

Public Assessment Report

Mutual Recognition Procedure

Humulin M3 Pen suspension for injection in a pre-filled pen 100 IU/ml & Humulin S Pen solution for injection in a pre-filled pen 100 IU/ml

(human insulin rDNA)

UK/H/030/48/E01 & UK/H/030/52/E01

UK licence no: PL 00006/0337 & 0341

Lilly Deutschland GmbH

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 3
Module 2: Summary of Product Characteristics	Page 4
Module 3: Product Information Leaflets	Page 20
Module 4: Labelling	Page 27
Module 5: Scientific Discussion	Page 31
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6 Steps taken after initial procedure	Page 39

Module 1

Product Name	Humulin M3 Pen suspension for injection in a pre-filled pen 100 IU/ml & Humulin S Pen solution for injection in a pre-filled pen 100 IU/ml
Type of Application	Full dossier, Article 8.3(i), known active substance
Active Substance	Human insulin rDNA
Form	Suspension for injection / Solution for injection
Strength	100 IU/ml
MA Holder	Lilly Deutschland GmbH
RMS	UK
CMS	DE
Procedure Number	1 st wave: UK/H/030/048, 0052 2 nd wave: UK/H/030/048, 0052/E/001
Timetable	1 st wave Day 90 – 16th March 1998 2 nd wave Day 90 – 6 th August 2007

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Humulin M3 Pen (Mixture 3) 100 IU/ml suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 IU human insulin (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, adjusted to a pH range of 6.9 to 7.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis. Humulin is also indicated for the initial control of diabetes mellitus and diabetes mellitus in pregnancy.

4.2 Posology and method of administration

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

Humulin M3 should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. These formulations 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.

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.

Instruction for use and handling

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

a) Preparing a dose

Humulin Pen containing Humulin M3 formulation should be rolled in the palms of the hands ten times and inverted 180⁰ ten times immediately before use to resuspend the insulin until it appears uniform 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 Pen for attaching the needle and administering the insulin injection.

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

b) Injecting a dose

Inject the correct dose of insulin, as directed by your doctor or diabetic 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.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to Humulin or to the formulation excipients, 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 special 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.

4.5 Interactions with other medicinal products and other forms of interaction

Some medicinal products are known to interact with glucose metabolism. The physicians should take possible interactions into account and ask patients about their other medications in addition to human insulin.

Insulin requirements may be increased by substances with hyperglycaemic activity, such as glucocorticoids, thyroid hormones, growth hormone, danazol, beta₂-sympathomimetics (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), non-selective beta-blocking agents and alcohol.

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

4.6 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).

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

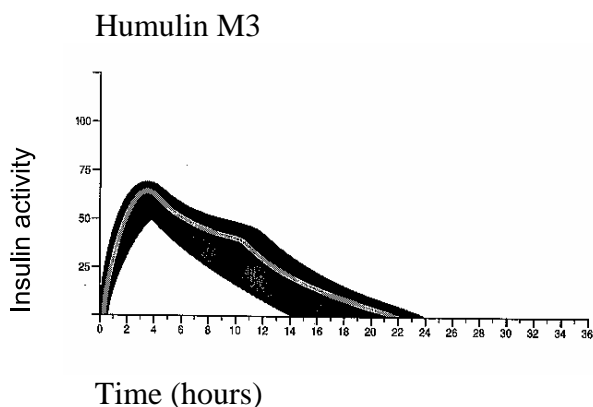
5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Humulin M3: A10A D01.
Humulin M3 is an intermediate acting insulin preparation.

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



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 sulphate
disodium phosphate anhydrous
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

Two years.

Once in use Humulin M3 Pen may be used for up to 28 days. Do not use beyond this period.

When in use Humulin M3 Pen should not be stored above 30 °C.

6.4 Special precautions for storage

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

6.5 Nature and content 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 Pen can be used until empty, then properly discard. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Limited Kingsclere Road, Basingstoke, Hampshire RG21 6XA

8. MARKETING AUTHORISATION NUMBER

PL 0006/ 0341

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE
AUTHORISATION**

19 September 1997 / 24 April 2006

10. DATE OF REVISION OF THE TEXT

28 July 2006

1. NAME OF THE MEDICINAL PRODUCT

Humulin S Pen (Soluble) 100 IU/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One pre-filled pen contains 3 ml equivalent to 300 IU of soluble insulin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A solution for injection in a pre-filled pen.

Humulin S is a sterile, clear, colourless, aqueous solution of human insulin adjusted to a pH range of 7.0 to 7.8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis. Humulin is also indicated for the initial control of diabetes mellitus and diabetes mellitus in pregnancy.

4.2 Posology and method of administration

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

Humulin S should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. It may also 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.

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 I (Isophane) may be administered in combination with Humulin S (Soluble).
(See Section Instructions for use and handling - for Mixing of Insulins).

Instructions for use and handling

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

a) Preparing a dose

Humulin Pen containing Humulin S formulation does not require resuspension and should only be used if it is clear, colourless, with no solid particles visible and if it is of water-like 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 S Pen for attaching the needle and administering the insulin injection.

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

b) Injecting a dose

Inject the correct dose of insulin, as directed by your doctor or diabetic 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.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to Humulin or to the formulation excipients, 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 special 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.

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

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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.

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Some medicinal products are known to interact with glucose metabolism. The physician should take possible interactions into account and ask patients about their other medications in addition to human insulin.

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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), non-selective beta-blocking agents and alcohol.

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4.6 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 reaction 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).

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

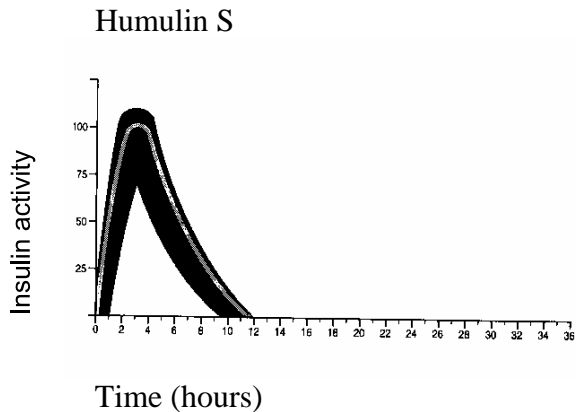
Pharmaco-therapeutic group: Humulin S: A10A B01
Humulin S is a rapidly acting insulin preparation.

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
water for injections.

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

6.3 Incompatibilities

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

6.3 Shelf life

Two years.

Once in use Humulin S Pen may be used for up to 28 days. Do not use beyond this period. When in use Humulin S Pen should not be stored above 30 °C.

