

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Ultratard. For information on changes after approval please refer to module 8.**

### 1. Introduction

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Acute, life-threatening consequences of diabetes are hypoglycaemia, and hyperglycaemia with ketoacidosis or non-ketotic hyperosmolar syndrome. Long-term complications of diabetes include retinopathy with potential loss of vision, nephropathy leading to renal failure, and peripheral neuropathy causing foot ulcers, gastrointestinal, genitourinary, and sexual dysfunction. The disease is also accompanied by an increased incidence of atherosclerotic cardiovascular, peripheral vascular and cerebrovascular disease.

**Type 1 diabetes**, which usually is of childhood or adolescence onset, accounts for 5 to 10% of diagnosed diabetes; it is characterised by loss of insulin production due to destruction of pancreatic  $\beta$  cells as a result of an autoimmune response or idiopathic causes. Patients with Type 1 diabetes depend on exogenous insulin for survival.

**Type 2 diabetes**, which usually is of adult onset, is by far the more common form of diabetes. In the Western World, it constitutes approximately 90% of all cases of diabetes. Type 2 diabetes is characterised by impaired insulin secretion, insulin resistance, increased hepatic glucose output and lipid disorders. Patients with Type 2 diabetes generally do not require insulin treatment for survival, although a substantial number (20-30%) of patients need insulin to achieve acceptable metabolic control.

Marketing authorisation for this human insulin for has been obtained for the treatment of patients with diabetes mellitus. The active substance of Ultratard is human insulin manufactured by recombinant DNA technology in *Saccharomyces cerevisiae*. The product is a long-acting protracted insulin formulation consisting of a suspension of crystalline (rhombohedral) insulin at neutral pH.

Ultratard is intended for marketing in dose strengths of 40 IU/ml and 100 IU/ml in 2 different presentations as follows:

Ultratard 40 IU/ml, 10ml vial  
Ultratard 100 IU/ml, 10ml vial

### 2. Chemical, pharmaceutical and biological aspects

#### Composition

The formulation designed for long duration of action is a suspension of crystalline (rhombohedral) insulin at neutral pH. The formulation contains the following agents for functions as follows: zinc (protracting agent –crystal forming), sodium chloride (isotonicity), sodium acetate (buffer) and methyl para-hydroxybenzoate (preservative).

Ultratard is presented in 10 ml vials in two strengths: 40 IU/ml and 100 IU/ml. The vial is a glass container sealed with a laminated insoprene/brombutyl rubber stopper (disc) and snap-off cap composed of aluminium and plastic. The glass container is produced from type I Ph.Eur. colourless glass.

#### Active substance

The active substance of Ultratard, human Insulin (rDNA) complies with Ph.Eur. monograph 1999:838 with additional tests as follows:

Identification by Amino acid composition

Nitrogen content

Total viable count (CFU/g)

DNA content

Methods of analysis for the additional tests developed by the applicant are fully described with relevant validations.

#### *Development Genetics*

Human insulin is produced using a genetically modified strain of *Saccharomyces cerevisiae*. The strain carries a plasmid which codes for the expression of a single chain insulin precursor attached to a pre-pro leader region of the yeast mating factor (MF $\alpha$ 1) gene.

The yeast transformant used to produce the insulin precursor is a transformant of *Saccharomyces cerevisiae* carrying the expression plasmid described above. The applicant has presented the complete DNA sequence of the plasmid. The sequencing presented is assembled from published sequences and in-house sequence determinations as relevant. The gene has also been fully characterised from isolated plasmids from long-term production scale fermentation and cell bank (Original Mother Culture (OMC)).

Constructional stability has been investigated in production strain, prolonged and very long term fermentation and cell bank (OMC).

#### *Cell bank system*

The cell bank system consists of Original Mother Culture (OMC), New Mother Culture (NMC), MCB and WCB. Satisfactory details of the preparation of the different types of cell banks have been provided and a clear description given of the numbering and origin of the various cell banks and their sublots.

#### *Production of active substance*

The encoded product of secretion during fermentation is a single chain insulin precursor consisting of the first 29 amino acid residues of the insulin B chain linked with three amino acids to the insulin A chain. This single chain precursor is converted enzymatically to an insulin methyl ester, which is subsequently hydrolysed to yield human insulin, consisting of two chains (A and B) linked together with disulphide bridges. The purification process employs several chromatography and precipitation steps for isolation of the precursor, the intermediates, and the active substance respectively. This process is well established and it should be noted the applicant has manufactured that human insulin rDNA over a period of many years during which time a number of improvements have been made.

Validation data have been provided for the fermentation, recovery and purification processes. In each case, critical parameters in these processes have been identified and investigated.

Satisfactory analytical data are provided for 10 recently produced batches of human insulin demonstrating a high degree of consistency in the manufacturing process.

#### *Stability of active substance*

The applicant has provided results of testing of 20 batches from the ongoing stability programme. Testing parameters include dry substance, insulin polymer, insulin dimer, A21 desamido insulin, other related substances and assay. The data confirm that active substance is stable for 60 months when stored at the recommended temperature.

#### **Other ingredients**

All excipients comply with Ph.Eur. specifications.

#### **Product development and finished product**

##### *Development Pharmaceuticals*

The current formulation represents an accumulation of experience the applicant has gained with a wide variety of insulin products over the years dating back to the early 1950's. The present formulation was developed in connection with the switchover from animal to semisynthetic human insulin in the early 1980's and the introduction of genetically engineered human insulin in the late 1980's. There have been no changes to the formulation since then.

