin M3 KwikPen should always be primed before each injection. Failure to prime Humulin M3 KwikPen may result in an inaccurate dose.

b) Injecting a dose

Inject the correct dose of insulin, as directed by your doctor or diabetes specialist nurse.
Use of the injection sites should be rotated so that the same is not used more than approximately once a month.

Each pack contains a patient information leaflet with instructions on how to inject insulin.

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
Netherlands

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