6.4 Special precautions for storage

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

6.5 Nature and content of container

3 ml solution 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 S Pen can be used until empty, then properly discard. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 6XA

8. MARKETING AUTHORISATION NUMBER

PL 00006/0337

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

19 September 1997 / 24 April 2006

10. DATE OF REVISION OF THE TEXT

28 July 2006

Humulin M3 Pen Suspension/Humulin S Pen Solution _ for injection
in a pre-filled pen 100IU/ml

UK/H/030/48/E001& UK/H/030/52/E01

Module 3

Product Information Leaflet

PA 9581 FSUKP

What you should know about Humulin M3 Pen (Mixture 3) 100 IU/ml suspension for injection (Human insulin [prb])

Lilly

Please read this leaflet carefully before you start to use your insulin. It does not contain all the information about your insulin that you may need to know, so please ask your doctor, pharmacist or diabetes nurse specialist if you have any questions. This leaflet only applies to Humulin M3 Pen.

What is in your insulin

Your medicine is called Humulin M3 Pen 100IU/ml suspension for injection. It is a brand of human insulin. Its strength is 100 units per millilitre (ml) and each Pen contains 3.0mls (300 units). The Humulin M3 Pen comes in packs of 5.

The insulin is the same as the insulin which comes in separate Humulin cartridges. The pen simply has a built-in cartridge. When the pen is empty you cannot use it again.



Humulin M3 is a sterile suspension of human insulin.

The mixture is 30% soluble and 70% isophane. Humulin M3 contains m-cresol, phenol, protamine sulphate, glycerol, zinc oxide, disodium phosphate anhydrous and water for injections.

Hydrochloric acid or sodium hydroxide (or both) may have been used during manufacture to adjust the acidity.

Use the type of Humulin that your doctor has told you to. Do not change your insulin unless you are told to by your doctor or nurse, and then be very careful. You should not mix Humulin with animal insulins, or with insulins made by a different manufacturer.



Humulin M3

Always check the pack and the pen label for the name and type of the insulin when you get it from your pharmacy. Make sure it is the type of Humulin your doctor has told you to use.

Human insulin is a natural hormone and is made by the pancreas. Humulin is made in the laboratory by a 'recombinant DNA technology' process and has the same structure as the natural hormone. So it is different from animal insulins.

Humulin is made and released onto the market by Lilly France SAS, Rue du Colonel Lilly, 67640 Fegersheim, France. The product authorisations are held by Eli Lilly and Company Limited, Basingstoke, RG21 6XA, England. It is distributed in the Republic of Ireland by Eli Lilly and Company (Ireland) Limited, Hyde House, 65, Adelaide Road, Dublin 2, Ireland.

Why Humulin?

You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Humulin is a substitute for your own insulin.

Before injecting your insulin

Make sure it is safe for you to use Humulin.

- **IF YOU THINK A 'HYPO' (LOW BLOOD SUGAR) IS STARTING, DO NOT INJECT YOUR INSULIN** and do not drive. Your ability to concentrate or react may be reduced if you have hypoglycaemia. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (for example driving a car or operating machinery). You should contact your doctor about the advisability of driving if you have:
 - frequent episodes of hypoglycaemia; or
 - reduced or no warning signs of hypoglycaemia.

The next section 'Using your insulin' tells you how to deal with a mild 'hypo'. If you have ever had an allergic reaction to Humulin (see section D of 'While using your insulin' on this leaflet) tell your doctor, pharmacist or diabetes nurse specialist.

- If you have had diabetes for more than one or two years, you may not experience the warning symptoms (see Section A of 'While using your insulin') when your blood sugar is falling too low. You must think carefully about when to have your meals, how often to exercise and how much to do. You must also keep a close watch on your blood sugar levels by frequently testing your blood glucose.
- A few patients who have had 'hypos' after switching from animal insulin to human insulin have said that the early warning symptoms were less obvious or different. If you have a lot of 'hypos' or have difficulty recognising them, please discuss this with your doctor.
- **If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse specialist.**

- Have you recently become ill?
- Are you taking any other medicines? Your insulin needs may change if you are taking steroids, thyroid hormones, growth hormone, danazol, beta-2 sympathomimetics (for example ritodrine, salbutamol, or terbutaline), diuretics (thiazides), oral hypoglycaemics, aspirin, beta-blockers, oestride, lanreotide, captopril, enalapril, or some antidepressants such as monoamine oxidase inhibitors (MAOIs).
- Do you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands?
- Are you exercising more than usual?
- Are you pregnant or thinking about becoming pregnant or are you breast-feeding? The amount of insulin you need usually falls during the first three months of pregnancy and increases for the other six months. If you are breast-feeding, you may need to change your insulin dose or diet. You should also tell your doctor, pharmacist or diabetes nurse specialist if you are planning to go abroad. The time difference between countries may mean that the timing of your injections and meals will have to be different from when you are at home.

Using your insulin

► Dosage

- Your doctor has told you which insulin to use, how much, when, and how often to inject. This is only for you. Follow your doctor's instructions exactly and visit your diabetes clinic regularly.
- If you change your insulin type (for example from animal to human), you may have to take more or less than before. This might just be the first dose or a gradual change over several weeks.
- Inject Humulin under the skin. You should only inject it into a muscle if your doctor has told you to.

► Preparing your insulin

- Humulin M3 **must be mixed every time you use it**. To do this, roll the pen between your hands about 10 times. Then turn it upside down and then the right way up again about 10 times. Do this slowly to allow the glass mixing bead to travel the length of the insulin cartridge. Do not shake the pen vigorously as bubbles and froth will make it difficult to measure the dose. Check what the insulin looks like. Humulin M3 must look evenly cloudy or milky after you have mixed it up. If it doesn't, mix it up again.
- Do not use the pen if the insulin substance (the white material) stays at the bottom of the insulin cartridge after you have mixed the cartridge. **Do not use the pen if the insulin is lumpy after mixing it, or if solid white pieces stick to the bottom or sides of the cartridge, giving it a frosted look.**

► Getting the pen ready to use

- First wash your hands.
- Please read the instructions on how to use your prefilled insulin pen, which are printed on the back of this leaflet. Please follow the instructions carefully. Here are some reminders.
- Clear the air bubbles from your pen as shown in the pen instructions. There may still be some small air bubbles left in the pen. These are harmless, but if the air bubbles are too large it may affect the insulin dose.

► Injecting the insulin

Thoroughly clean your skin where you are going to make the injection. Inject under the skin, as you were taught. Do not inject directly into a vein. After your injection, leave the needle in the skin for five seconds to make sure you have taken the whole dose. Do not rub the area you have just injected. Make sure you inject at least half an inch (1cm) from your last injection and that you 'rotate' the places you inject, as you have been taught.

► After injecting

As soon as you have done the injection, unscrew the needle from the pen using the outer needle cap. This will keep the insulin sterile and stop it leaking. It also stops air entering the pen and your needle clogging. Do not share your needles. Replace the cap on the pen.

► Further injections

You must mix your insulin every time you use a pen, and you must use a new needle. Before every injection, clear any air bubbles (as we told you above). You can see how much insulin is left by holding the pen with the needle pointing down. The scale on the insulin cartridge shows about how many units you have left.

Do not mix any other insulin in a pen. Once the pen is empty, do not use it again. Please get rid of pens and needles carefully - your clinic will tell you how to do this.