Emphasis has been placed on correct insulin crystal size and form in the product. This is achieved through a combination of optimised zinc concentrations in the formulation and through a carefully defined and controlled manufacturing process.

Compatibility of the container components and product is shown to be satisfactory via stability studies.

Sterilisation by filtration is essential given the heat sensitivity of the active ingredient.

#### *Manufacturing process*

The insulin and buffer solutions are made separately and are mixed after sterile filtration into a crystallisation tank. The solution is then allowed to crystallise with gentle mixing. After crystallisation sterile solutions containing zinc, preservative and base are combined with the sterile crystal suspension to form the formulated bulk. The formulated bulk is aseptically filled into the final vial container.

Filling occurs in a grade A zone. Vials are inspected individually by manual or automated inspection.

Due to the nature of this application i.e. transfer of MRP product to the centralised procedure, and based on the extensive experience the applicant has with their products, no new validation studies have been initiated for this application. An overview of the processes used together with a description of the critical production parameters is provided. Summary results have also been provided for Ultratard products manufactured at the approved sites and in different batch sizes. Available data show a consistent, well-controlled manufacturing process.

Ultratard complies with the requirements of the following Ph.Eur. monographs:

01/2002:0854 Insulin Preparations, Injectable

1999:0836 Insulin Zinc Injectable Suspension (crystalline)

In addition to monograph tests the products are tested by in-house methods for crystal size, identity and ID and content of preservative.

Full methodologies have been provided for all in-house methods. A complete justification of the tests employed has been provided.

Batch analysis data have been provided for 3 recently produced batches of the 100 IU/ml presentation and 2 recently produced batches of the 40 IU/ml presentation. All batches comply with their respective specifications.

#### **Stability of the Product**

Stability reports are provided covering the different strengths and production sites for Ultratard.

Results have been generated by validated, stability indicating methods and indicate satisfactory stability. These results support the shelf life stated in the SPC.

#### **Viral Safety and TSE risk assessment**

A number of animal derived raw materials are used in the production of human insulin, rDNA. These are peptone, beef extract and pepticase which are used in the preparation and storage of cell banks, L-threonine and trypsin used in the purification process to convert human insulin precursor to human insulin methyl ester. Bovine insulin microcrystals are used for seeding the crystals in the product. L-threonine is sourced from avian feathers and porcine gelatine, trypsin from porcine pancreas, and bovine insulin from bovine pancreas.

Pepticase falls outside the scope of the TSE Guideline as it is derived from casein from milk from healthy cows only and no other ruminant materials are used in its preparation.

For peptone (CEP-2000-175) and beef extract (CEP-2000-181) Certificates of Suitability of the EDQM have been submitted.

Although a certificate of suitability has been provided by the applicant for bovine insulin from German sourced pancreas (RO-CEP 200-135-Rev OO), suitability of the material for its intended use in the finished product must be taken into consideration. The chance of contamination of German sourced pancreases used to produce the current batch of microcrystals is remote. In addition, the

manufacturing process for bovine insulin is stated to provide a total reduction of 8.7 logs for BSE-agents in the early steps of insulin extraction. Therefore, it is considered that the risk of transmission of BSE is highly unlikely. However, the applicant should undertake to source glands from lands categorised as GBR 1 or 2 in future.

The risk of transmission of TSE from Ultratard to human beings has been appropriately addressed in accordance with CPMP/CVMP Note for Guidance for minimising the risk of transmitting animal spongiform encephalopathy via medicinal products (EMEA/410/01).

Viral safety issues have been addressed and compliance with relevant guidelines are considered to be met.

### **Discussion on chemical, pharmaceutical and biological aspects**

Satisfactory evidence is provided that product manufacture is well controlled, that consistency of production is achieved and that a stable product results. The requirements of the relevant directives and guidelines are met. The pharmaceutical portions of the SPC, package insert and product label are supported by the information provided in the dossier. Several minor quality issues will be addressed by the applicant on an ongoing (post-approval) basis.

### **3. Toxicopharmacological aspects**

The active substance of Ultratard is human insulin manufactured by recombinant DNA technology in *Saccharomyces cerevisiae*. Ultratard is very long acting insulin with the protracting principle being based on addition of a small amount of zinc ions provided that the preparation has a neutral pH and that no interfering ions, like phosphate and citrate, are present. Ultratard is presented in two strengths, 40 IU/ml and 100IU/ml.

The preclinical evaluation of the present product is based on the documentation for the active ingredients; insulin human (rDNA) and protamine-insulin human. The programme includes recent studies performed with the insulin analogue insulin aspart. In several studies, insulin human (rDNA) was used as a reference substance.

#### **Pharmacodynamics**

- **Primary pharmacology programme.**

The programme includes studies performed in the eighties demonstrating the similarity between insulin human (rDNA) and semi-synthetic insulin human, later studies supplementing above studies and recent studies where insulin human (rDNA) was used as a reference substance for insulin analogues.

- ***In vitro* studies**

Insulin is a hormone composed of two polypeptides (two protein chains named A and B chains having respectively 30 and 21 amino-acids). Two disulfide bonds link these two chains. The structure of the insulin is similar of those of several other hormones or growth-factors (including insulin-like growth factors IGF-1 and IGF-2). IGF-1 and IGF-2 have some affinity for the insulin receptor, however both growth factors have their own receptors. The insulin and IGFs receptors both belong to the tyrosine kinase family receptors. The activation of the receptors is obtained when the endogenous ligand occupies the receptor. Once activated the signal transduction produced by these receptors, which mediates the physiological action of the hormone, starts with an autophosphorylation of the receptor. The *in vitro* studies explored the affinity of insulin analogues for other receptors belonging to the tyrosine kinase family.

The receptor binding activity of insulin human was studied in connection with the pre-clinical development of the insulin aspart (see table 1 below).

**Table 1: Determination of the receptor affinity of insulin human (rDNA).**

Affinity for Insulin Receptor	Affinity for IGF1-Receptor
=100%	0.03%

- ***In vivo* studies**

The effect on blood glucose in diabetic rats after subcutaneous administration was studied in diabetic rats which received by a single subcutaneous injection either insulin human, semi-synthetic insulin or vehicle. The effect on blood glucose was measured by blood sampling. Insulin human and semi-synthetic insulin showed dose and time dependant antidiabetic effect.

The pharmacological effect of insulin human 40 U/ml was studied in a cross-over assay in rabbits. A standard crossover study (British Pharm., 1980) of the hypoglycaemic effect after SC administration in Rabbits (n=36) was done. There was no difference between equivalent preparations made from human insulin or semi-synthetic insulin.

- **Safety pharmacology programme.**

In the Irwin test, a few mice showed a slight reduction in exploratory and spontaneous activity. In the Animex test, which is more sensitive, mice showed a decrease in motor activity at the highest dose (5 U/kg). Reduced performance in the rotarod test was also observed in mice at the highest dose (5 U/kg) in one study, but no effects were observed at 100 U/kg in a later study. The locomotion activity in rats were slightly reduced at 100 U/kg, which was the only dose tested.

Newer studies support the original ones.

The time from disappearance to reappearance of the righting reflex (sleeping time) induced by pentobarbital in mice was prolonged after treatment with 5 U/kg. The same applies to hexobarbital after treatment with 100 U/kg; the effect was reversed with glucose administration. A dose of 100 U/kg after administration of ethanol significantly increased the mortality and sleeping time. No antagonistic effect on pentylenetetrazol-induced convulsions in mice was observed at 100 U/kg, and this treatment did not act as a pro-convulsant either. Insulin human did not show any inhibitory effects on acetic acid induced writhing in mice at 100 U/kg (P-27), indicating absence of analgesic potential. The Body temperature in mice was unaffected by 100 U/kg (P-28). Neither insulin human nor semi synthetic insulin human produced any “curarizing” effect on neuromuscular transmission after treatment of rats up to 5 U/kg IV. No effects attributed to treatment were observed in an in vitro preparation of guinea-pig ileum and *vas deferens*.

No effects on cardiovascular and respiratory system attributed to treatment were observed in cats and in pigs. The gastro-intestinal motility of mice was unaffected. A transient fall in diuresis was observed in rats, however this effect was reversed after SC administration of glucose. A bromsulphthalein-test showed no indications of pathological effects to liver parenchyma in pigs. Blood platelets of human Rich Platelet Plasma were not affected after in vitro treatment with insulin human.

Effects seen in the original and newer safety pharmacology studies can all be related to hypoglycaemia.

## **Pharmacokinetics**

### **Single Dose Pharmacokinetics Studies**

The pharmacokinetics properties of insulin human were investigated after a single dose IV and SC in the Rat. These experiments have all shown that insulin human has regular, predictable kinetics in the rat after SC injection of various high doses.

A single dose pharmacokinetic study in the pig where insulin human was administered IV and SC showed that  $T_{max}$  equals 79 min [ $T_{max}$  is the time at which the highest drug concentration occurs following administration of an extra vascular dose.  $T_{max}$  is expressed in min or hr].

### **Multiple Dose Pharmacokinetics Studies**

A multiple SC dose kinetics study was performed in rats and compared the pharmacokinetic profile of insulin aspart and insulin human. A small relative increase in the  $t_{max}$  and  $C_{max}$  of insulin human after SC administration twice daily for 7 days has been observed. The kinetics after multiple doses were basically similar to those after single doses injected SC.

**Table 2: Pharmacokinetic Parameters of Insulin Human (rDNA)**

		Insulin human (rDNA)			
Administration	Endpoint	Man 022/UK  (0.1 U/kg)	Pig NN 950475  (0.125U/kg)	Dog NN 960548  (1U/kg)	Rat NN 960550  (6U/kg)
SC	t <sub>1/2</sub> (min)	122	121	57	23
	C <sub>max</sub> (pM)	102	122	2871	18000
	T <sub>max</sub> (min)	145	99	60	15
IV	Cl (l·min/kg)		0.021	0.048	0.058

As the majority of the insulin human preparation is of same composition as the semi-synthetic insulin human preparations, no pharmacokinetic studies were conducted in the original preclinical programme. Linearity concerning AUC/dose was confirmed in different species, meaning that there was no insulin accumulation.

### Toxicokinetics

Toxicokinetic studies were done during the 52 weeks repeated dose toxicity studies in the rat and the dog and the Segment II test (teratogenicity studies) in the pregnant rabbit. They demonstrated linearity of the plasma levels of insulin human with the dose, the C<sub>max</sub>, occurred 1-5 hours after administration of either type of insulin. The plasma levels and AUCs of insulin human remained directly related to dose throughout the 52 weeks of treatment and that the rate of elimination did not increase with time.

### Toxicology

- **Single dose toxicity studies.**

Mice and Rats were given a single dose of insulin human subcutaneous at dosage up to 4000 U/kg. In higher dosage groups insulin human was compared to semi-synthetic insulin. Apart from few sporadic hypoglycaemic reactions on the day of dosing, no treatment related signs were seen. No significant difference between insulin human and semi-synthetic insulin was observed.