► Emergencies and overdoses: If your blood sugar is low, eat glucose tablets or sugar, followed by fruit or biscuits, and then rest. This will often get you over a mild 'hypo' or minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat moderately severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to be treated in hospital. Ask your doctor to tell you about glucagon.



If 'hypos' or 'hypers' (see A and B) are not treated they can be very serious and cause nausea, vomiting, dehydration, unconsciousness, coma or even death.

- Always keep spare syringes and a spare bottle of Humulin in case you lose your pens or they get damaged.
- Always carry something to show you are diabetic.
- Always carry sugar with you.

While using your insulin

Common problems of diabetes

A. Hypoglycaemia

Hypoglycaemia ('hypo' - low blood sugar) means there is not enough sugar in the blood. This can be caused if:

- you take too much insulin;
- you miss or delay meals or change your diet;
- you exercise or work too hard just before a meal;
- you have an infection or illness (especially diarrhoea or vomiting);
- there is a change in your need for insulin;
- you have trouble with your adrenal, pituitary or thyroid glands, or kidney or liver trouble gets worse.

Alcohol and some medicines can affect your blood sugar levels.

First symptoms of low blood sugar usually come on quickly and include:

- tiredness;
- nervousness or shakiness;
- headache;
- rapid heartbeat;
- nausea;
- cold sweat.

B. Hyperglycaemia and diabetic ketoacidosis

Hyperglycaemia ('hyper' - too much sugar in the blood) means that your body does not have enough insulin. Hyperglycaemia can be brought about by:

- not taking your insulin;
- taking less insulin than your doctor tells you to;
- eating a lot more than your diet allows;
- fever, infection or emotional stress.

Hyperglycaemia can lead to diabetic ketoacidosis. The first symptoms come on slowly over many hours or days. They are:

- sleepy feeling;
- flushed face;
- thirst;
- no appetite;
- fruity smell on the breath;
- feeling or being sick.

Severe symptoms are heavy breathing and a rapid pulse.

Get medical help immediately.

C. Illness

If you are ill, especially feeling or being sick, your insulin needs may change. Even when you are not eating normally, you still need insulin. Test your urine or blood, follow your 'sick rules' and tell your doctor.

D. Allergy to insulin

Local allergy (affects less than 1 person in 10): Some people get redness, swelling or itching around the area where they injected themselves. This usually clears up in anything from a few days to a few weeks. If this happens to you, tell your doctor.

Systemic allergy (affects less than 1 person in 10,000): This allergy to insulin is not common. The symptoms are:

- rash over the whole body;
- difficulty in breathing;
- wheezing;
- blood pressure dropping;
- heart beating fast;
- sweating.

If you think you are having this sort of insulin allergy, tell your doctor at once.

E. Lipodystrophy (affects less than 1 person in 100)

If you notice your skin thickening or pitting where you inject yourself, tell your doctor.

If you have these or any other side effects, tell your doctor.

How to store your pen

Keep the pen cap on the pen when you are not using it. Keep the pen away from very hot or very cold temperatures and direct sunlight. Do not freeze the pen. Before use, the pens should be kept in their carton, in a fridge between 2°C and 8°C in order to protect them from light. Once in use, you can use your pen for up to 28 days if it is not stored above 30°C. Keep your medicine where children cannot see or reach it. Do not use after the expiry date which is stated on the carton and label after 'EXP'.

REMEMBER: This medicine is for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

Date of leaflet preparation : September 2006.

'Humulin' is a registered trademark of Eli Lilly and Company (USA)

If you would like a large-print version of this leaflet, please phone 01256 315999 (UK) or 01 6614377 (Ireland).

Instructions for Use

Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.

Every time you inject:

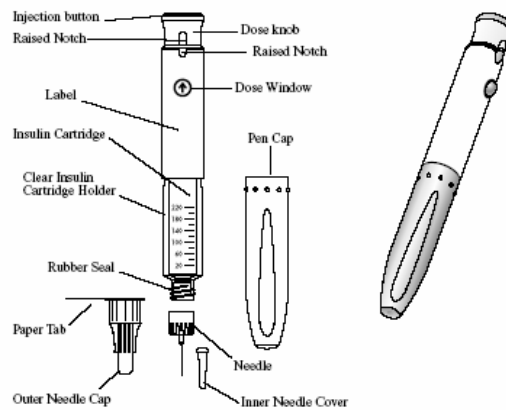
- Use a new needle
- Prime to make sure the pen is ready to dose
- Make sure you got a full dose

Also, read the Patient Information Leaflet printed on the back of this manual.

Pen Features

- A multiple dose, disposable prefilled pen containing 300 units of U-100 insulin
- Delivers up to 60 units per dose in single unit increments
- Easy to use; compact size

Pen Parts

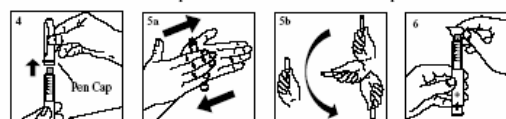


Important Notes

- Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.
- Use a new needle for each injection.
 - Be sure a needle is completely attached to the pen before priming, setting (dialling) the dose and injecting your insulin.
- Prime every time.
 - The pen must be primed before each injection to make sure the pen is ready to dose. Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridges during normal use. See Section "III. Priming the Pen".
 - If you do not prime, you may get too much or too little insulin.
- Make sure you get a full dose.
 - To make sure you get a full dose, you must push the injection button all the way down until you see a diamond (◆) or an arrow (➔) in the centre of the dose window. See Section "VI. Following an Injection".
- The numbers on the clear insulin cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your pen.
- Keep your pen out of the reach and sight of children.
- Pens not being used should be stored in a refrigerator but not in a freezer. Refer to the Patient Information Leaflet for complete storage instructions.
- Do not store your pen with the pen needle attached. Doing so may allow insulin to leak from the pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra pen in case yours is lost or damaged.
- Dispose of empty pens as instructed by your Health Care Professional and without the needle attached.
- This pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- The directions regarding needle handling are not intended to replace local, Health Care Professional or institutional policies.
- Any changes in insulin should be made cautiously and only under medical supervision.

I. Preparing the Pen

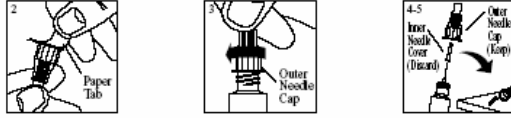
1. Before proceeding, refer to the Patient Information Leaflet for instructions on checking the appearance of your insulin.
2. Check the label on the pen to be sure the pen contains the type of insulin that has been prescribed for you.
3. Always wash your hands before preparing your pen for use.
4. Pull the pen cap to remove.
5. If your insulin is a suspension (cloudy):
 - a. Roll the pen back and forth 10 times then perform step b.
 - b. Gently turn the pen up and down 10 times until the insulin is evenly mixed.
6. Use an alcohol swab to wipe the rubber seal on the end of the pen.



II. Attaching the Needle

This device is suitable for use with Becton Dickinson and Company's insulin pen needles.

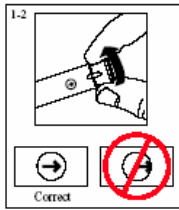
1. Always use a new needle for each injection. Do not push injection button without a needle attached. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
2. Remove the paper tab from the capped needle.
3. Attach the capped needle onto the end of the pen by turning it clockwise until tight.
4. Hold the pen with the needle pointing up and remove the outer needle cap. Keep it to use during needle removal.
5. Remove the inner needle cover and discard.



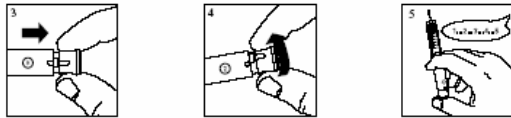
III. Priming the Pen

- The pen must be primed before each injection to make sure the pen is ready to dose. Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.
- If you do not prime, you may get too much or too little insulin.
- Always use a new needle for each injection.

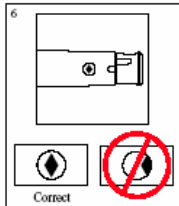
1. Make sure the arrow is in the centre of the dose window as shown.
2. If you do not see the arrow in the centre of the dose window, push in the injection button fully and turn the dose knob until the arrow is seen in the centre of the window.



3. With the arrow in the centre of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window.
4. Turn the dose knob clockwise until the number "2" is seen in the dose window.
5. Hold your pen with the needle pointing up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top. Using your thumb, if possible, push in the injection button completely. Keep pressing and continue to hold the injection button firmly while counting slowly to 5. You should see either a drop or a stream of insulin come out of the tip of the needle. If insulin does not come out of the tip of the needle, repeat steps 1 through 5. If after several attempts insulin does not come out of the tip of the needle, change the needle and repeat the priming steps.



6. At the completion of the priming step, a diamond (♦) must be seen in the centre of the dose window. If a diamond (♦) is not seen in the centre of the dose window, continue pushing on the injection button until you see a diamond (♦) in the centre of the dose window. Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the pen, this small air bubble will not affect your insulin dose.

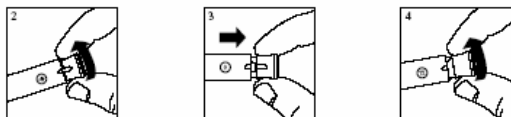


7. Now you are ready to set your dose. See next section.

IV. Setting a Dose

- Always use a new needle for each injection. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
- Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in getting too much or too little insulin. If you accidentally push the injection button while setting your dose, you must prime the pen again before injecting your dose. See Section "III. Priming the Pen".

1. A diamond (♦) must be seen in the centre of the dose window before setting your dose. If you do not see a diamond (♦) in the centre of the dose window, the pen has not been primed correctly and you are not ready to set your dose. Before continuing, repeat the priming steps.
2. Turn the dose knob clockwise until the arrow (➡) is seen in the centre of the dose window and the notches on the pen and dose knob are in line.
3. With the arrow (➡) in the centre of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window. A dose cannot be dialled until the dose knob is pulled out.
4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialled is too high, simply turn the dose knob backward (anticlockwise) until the correct dose is seen in the dose window.



5. If you cannot dial a full dose, see the "Questions and Answers" section, Question 5, at the end of this manual.

V. Injecting a Dose

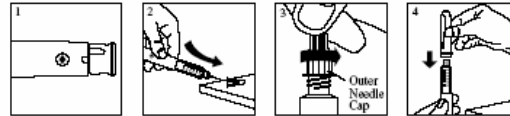
- Always use a new needle for each injection. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
- Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in getting too much or too little insulin.
- The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the "Questions and Answers" section, Question 7, at the end of this manual.
- Do not inject a dose unless the pen is primed, just before injection, or you may get too much or too little insulin.
- If you have set (dialled) a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the "Questions and Answers" section, Questions 1 and 2.

1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.
2. Insert the needle under your skin as instructed. Inject the insulin by using your thumb, if possible, to push in the injection button completely.
3. Keep pressing and continue to hold the injection button firmly while counting slowly to 5.
4. When the injection is done, a diamond (♦) or arrow (➡) must be seen in the centre of the dose window. This means your full dose has been delivered. If you do not see the diamond or arrow in the centre of the window, you did not get a full dose. Contact your Health Care Professional for additional instruction.



VI. Following an Injection

1. Make sure you got a full dose by checking that the injection button has been completely pushed in and you can see a diamond (♦) or arrow (➡) in the centre of the dose window. If you do not see the diamond (♦) or arrow (➡) in the centre of the dose window, you have not received a full dose. Contact your Health Care Professional for additional instructions.
2. Carefully replace the outer needle cap as instructed by your Health Care Professional.
3. Remove the capped needle by turning it anticlockwise and place the used needle in a puncture-resistant disposable container and properly throw it away as directed by your Health Care Professional.
4. Replace the cap on the pen.



5. The pen that you are currently using should be kept at a temperature below 30°C and away from heat and light. It should be discarded according to the time specified in the Patient Information Leaflet, even if it still contains insulin.

Do not store or dispose of the pen with a needle attached. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.

Questions and Answers

PROBLEM	ACTION
1. Dose dialled and injection button pushed in without a needle attached.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (➡) is seen in the centre of the dose window. 3) Prime the pen.
2. Insulin does not come out of the needle.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (➡) is seen in the centre of the dose window. 3) Prime the pen. See Section "III. Priming the Pen".
3. Wrong dose (too high or too low) dialled.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
4. Not sure how much insulin remains in the cartridge	Hold the pen with the needle end pointing down. The scale (20 units between marks) on the clear insulin cartridge holder shows an estimate of the number of units remaining. These numbers should not be used for measuring an insulin dose.
5. Full dose cannot be dialled.	The pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the pen you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the pen you may either: 1) Give the partial dose and then give the remaining dose using a new pen, or 2) Give the full dose with a new pen.
6. A small amount of insulin remains in the cartridge but a dose cannot be dialled.	The pen design prevents the cartridge from being completely emptied. The pen has delivered 300 units of usable insulin.
7. Cannot completely push in the injection button when priming the pen or injecting a dose.	1) Needle is not attached or is clogged. a. Attach a new needle. b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (➡) is seen in the centre of the dose window. c. Prime the pen. 2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

PA MAQ019 UKP

What you should know about Humulin S Pen (Soluble) 100 IU/ml solution for injection (Human insulin [prb])

Lilly

Please read this leaflet carefully before you start to use your insulin. It does not contain all the information about your insulin that you may need to know, so please ask your doctor, pharmacist or diabetes nurse specialist if you have any questions. This leaflet only applies to Humulin S Pen.

What is in your insulin

Your medicine is called Humulin S Pen 100IU/ml solution for injection. It is a brand of human insulin. Its strength is 100 units per millilitre (ml) and each Pen contains 3.0mls (300 units). The Humulin S Pen comes in packs of 5.

The insulin is the same as the insulin which comes in separate Humulin cartridges. The pen simply has a built-in cartridge. When the pen is empty you cannot use it again.