- **Repeated doses toxicity.**

The subacute toxicity was examined in rats and dogs during a 4weeks SC study in Wistar Rats and a 13 weeks SC study in Beagle Dogs.

Insulin human was administrated subcutaneous for 1 year to Sprague Dawley Rats. At necropsy, there was an increased incidence of mammary gland cyst and mammary tumours were found at microscopic examination. The incidence of total number of mammary tumours as well as fibroadenomas and adenocarcinomas were however not significant from the control group. There were no other treatment-related effects in any organ, including the pituitary.

Beagle dogs were given insulin human 1 U/kg twice daily SC for 12 months. Besides one case of abnormal weight gain, there were no other important effects of the treatments.

- **Genotoxicity.**

The genotoxic potential of insulin human was evaluated through a bacterial reverse mutation test in 4 strains of *Salmonella typhimurium*, a clastogenic activity test in cultured human lymphocytes, a mutagenic activity test on the HGPRT-locus in chinese hamster V79 cells and a micronucleus test in bone marrow erythrocytes. In all the tests insulin human was found non-mutagenic.

Insulin human was included as reference substance in a gene mutation study in mouse lymphoma L5178Y cells (TFT-resistance). Negative findings were obtained with no signs of cytotoxicity.

- **Carcinogenicity.**

MCF-7 human breast cancer cells were incubated with different concentrations of insulin aspart, insulin human and an experimental insulin analogue. Dose response curves from seven studies were the same for insulin aspart and insulin human, whereas the experimental insulin analogue had at least 10-times their mitogenic potential.

In an exploratory 12-month test and in the formal 12-month toxicity study in the Sprague-Dawley rat the effects of chronic administration of insulin aspart and insulin human on mammary tissues in the Rat were explored. In these studies some animals developed neoplasms of mammary tissue. All animals in all treatment groups showed hyperplasia of mammary glandular epithelial cells. In both tests most mammary gland tumours were fibroadenomas all had a typical histological appearance. The small number of adenocarcinomas had remained local and had not metastasised. The pituitary glands appeared normal.

A study exploring the effects of repeated subcutaneous injection of insulin aspart and insulin human for 52 weeks in rats has been conducted. This study has been performed in Sprague-Dawley rats. A dose-related increase in palpable subcutaneous masses has been observed at 30 and 75 U/kg twice daily. A statistically significant ( $p < 0.01$ ) increased incidence of female animals bearing mammary gland tumours at 75 U/kg/bid were found. The increase was evident in benign/malign combined as well as in malign tumours alone. No evidence of mammary gland hyperplasia or of tumours was seen in the test up to 12 months in the dog.

Particularly under certain experimental conditions insulin may induce mammary tumours in the female Sprague Dawley rat (a sensitive species, strain and sex) probably related to a mitogenic and growth-promoting action of insulin mediated by the insulin receptor.

An increase in the number of benign mammary adenomas and fibroadenomas has been shown in Sprague Dawley rats. In one 12 month study, there was a statistically significant increase of female animals bearing benign and malign mammary gland tumours at the highest dose. There was no increase of mammary gland hyperplasia or tumours in the 12 month dog study.

- **Reproduction Toxicity.**

Fertility and Embryo-Foetal Development studies have been conducted in the Sprague Dawley Rat. Fertility was not affected. Males showed slight reduction in the epididymal sperm count. Dams treated with high doses (200 U/kg) of insulin human showed pre- and post-implantation loss, and a specific pattern of anatomical abnormalities of the foetuses was seen. The findings are regarded as a consequence of the severe maternal hypoglycaemia.

The pre- and post-natal development of Sprague Dawley rats born from pregnant females exposed to insulin human has been studied. Maternal hypoglycaemia with a few deaths and effects on weight gain and food consumption were observed in the dams.

Newborn pups showed slightly increased weight gain, which had become normalised by weaning. There were a few other variations in F<sub>1</sub> animals but no major effect was found.

Embryo-foetal development of rabbits born from pregnant females exposed to insulin human has also been studied. The high doses of insulin led to increased food consumption and accelerated weight gain, which persisted to the end of the experiment. There was a dose-related reduction in plasma glucose. In the mid- and low doses it had recovered by 4h after the first dose. Top-dose group (5 U/kg) showed embryonic deaths and related depression of litter size and weight. At 1.5 U/kg and above, foetuses showed skeletal abnormalities. These effects were considered to be due to the induced maternal hypoglycaemia.

In Segments I/II study, fertility was not affected in rats given insulin human. Males had a slightly reduced epididymal sperm count. Pre- and post-implantation loss was increased and a proportion of foetuses had characteristic abnormalities attributed to reduction of maternal blood glucose. In an embryo-foetal development study in rabbits, an increase in early embryonic deaths with associated decrease in litter size and litter weight was observed at 10 U/kg. A dose-dependent increase in foetuses with skeletal abnormalities was seen.

During gestation, abortion and foetal death and malformations were seen, but only during severe maternal hypoglycaemia and are already known to occur in incorrectly treated diabetic women.

- **Local Tolerance.**

The local tolerance was studied in rabbits after IM injections of insulin human. It was concluded that insulin human caused damages which were similar to those found after injection of isotonic saline solution.

A test for local irritation in rabbits showed that there were no differences in the damages caused by isotonic saline solution and by insulin human.

- **Immunotoxicity studies.**

Insulin antibodies, even in moderate and low amounts, may prevent rapid rise in free blood insulin, thereby leading to higher postprandial glucose levels, or cause increased risk of hypoglycaemia when insulin is released from circulating insulin antibody complexes. The purity of the injected insulin has been shown to be of crucial importance on the amount of insulin antibody formed. Thus, 5-times crystallised porcine insulin induces more insulin antibodies than the same preparation containing mono component insulin.