Humulin S (Soluble) is a sterile, clear, colourless liquid of human insulin dissolved in water - with a pH of between 7.0 and 7.8. Humulin S contains m-cresol as a preservative, glycerol and water for injections.

Hydrochloric acid or sodium hydroxide (or both) may have been used during manufacture to adjust the acidity.

Use the type of Humulin that your doctor has told you to. Do not change your insulin unless you are told to by your doctor or nurse, and then be very careful. You should not mix Humulin with animal insulins, or with insulins made by a different manufacturer.



Humulin S

Always check the pack and the pen label for the name and type of the insulin when you get it from your pharmacy. Make sure it is the type of Humulin your doctor has told you to use.

Human insulin is a natural hormone and is made by the pancreas. Humulin is made in the laboratory by a 'recombinant DNA technology' process and has the same structure as the natural hormone. So it is different from animal insulins.

Humulin is made and released onto the market by Lilly France SAS, Rue du Colonel Lilly, 67640 Fegersheim, France. The product authorisations are held by Eli Lilly and Company Limited, Basingstoke, RG21 6XA, England. It is distributed in the Republic of Ireland by Eli Lilly and Company (Ireland) Limited, Hyde House, 65 Adelaide Road, Dublin 2, Ireland.

Why Humulin?

You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Humulin is a substitute for your own insulin.

Before injecting your insulin

Make sure it is safe for you to use Humulin.

- **IF YOU THINK A 'HYPO' (LOW BLOOD SUGAR) IS STARTING, DO NOT INJECT YOUR INSULIN** and do not drive. Your ability to concentrate or react may be reduced if you have hypoglycaemia. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (for example driving a car or operating machinery). You should contact your doctor about the advisability of driving if you have:
 - frequent episodes of hypoglycaemia; or
 - reduced or no warning signs of hypoglycaemia.

The next section 'Using your insulin' tells you how to deal with a mild 'hypo'. If you have ever had an allergic reaction to Humulin (see section D of 'While using your insulin' on this leaflet) tell your doctor, pharmacist or diabetes nurse specialist.

- If you have had diabetes for more than one or two years, you may not experience the warning symptoms (see Section A of 'While using your insulin') when your blood sugar is falling too low. You must think carefully about when to have your meals, how often to exercise and how much to do. You must also keep a close watch on your blood sugar levels by frequently testing your blood glucose.
- A few patients who have had 'hypos' after switching from animal insulin to human insulin have said that the early warning symptoms were less obvious or different. If you have a lot of 'hypos' or have difficulty recognising them, please discuss this with your doctor.
- **If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse specialist.**

- Have you recently become ill?
- Are you taking any other medicines? Your insulin needs may change if you are taking steroids, thyroid hormones, growth hormone, danazol, beta-2 sympathomimetics (for example ritodrine, salbutamol, or terbutaline), diuretics (thiazides), oral hypoglycaemics, aspirin, beta-blockers, ocreotide, lanreotide, captopril, enalapril, or some antidepressants such as monoamine oxidase inhibitors (MAOIs).
- Do you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands?
- Are you exercising more than usual?
- Are you pregnant or thinking about becoming pregnant or are you breast-feeding? The amount of insulin you need usually falls during the first three months of pregnancy and increases for the other six months. If you are breast-feeding, you may need to change your insulin dose or diet. You should also tell your doctor, pharmacist or diabetes nurse specialist if you are planning to go abroad. The time difference between countries may mean that the timing of your injections and meals will have to be different from when you are at home.

Using your insulin

► Dosage

- Your doctor has told you which insulin to use, how much, when, and how often to inject. This is only for you. Follow your doctor's instructions exactly and visit your diabetes clinic regularly.
- If you change your insulin type (for example from animal to human), you may have to take more or less than before. This might just be the first dose or a gradual change over several weeks.
- Inject Humulin under the skin. You should only inject it into a muscle if your doctor has told you to.

► Preparing your insulin

- Humulin S is dissolved in water, so it does not need to be mixed. But you must use it **only** if it looks like water. It must be clear, have no colour and no solid pieces in it.

► Getting the pen ready to use

- First wash your hands.
- Please read the instructions on how to use your prefilled insulin pen, which are printed on the back of this leaflet. Please follow the instructions carefully. Here are some reminders.
- Clear the air bubbles from your pen as shown in the pen instructions. There may still be some small air bubbles left in the pen. These are harmless, but if the air bubbles are too large it may affect the insulin dose.

► Injecting the insulin

Thoroughly clean your skin where you are going to make the injection. Inject under the skin, as you were taught. Do not inject directly into a vein. After your injection, leave the needle in the skin for five seconds to make sure you have taken the whole dose. Do not rub the area you have just injected. Make sure you inject at least half an inch (1cm) from your last injection and that you 'rotate' the places you inject, as you have been taught.

► After injecting

As soon as you have done the injection, unscrew the needle from the pen using the outer needle cap. This will keep the insulin sterile and stop it leaking. It also stops air entering the pen and your needle clogging. Do not share your needles. Replace the cap on the pen.

► Further injections

You must mix your insulin every time you use a pen, and you must use a new needle. Before every injection, clear any air bubbles (as we told you above). You can see how much insulin is left by holding the pen with the needle pointing down. The scale on the insulin cartridge shows about how many units you have left.

Do not mix any other insulin in a pen. Once the pen is empty, do not use it again. Please get rid of pens and needles carefully - your clinic will tell you how to do this.

► Emergencies and overdoses: If your blood sugar is low, eat glucose tablets or sugar, followed by fruit or biscuits, and then rest. This will often get you over a mild 'hypo' or minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat moderately severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to be treated in hospital. Ask your doctor to tell you about glucagon.



If 'hypos' or 'hypers' (see A and B) are not treated they can be very serious and cause nausea, vomiting, dehydration, unconsciousness, coma or even death.

- Always keep spare syringes and a spare bottle of Humulin in case you lose your pens or they get damaged.
- Always carry something to show you are diabetic.
- Always carry sugar with you.

While using your insulin

Common problems of diabetes

A. Hypoglycaemia

Hypoglycaemia ('hypo' - low blood sugar) means there is not enough sugar in the blood. This can be caused if:

- you take too much insulin;
- you miss or delay meals or change your diet;
- you exercise or work too hard just before a meal;
- you have an infection or illness (especially diarrhoea or vomiting);
- there is a change in your need for insulin;
- you have trouble with your adrenal, pituitary or thyroid glands, or kidney or liver trouble gets worse.

Alcohol and some medicines can affect your blood sugar levels.

First symptoms of low blood sugar usually come on quickly and include:

- tiredness;
- nervousness or shakiness;
- headache;
- rapid heartbeat;
- nausea;
- cold sweat.

B. Hyperglycaemia and diabetic ketoacidosis

Hyperglycaemia ('hyper' - too much sugar in the blood) means that your body does not have enough insulin. Hyperglycaemia can be brought about by:

- not taking your insulin;
- taking less insulin than your doctor tells you to;
- eating a lot more than your diet allows;
- fever, infection or emotional stress.