The immunogenicity of insulin human has been studied in Rabbits. Freund's adjuvant and 20 U of respectively insulin human, semi-synthetic insulin and 5 times crystallized porcine insulin were injected intramuscularly to groups of rabbits twice a week. Serum insulin binding was estimated until 97 days. No statistically significant differences between the immunogenicity of insulin human and semi-synthetic insulin was found, whereas they both were demonstrated to be significantly less immunogenic than 5-times crystallized porcine insulin. It was concluded, that insulin human fulfils the demand of low potential to induce insulin antibodies in accordance with other mono component insulins.

There was no statistically significant difference between the immunogenicity in rabbits of insulin human and semi synthetic human insulins. These insulins were found to be significantly less immunogenic than 5 times crystallised pork insulin. The potential for human antibody production against insulin human is thus considered to be low.

- **Ecotoxicity/Environmental Risk Assessment.**

Insulin human is considered readily degradable, hence do not suggest any environmental risk for clinical use. The containers and devices in which it is supplied are appropriate for disposal by the means normally employed for simple medical devices.

### **Discussion on toxico-pharmacological aspects**

The main purpose in the studies for primary and secondary pharmacodynamics was to demonstrate the similarity between the new insulin human and semi synthetic human insulin. Effects seen in the safety pharmacology studies can all be related to hypoglycaemia.

As the majority of the insulin human preparation is of same composition as the semi-synthetic insulin preparations, no pharmacokinetic studies were conducted in the original preclinical programme. Linearity concerning AUC/dose was confirmed in different species, meaning that there was no drug accumulation.

The toxic effects seen in the single dose and repeated dose toxicity studies were attributed to the hypoglycaemic activity and thus an exaggerated pharmacological effect caused by the high doses of the insulin. Increased weight, depressed activity, convulsions and death were some of these effects.

The noted effects on embryos and foetuses were only seen at severe maternal hypoglycaemia and are already known to occur in incorrectly treated diabetic women.

All conducted genotoxicity studies were negative for mutagenic potential. An increase in the number of benign mammary adenomas and fibroadenomas has been shown in Sprague Dawley rats. It is concluded that the increased incidence of mammary tumours seen in rats is probably caused by mitogenic and growth-promoting action via the insulin receptor, but is probably also related to the fact that Sprague Dawley rats are especially sensitive and were given large doses. There was no increase of mammary gland hyperplasia or tumours in the 12-month dog study.

Finally; a test for local irritation in rabbits showed that there were no differences in the damages caused by isotonic saline solution and by insulin human. The potential for human antibody production against insulin human is thus considered to be low.

## **4. Part IV: Clinical aspects**

Diabetes is a group of metabolic disorders characterised by hyperglycaemia due to defects in insulin secretion and/or insulin action. The two most common forms of diabetes mellitus are type 1 and type 2 diabetes. Type 1 diabetes is characterised by an absolute deficiency of insulin due to destruction of the

pancreatic  $\beta$ -cells. Although the rate of  $\beta$ -cell destruction is variable, all type 1 diabetic patients will eventually require exogenous insulin for survival. In contrast, type 2 diabetes is characterised by insulin resistance, relative impairment of insulin secretion and increased hepatic glucose output. In general, patients with type 2 diabetes do not require exogenous insulin for survival. Nevertheless, during the course of the disease, a large minority of these patients will be treated with exogenous insulin to correct persistent hyperglycaemia.

The goal of insulin treatment is to mimic the physiologic pattern of insulin secretion, which under normal conditions consist of a basal secretion and meal related short peaks. The most commonly used insulin regimen is the so-called basal-bolus regimen in which basal insulin requirements are provided by one or two injections of long (intermediate) -acting insulin and mealtime requirements are provided by meal related injections of fast/rapid acting soluble human insulin/insulin analogues. Instead of separate injections of long (intermediate)-acting and fast-acting insulins, the two insulin preparations may be mixed (by the patient or as ready-made premixed insulin) before injection. It is generally accepted that the basal-bolus regimen offers the best glycaemic control. However, many patients, especially type 2 diabetic patients who produce significant amounts of insulin themselves, may be adequately controlled on twice-daily injections of long (intermediate)-acting insulins or mixtures of fast-acting and long (intermediate)-acting insulins. Although this regimen may not offer optimal glycaemic control, patient compliance is generally is better for this simpler regimen than for the multiple injections regimens. Therefore, for some patients, the twice-daily regimen may be an acceptable alternative to the basal-bolus regimens.

Intensified insulin therapy can reduce the incidence of complications, and delay the progression of existing complications in Type 1 and 2 diabetes. One type of intensified insulin therapy is multiple injection therapy, which attempts to mimic the physiological insulin secretion of normal man. Basal insulin requirements are supplied as injections of long/intermediate acting insulin, and meal-related insulin requirements are supplied by bolus injections of regular fast-acting human insulin (HI).

### **Clinical pharmacology**

Nine different studies are supporting the pharmacodynamics of Ultratard. Of these, two were conducted in healthy subjects, six studies were conducted in type 1 diabetics (including two performed in children/adolescents) and two trials enrolled type 2 diabetics patients (two studies were performed in both type 1 and type 2 diabetic patients, see table 3 below).

**Table 3: Clinical pharmacodynamics trials**

<b>Study</b>	<b>Population (number of subjects)</b>	<b>Design</b>	<b>Dose regimens</b>
<i>Healthy subjects.</i>			
<b>Seigler et al. 1991</b>	Healthy subject (6-9 per preparation)	Placebo-controlled, single-dose, single-centre.	One single dose of five different ultralente insulin formulations including Ultratard human insulin, and placebo. The dose of the insulin preparations was 0.4 U/kg.
<b>Owens et al. 1986</b>	Healthy males (6 subjects)	Randomised, cross-over, single-dose, single-centre.	One single dose of Ultratard human, Ultratard porcine, Ultratard bovine and diluent. The dose of the insulin preparations was 0.3 U/kg.
<i>Patients with either type 1 or type 2 diabetes mellitus.</i>			
<b>Hildebrandt et al. 1985</b>	Male and female patients with type 1 diabetes (8 subjects)	Randomised, cross-over, single-dose, single-centre.	125-I labelled Ultratard (human insulin) and 125-I-labelled Ultralente MC (bovine insulin). The doses were 6 and 24 U.
<b>Edsberg et al. 1987</b>	Male and female patients with type 1 diabetes (9 subjects)	Cross-over, multiple-dose, single-centre.	Ultratard (human insulin) 30 min before breakfast for a 14-day period and Ultratard (human insulin) at 2200 h for a 14-day period.
<b>Jørgensen et al. 1989</b>	Male and female patients with type 1 diabetes (7 subjects)	Randomised, cross-over, multiple-dose, single-centre.	125-I labelled Ultratard (human insulin) 16 U daily for 4 days and 125-I-labelled long-acting insulin analogue 16 U daily for 4 days.

<b>Mellvig et al. 1990</b>	Male and female children/adolescents with type 1 diabetes (15 subjects)	Double-blind, randomised, cross-over, multiple-dose, single-centre.	Ultratard daily for 3 months and a long-acting human insulin daily for 3 months.
<b>Bougnères et al. 1992</b>	Male and female children/adolescents with type 1 diabetes (205 subjects)	Randomised, parallel-group, multiple-dose, multi-centre.	Three injection regimen (including fast-acting insulin human alone or in combination with Ultratard) or two-injection regimen (including fast-acting insulin human and a long-acting human insulin). Duration 1 year.
<b>Holman et al. 1984</b>	Male and female patients with type 1 or type 2 diabetes (18 subjects)	Randomised, double-blind, cross-over, multiple-dose, single-centre.	Ultratard (human ultralente insulin) for 6 weeks and highly purified beef ultralente insulin for 6 weeks.
<b>Iwamoto et al. 1987</b>	Male and female patients with type 2 diabetes (8 subjects)	Multiple-dose, uncontrolled, single-centre.	Ultratard (insulin human) 0.3 U/kg before breakfast for an 8-day period.

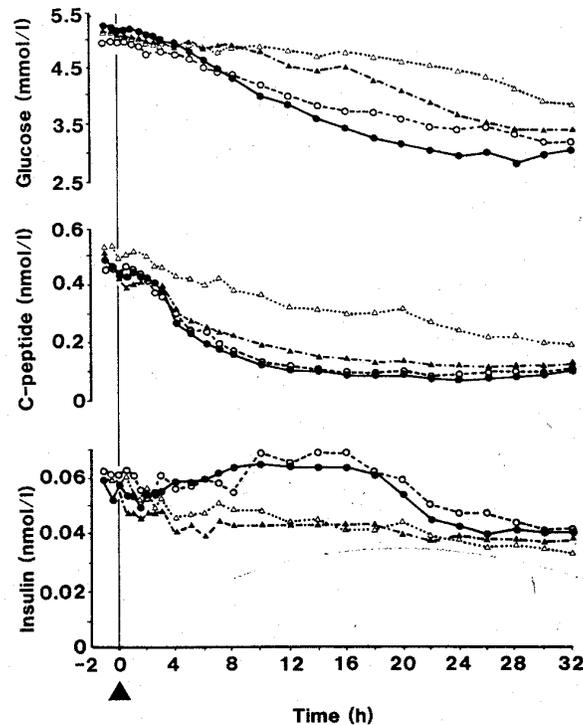
### Pharmacodynamics in healthy subjects

A first study (**Seigler et al. 1991**) compared the pharmacodynamic and pharmacokinetic properties of five different ultralente insulin preparations from different species of origin (beef, pork, human) including Ultratard human insulin and different manufacturers. A placebo comparator was also included in the study. Six to nine healthy young fasting subjects (per product) received a subcutaneous injection in the abdominal wall. The dose was 0.4 U/kg. Blood glucose was maintained as basal levels for a 40-hour period by a euglycaemic clamp using dextrose infusion. Plasma insulin and plasma C-peptide levels were obtained during the 40-hour period following injection. From the dextrose infusion profiles for Ultratard human insulin, the mean time of onset was 5.3h, mean time of peak action was 15.2h, and average duration of action was 32.5h.

Another study (**Owens et al. 1986**) compared the pharmacodynamic properties (hypoglycaemic activity, plasma insulin and c-peptide concentrations) of three Ultratard preparations (human, porcine and bovine). Six healthy fasting subjects were given injections of each product in randomised cross-over design. The dose administered subcutaneously to the subjects was 0.3 U/kg in the anterior abdominal wall. The study also included treatment with a diluent medium as control. During the 32-h study period, the subjects remained fasting. During this period of time plasma glucose, plasma C-peptide and plasma insulin concentrations were measured. For the Ultratard human insulin preparation, the hypoglycaemic response started 3-4 h after injection and progressed to a nadir at 20-24 h (see figure 1 below).