Hyperglycaemia can lead to diabetic ketoacidosis. The first symptoms come on slowly over many hours or days. They are:

- sleepy feeling;
- flushed face;
- thirst;
- no appetite;
- fruity smell on the breath;
- feeling or being sick.

Severe symptoms are heavy breathing and a rapid pulse.

Get medical help immediately.

C. Illness

If you are ill, especially feeling or being sick, your insulin needs may change. **Even when you are not eating normally, you still need insulin.** Test your urine or blood, follow your 'sick rules' and tell your doctor.

D. Allergy to insulin

Local allergy (affects less than 1 person in 10): Some people get redness, swelling or itching around the area where they injected themselves. This usually clears up in anything from a few days to a few weeks. If this happens to you, tell your doctor.

Systemic allergy (affects less than 1 person in 10,000): This allergy to insulin is not common. The symptoms are:

- rash over the whole body;
- difficulty in breathing;
- wheezing;
- blood pressure dropping;
- heart beating fast;
- sweating.

If you think you are having this sort of insulin allergy, **tell your doctor at once.**

E. Lipodystrophy (affects less than 1 person in 100)

If you notice your skin thickening or pitting where you inject yourself, tell your doctor.

If you have these or any other side effects, tell your doctor.

How to store your pen

Keep the pen cap on the pen when you are not using it. Keep the pen away from very hot or very cold temperatures and direct sunlight. Do not freeze the pen. Before use, the pens should be kept in their carton, in a fridge between 2°C and 8°C in order to protect them from light. Once in use, you can use your pen for up to 28 days if it is not stored above 30°C. Keep your medicine where children cannot see or reach it. Do not use after the expiry date which is stated on the carton and label after 'EXP'.

REMEMBER: This medicine is for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

Date of leaflet preparation : September 2006.

'Humulin' is a registered trademark of Eli Lilly and Company (USA)

If you would like a large-print version of this leaflet, please phone 01256 315999 (UK) or 01 6614377 (Ireland).

Instructions for Use

Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.

Every time you inject:

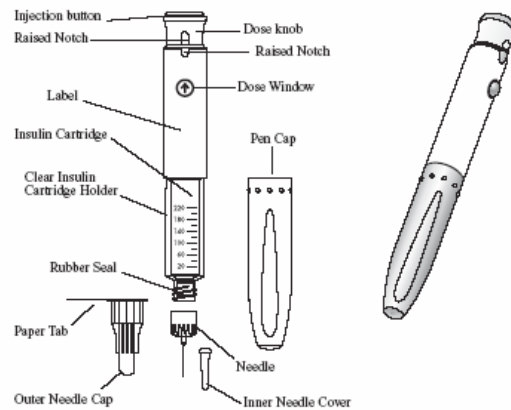
- Use a new needle
- Prime to make sure the pen is ready to dose
- Make sure you get a full dose

Also, read the Patient Information Leaflet printed on the back of this manual.

Pen Features

- A multiple dose, disposable prefilled pen containing 300 units of U-100 insulin
- Delivers up to 60 units per dose in single unit increments
- Easy to use; compact size

Pen Parts

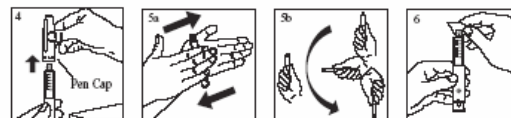


Important Notes

- Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.
- Use a new needle for each injection.
 - Be sure a needle is completely attached to the pen before priming, setting (dialling) the dose and injecting your insulin.
- Prime every time.
 - The pen must be primed before each injection to make sure the pen is ready to dose. Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use. See Section "III. Priming the Pen".
 - If you do not prime, you may get too much or too little insulin.
- Make sure you get a full dose.
 - To make sure you get a full dose, you must push the injection button all the way down until you see a diamond (♦) or an arrow (➔) in the centre of the dose window. See Section "VI. Following an Injection".
- The numbers on the clear insulin cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your pen.
- Keep your pen out of the reach and sight of children.
- Pens not being used should be stored in a refrigerator but not in a freezer. Refer to the Patient Information Leaflet for complete storage instructions.
- Do not store your pen with the pen needle attached. Doing so may allow insulin to leak from the pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra pen in case yours is lost or damaged.
- Dispose of empty pens as instructed by your Health Care Professional and without the needle attached.
- This pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- The directions regarding needle handling are not intended to replace local, Health Care Professional or institutional policies.
- Any changes in insulin should be made cautiously and only under medical supervision.

I. Preparing the Pen

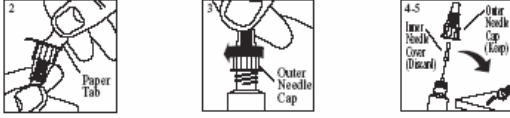
1. Before proceeding, refer to the Patient Information Leaflet for instructions on checking the appearance of your insulin.
 2. Check the label on the pen to be sure the pen contains the type of insulin that has been prescribed for you.
 3. Always wash your hands before preparing your pen for use.
 4. Pull the pen cap to remove.
 5. If your insulin is a suspension (cloudy):
 - a. Roll the pen back and forth 10 times then perform step b.
 - b. Gently turn the pen up and down 10 times until the insulin is evenly mixed.
- Note: Suspension (cloudy) insulin cartridges contain a small bead to assist in mixing.
6. Use an alcohol swab to wipe the rubber seal on the end of the pen.



II. Attaching the Needle

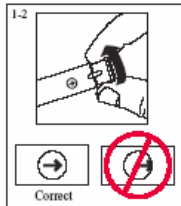
This device is suitable for use with Becton Dickinson and Company's insulin pen needles.

1. Always use a new needle for each injection. Do not push injection button without a needle attached. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
2. Remove the paper tab from the capped needle.
3. Attach the capped needle onto the end of the pen by turning it clockwise until tight.
4. Hold the pen with the needle pointing up and remove the outer needle cap. Keep it to use during needle removal.
5. Remove the inner needle cover and discard.

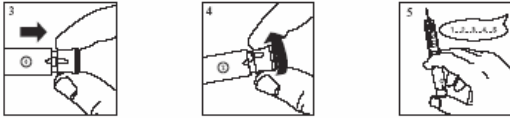


III. Priming the Pen

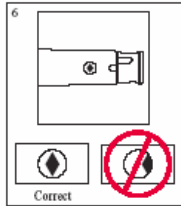
- The pen must be primed before each injection to make sure the pen is ready to dose. Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.
 - If you do not prime, you may get too much or too little insulin.
 - Always use a new needle for each injection.
1. Make sure the arrow is in the centre of the dose window as shown.
 2. If you do not see the arrow in the centre of the dose window, push in the injection button fully and turn the dose knob until the arrow is seen in the centre of the window.



3. With the arrow in the centre of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window.
4. Turn the dose knob clockwise until the number "2" is seen in the dose window.
5. Hold your pen with the needle pointing up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top. Using your thumb, if possible, push in the injection button completely. Keep pressing and continue to hold the injection button firmly while counting slowly to 5. You should see either a drop or a stream of insulin come out of the tip of the needle. If insulin does not come out of the tip of the needle, repeat steps 1 through 5. If after several attempts insulin does not come out of the tip of the needle, change the needle and repeat the priming steps.



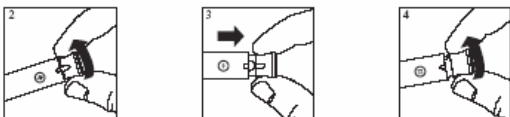
6. At the completion of the priming step, a diamond (♦) must be seen in the centre of the dose window. If a diamond (♦) is not seen in the centre of the dose window, continue pushing on the injection button until you see a diamond (♦) in the centre of the dose window. Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the pen, this small air bubble will not affect your insulin dose.



7. Now you are ready to set your dose. See next section.

IV. Setting a Dose

- Always use a new needle for each injection. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
 - Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in getting too much or too little insulin. If you accidentally push the injection button while setting your dose, you must prime the pen again before injecting your dose. See Section "III. Priming the Pen".
1. A diamond (♦) must be seen in the centre of the dose window before setting your dose. If you do not see a diamond (♦) in the centre of the dose window, the pen has not been primed correctly and you are not ready to set your dose. Before continuing, repeat the priming steps.
 2. Turn the dose knob clockwise until the arrow (→) is seen in the centre of the dose window and the notches on the pen and dose knob are in line.
 3. With the arrow (→) in the centre of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window. A dose cannot be dialled until the dose knob is pulled out.
 4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialled is too high, simply turn the dose knob backward (anticlockwise) until the correct dose is seen in the dose window.



5. If you cannot dial a full dose, see the "Questions and Answers" section, Question 5, at the end of this manual.

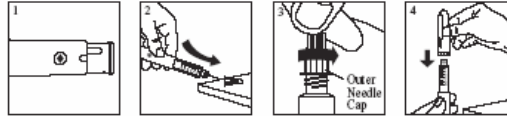
V. Injecting a Dose

- Always use a new needle for each injection. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.
 - Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in getting too much or too little insulin.
 - The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the "Questions and Answers" section, Question 7, at the end of this manual.
 - Do not inject a dose unless the pen is primed, just before injection, or you may get too much or too little insulin.
 - If you have set (dialled) a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the "Questions and Answers" section, Questions 1 and 2.
1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.
 2. Insert the needle under your skin as instructed. Inject the insulin by using your thumb, if possible, to push in the injection button completely.
 3. Keep pressing and continue to hold the injection button firmly while counting slowly to 5.
 4. When the injection is done, a diamond (♦) or arrow (→) must be seen in the centre of the dose window. This means your full dose has been delivered. If you do not see the diamond (♦) or arrow (→) in the centre of the window, you did not get a full dose. Contact your Health Care Professional for additional instruction.



VI. Following an Injection

1. Make sure you got a full dose by checking that the injection button has been completely pushed in and you can see a diamond (♦) or arrow (→) in the centre of the dose window. If you do not see the diamond (♦) or arrow (→) in the centre of the dose window, you have not received a full dose. Contact your Health Care Professional for additional instructions.
2. Carefully replace the outer needle cap as instructed by your Health Care Professional.
3. Remove the capped needle by turning it anticlockwise. Place the used needle in a puncture-resistant disposable container and properly throw it away as directed by your Health Care Professional.
4. Replace the cap on the pen.



5. The pen that you are currently using should be kept at a temperature below 30°C and away from heat and light. It should be discarded according to the time specified in the Patient Information Leaflet, even if it still contains insulin.

Do not store or dispose of the pen with a needle attached. Storing the pen with the needle attached may allow insulin to leak from the pen and air bubbles to form in the cartridge.

Questions and Answers

PROBLEM	ACTION
1. Dose dialled and injection button pushed in without a needle attached.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the centre of the dose window. 3) Prime the pen.
2. Insulin does not come out of the needle.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the centre of the dose window. 3) Prime the pen. See Section "III. Priming the Pen".
3. Wrong dose (too high or too low) dialled.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
4. Not sure how much insulin remains in the cartridge	Hold the pen with the needle end pointing down. The scale (20 units between marks) on the clear insulin cartridge holder shows an estimate of the number of units remaining. These numbers should not be used for measuring an insulin dose.
5. Full dose cannot be dialled.	The pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the pen you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the pen you may either: 1) Give the partial dose and then give the remaining dose using a new pen, or 2) Give the full dose with a new pen.
6. A small amount of insulin remains in the cartridge but a dose cannot be dialled.	The pen design prevents the cartridge from being completely emptied. The pen has delivered 300 units of usable insulin.
7. Cannot completely push in the injection button when priming the pen or injecting a dose.	1) Needle is not attached or is clogged. a. Attach a new needle. b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the centre of the dose window. c. Prime the pen. 2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

Module 4 Labelling

Lot:

EXP:

3 ml **HP 8770**

Humulin[®] M3 Pen 100 IU/ml

*Suspension for Injection
Human Insulin*

**30% Soluble Insulin
70% Isophane Insulin**

For SC (or IM) injection only

PL 0006/0341 POM PA 47/92/1 

Lilly

YL1111FSUKX



Lot:

EXP:

3 ml **HP 8720**



Humulin[®] S Pen 100 IU/ml

*Solution for Injection
Human Insulin*

Soluble Insulin

For SC (or IM or IV) injection only

PL 0006/0337 POM PA 47/89/1



Lilly

Y L M A Q 0 1 4 U K X



Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Humulin M3 Pen suspension for injection and Humulin S Pen solution for injection, 100IU/ml for the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis, could be approved. Humulin is also indicated for the initial control of diabetes mellitus and diabetes mellitus in pregnancy. A national marketing authorisation was granted on 19th September 1997.

The mutual recognition applications concerned Humulin M3 Pen suspension for injection and Humulin S Pen solution for injection, 100IU/ml which were granted marketing authorisations in the UK on 19th September 1997.

The Marketing Authorisation Holder Lilly Deutschland GmbH applied for marketing authorisations in several CMS's via two mutual recognition procedures as outlined below.

A first use mutual recognition procedure determined on 16th March 1998 led to the grant of marketing authorisation in: Austria, Belgium, Denmark, Germany, Greece, France, Ireland, Italy, Luxembourg, Netherlands, Portugal and Sweden.

A repeat use (2nd wave) mutual recognition procedure determined on 6th August 2007 led to the renewal of marketing authorisation in: Germany.

Overall Benefit/Risk Assessment

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted a satisfactory inspection summary report issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

No new toxicologically meaningful data have been produced that may affect the conclusions of the original expert opinion on toxicology and pharmacology. The comprehensive set of clinical data available on Humlin products provides adequate information to ensure the safe use of the compound. Additional animal data would not add substantial scientifically relevant information to the safety profile.

The well-established efficacy of Humulin and Humulin products has been described in previous Humulin application procedures and periodic safety updates. There have been no new or ongoing clinical trials involving clinical efficacy as an endpoint or safety concern.