The euglycaemic clamp technique is the appropriate method to assess the pharmacodynamics of insulins. This has only been done to a limited extent for Ultratard. Seigler *et al.* found duration of action to be 32.5 h. From the study by Owens *et al.* it seems that blood glucose was still below the control (diluent) at 32 h. The onset of action for Ultratard is obtained within about 5 hours, reaches a maximum effect within 8-24 hours and the entire time of duration is about 32 hours.

**Figure 1:** Plasma glucose, plasma C-peptide and plasma insulin and serum C-peptide measured after injections of human, porcine and bovine Ultratard. Human Ultratard = ●. Diluent control = Δ.(Owens et al. 1986).



Pharmacodynamics in type 1 diabetic patients

Nine type 1 diabetic patients were given Ultratard either in the morning before breakfast or at bedtime for a 14-day period in crossover design (Edsberg et al. 1987). The patients also received a fast acting insulin human except for a 24-h profile period at the end of each study period. The doses of Ultratard and the fast acting insulin human were estimated from the patient’s previous total insulin doses. The chosen Ultratard doses were the maximum, which the patient could tolerate without experiencing hypoglycaemia at night or between meals (the Ultratard dose was adapted to each patient but remained constant during the entire study period). The blood glucose profiles during the two periods were very similar with no significant differences. Plasma glucose levels were relatively high during both periods, probably reflecting the fact that fast acting insulin was not administered during the 24-h profile period.

Holman et al. 1984 compared the pharmacodynamics of Ultratard human insulin and bovine ultralente insulin. Nine type 1 and nine type 2 diabetic patients received treatment for six weeks with each insulin type in a randomised crossover design. Fast acting insulin was administered as soluble porcine insulin. Doses were chosen individually for each patient. The patients were seen every 14 days for blood glucose measurements and at the end of each study period for a plasma glucose profile from 17:30 to 7:00. The blood glucose was generally well controlled. However for a group of four type 1 diabetic patients, blood glucose control was less optimal with mean blood glucose values from 12-16 mmol/l.

Two studies in children/adolescents have been performed. None of these studies are clinical pharmacological studies in a strict sense.

Mellvig et al. 1990 compared Ultratard and a long-medium-acting human insulin as basal insulin in children/adolescents aged 12-19 years with diabetes mellitus. In a double-blind, crossover design, 15 patients were given each insulin type for three months. The dose was calculated as 35% of the total daily insulin requirement and administered at bedtime. In addition, fast-acting insulin was given before meals and larger snacks 4-5 times daily. Blood glucose was monitored 7 times daily on one day per week. Free insulin and blood glucose profiles were obtained after each 3-month period. The mean levels of fasting

blood glucose were quite high in the Ultratard group as well as the long-medium-acting human insulin group, 12.3 mmol/l and 10.8 mmol/l, respectively. However, glycosylated haemoglobin HbA<sub>1c</sub> decreased in both groups to 7.4% and 7.5%, respectively. There were no statistically significant differences between the two insulin types, both with regard to glycaemic control and hypoglycaemic episodes.

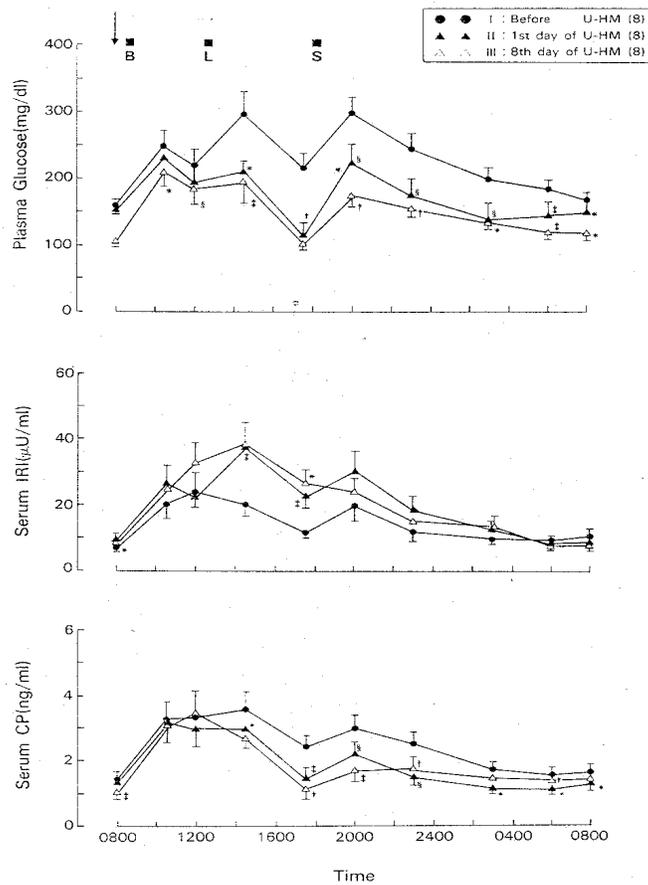
**Bougnères *et al.* 1992** conducted a large study in 205 children with diabetes mellitus. A three-injection regimen or to a two-injection insulin regimen was randomly allocated to the patients. The three-injection regimen included a fast-acting insulin 15 min before breakfast and lunch, and Ultratard mixed with the fast-acting insulin 15 before dinner. Patients in the two-injection regimen continued to be treated with pre-breakfast and pre-dinner injections of a mixture of fast-acting insulin and a long-acting human insulin. The patients were evaluated after one year. Glycosylated haemoglobin (HbA<sub>1c</sub>) decreased from 9.8% to 9.3% in the three-injection group, but increased in the two-injection group from 9.5% to 9.8%, resulting in a small, but statistically significant difference between the two regimens. The frequencies of hypoglycaemia were similar in the two groups.