2. PHARMACEUTICAL ASSESSMENT

INTRODUCTION

The above abridged applications were approved in the UK in September 1997. The applications are essentially for the introduction of a new disposable pen (in the original report the name is HumaPen, but the pre-filled pen is currently called The Pen) to the Humulin product range. The 3ml insulin cartridges to be included in the HumaPen pen injector device are the same insulin cartridges that have already been authorised to be used with the reusable pens and the non-reusable HumaJect pen device. The HumaPen pen device has already been considered by the CPMP in connection with the 3.0ml Humalog cartridges and received a positive opinion in February 1997.

Humulin contains human insulin, produced by recombinant DNA technology, which has been approved through the former Concertation procedure. Humulin products are currently available in 10ml vials and 3.0ml cartridges and pre-filled pens.

CRITICAL EVALUATION OF PART II DATA

The HumaPen pen injector consists of two main components – the injector mechanism and a non-replaceable 3.0ml Humulin cartridge. The unlabelled cartridge is permanently sealed inside the pen's clear protective housing. A non-removable label is then placed around the body of the device.

Insulin Cartridges

The 3.0ml insulin cartridges proposed to be included in the HumaPen device are authorised in most Member States. The same Humulin range of products, in 10ml vials or 3ml cartridges, appear to have been authorised in all member states.

Composition

Adequate information is provided on the formulation of the products. A summary of the composition of the biosynthetic human insulin, 3.0ml cartridge, regular insulin, 100 IU/ml is provided in the following table.

Ingredients	Reference to Standards
Humulin Insulin (recombinant DNA origin)	Ph.Eur
Metacresol Distilled	Ph.Eur
Glycerin	Ph.Eur
Water for Injections q.s.	Ph.Eur
Hydrochloric Acid Solution 10%	Refer to footnote ¹
Sodium Hydroxide Solution 10%	Refer to footnote ¹

Please note that the plunger heads and the glass cartridges are siliconised.

¹ Hydrochloric Acid, solution 10% and sodium hydroxide solution 10% are manufactured from Ph. Eur. quality water for injections and reagents.

Control of Starting Materials

The active ingredient used in the 3.0ml cartridges is the same as that used in the other Humulin products authorised by all member states. The applicant notes that the active

ingredient, human insulin, complies with the Ph.Eur monograph requirements if so tested. A copy of the active ingredient specification is provided and is considered satisfactory. The specifications provided for the control of silicone emulsion and m-cresol are considered satisfactory. All excipients are of Ph. Eur. standards.

The cartridges employed for the primary packaging of the products are of Ph.Eur Type I flint glass. Each cartridge is sealed with rubber closures, which consist of a plunger head at the bottom and a disc seal at the top of the cartridge. The applicant notes that the closures are tested as per elastomeric closures for injection described in the Ph. Eur. For the actual pen device, please refer to the section below.

Manufacture of the Finished Product Dosage Forms

The manufacturing process is unremarkable and adequately described in the dossier. Adequate information is provided on the facilities and equipment. The in-process controls performed are considered adequate.

Finished Product Specifications

The specifications for the 3.0ml cartridges are considered satisfactory and are in line with the currently authorised Humulin products. In addition, the HumaPen will meet the test requirements for visual inspection, function test and dose accuracy.

Stability

The applicant refers to previously submitted data for the stability evaluation of the active substance. This is considered acceptable since the active substance used in the HumaPen presentations is identical to that used in the currently authorised Humulin range of products.

Stability data are provided for the range of Humulin products in 3ml cartridges. The cartridges have been stored at 5°C for up to 30 or 36 months, at 40 °C for up to 3 months and some batches have also been stored at 30 °C for 3 months. The proposed shelf life of 24 months is considered justified by the data submitted.

Protocols are also submitted for the stability evaluation of routine batches of the products. The applicant notes that routine lots will be placed on stability at the rate of at least one per year. The proposed protocol is considered acceptable.

HumaPen Device

The HumaPen is a disposable pen-injector device designed specifically for use with Eli Lilly 3.0ml cartridges. It is noted that attempts to separate the cartridge from the pen will result in the destruction of the injector mechanism. The components of the pen device and its operating mechanisms are adequately described. Detailed diagrammatic representations of the different components are included in the dossier.

Results from accuracy and functional assessments show HumaPen to be robust, repeatable and consistent across a range of environmental and mechanical challenges.

HumaPen Assembly

The assembly process is described in adequate details. The applicant notes that the presence and orientation of the critical parts is checked throughout the automated assembly manufacturing process for HumaPen. As each HumaPen assembly step is accompanied by 100% inspection, the assembly process is considered validated for each HumaPen produced.

SPC, Labels and Leaflets

The SPC and leaflets are considered satisfactory.

STATEMENT ON GOOD MANUFACTURING PRACTICE

The human insulin cartridges are manufactured at:

Lilly France S.A.S.
Rue du Colonel Lilly
67640 Fegersheim
France

Lilly France S.A.S. is also the site used for the assembly of the HumaPens.

The products are labelled, packaged and released at

Lilly France S.A.S.
Rue du Colonel Lilly
67640 Fegersheim
France

or

Eli Lilly Italia S.p.A
Via A. Gramsci 731-733
50019 Sesto Fiorentino
Italy

In-process control testing and final drug product control testing is conducted at:

Lilly France S.A.S.
Rue du Colonel Lilly
67640 Fegersheim
France

or

Eli Lilly Italia S.p.A

Humulin M3 Pen Suspension/Humulin S Pen Solution _ for injection
in a pre-filled pen 100IU/ml

UK/H/030/48/E001& UK/H/030/52/E01

Via A. Gramsci 731-733
50019 Sesto Fiorentino
Italy

Copies of the manufacturing authorisations and certificate of GMP issued by the respective competent authorities have been submitted in the dossier. The site mentioned above is considered appropriate and acceptable for the proposed functions.

3. NON CLINICAL ASSESSMENT

No preclinical assessment was carried out for this product, nor was it necessary as the active ingredient is already approved in the CMS in different humulin presentations.

4. CLINICAL ASSESSMENT

No clinical assessment was carried out for this product, nor was it necessary as the active ingredient is already approved in the CMS in different humulin presentations.

Module 6

Steps taken after the initial procedure:-

Scope	Procedure Number	Type of modification	Approval/ non approval	Assessment report attached (Y/N)
To register a change to the 'lens mask' around the lens on the body A of the pen-injector. The printed 'lens mask' around the lens is replaced with a 'textured area' around the lens.	UK/H/0030/048/IA/071	Variation Type 1A Mutual Recognition	Approved 06.09.07	N
To register a change in the address of the marketing authorisation holder 'Eli Lilly and Company Limited', from 'Kingsclere Road, Basingstoke, Hampshire, RG21 6XA' to 'Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL'. The trading style of 'Lilly Industries' remains unchanged. Consequential changes to PIL, carton, label and sections 7.0 and 10.0 have been made.	UK/H/0030/048/IA/072	Variation Type 1A Mutual Recognition	Approved 12.11.07	N