#### Pharmacodynamics in type 2 diabetic patients

One study (**Holman *et al.* 1984**) enrolled both type 1 and type 2 diabetic patients (see above).

**Iwamoto *et al.* 1987** investigated the pharmacodynamic effect of a pre-breakfast injection of Ultratard HM. The product was administered during eight days to eight patients with type 2 diabetes mellitus not adequately controlled with a diet. The dose was 0.3 U/kg administered before breakfast as a subcutaneous injection in the thigh. Daily profiles of plasma glucose, serum insulin and serum C-peptide were obtained before and during the study. Before Ultratard treatment, plasma glucose at all times remained higher than 160 mg/dl (8.9 mmol/l) with a mean whole-day level of 223 mg/dl (12.4 mmol/l). On the first day of Ultratard treatment, plasma glucose levels began to decrease significantly about 6 hours after injection and remained lower throughout the day with mean whole-day plasma glucose at 174 mg/dl (9.6 mmol/l). On the eighth day, the mean whole-day plasma glucose was 151 mg/dl (8.4 mmol/l) (see figure 2 below).

**Figure 2: Plasma glucose, serum (immunoreactive) insulin and serum c-peptide before measured during first day and during eighth day of Ultratard treatment. (Iwamoto et al. 1987).**



Pharmacokinetics

• **Absorption and bioavailability**

In the study in **healthy subjects** by Siegler *et al.* 1991, the insulin profile of Ultratard human insulin mirrored the pharmacodynamic results.  $T_{max}$  was about 10-15 h, and insulin levels returned to basal level approximately after 30h. Owens *et al.* 1986 investigated the insulin and C-peptide profiles in healthy subjects treated with Ultratard human insulin 0.3 U/kg. Calculated exogenous insulin concentrations increased to reach maximum at 14 h.

The study by Edsberg *et al.* 1987 in **type 1 diabetic patients** found similar plasma insulin profiles. A tendency towards higher insulin levels from 1:00 to 13:00 was seen when Ultratard was injected at bedtime, but the only statistically significant difference was seen at 12:00.

Hildebrandt *et al.* 1985 compared the absorption of Ultratard human insulin with that of highly purified beef ultralente insulin at different dose levels in eight type 1 diabetic patients. The study had a randomised crossover design. The mean age of the patients was 36.8 years. The doses were 6 and 24 U administered subcutaneously alternating between different sites. A dose-dependent absorption was found for bovine ultralente insulin with significantly higher residual activity (percentage) in the high dose compared to the low dose. Concerning Ultratard [containing insulin human], the mean time for half of the initial activity to disappear was 9.4 h (after the administration of 6 IU in the abdominal wall), 13.0 h (after the administration of 6 IU in thigh), and 15.1 h (after the administration of 24 IU in thigh). There were no statistically significant differences between the two doses of human Ultratard. Four and six hours after the administration there was significantly higher residual activity in the thigh than in the abdomen. From the residual activity versus time curves it appears that absorption starts within 4 h after injection and lasts approximately 32 h.

In a similar study, Jørgensen *et al.* 1989 investigated the absorption and intra-individual and inter-individual variations in absorption of Ultratard (human insulin). The patients enrolled in this study were seven type 1 diabetic patients. These patients were given 16 IU administered subcutaneously into alternating sites of the thighs once daily (morning) over four days in a randomised crossover design. The patients received their usual doses of mealtime insulin. The mean blood glucose concentration during Ultratard HM treatment was 9.5 mmol/l. The mean time for half of the initial activity to disappear was 25.5 h. The mean variation in absorption observed in the same patient (intra-individual variation) was 44.5% and the variation observed among all the patients enrolled in the study (inter-individual) was 36.9%.

Finally in one study conducted **in type 2 diabetic patients** (Iwamoto *et al.* 1987) insulin levels reached at peak at 14.30 h (6½ h after injection), and insulin levels were significantly higher than before Ultratard treatment.

- **Distribution**

No formal distribution studies were performed with insulin human. Insulin is not bound to plasma proteins unless circulating antibodies directed against insulin are present.

- **Elimination**

Ultratard cannot be administered intravenously therefore clearance after intravenous administration could not be studied. As the half-life of intravenously injected human insulin is relatively short, the terminal half-life of human insulin following subcutaneous injection is a measure of the terminal absorption rather than the elimination of insulin from plasma *per se*. The terminal elimination half-life of human insulin following subcutaneous injection of Ultratard has not been calculated in the publications.

#### *Metabolism*

Metabolism of insulin human was not formally investigated. From previously published data it is known that insulin is catabolised by various proteases. The degradation products are not active.

#### *Excretion*

Excretion of Ultratard was not formally investigated. As insulin is eliminated by metabolism, excretion of unchanged drug is minimal or non-existent.

- **Pharmacokinetics in special populations**

#### *Patients with impaired renal or hepatic function*

The applicant has not submitted any data on the pharmacokinetics in patients with impaired renal/hepatic function. It is known that the liver, the kidneys and the muscles are primary sites of insulin degradation. Renal and hepatic impairment may reduce insulin degradation and thus reduce insulin requirements.

#### *Pregnancy and lactation*

No studies have been performed. Diabetes is associated with an increased risk of complications during pregnancy and congenital malformations in the baby. Optimising metabolic control before and during pregnancy can reduce this risk. For most of the patients with type 2 diabetes and all patients with type 1 diabetes, insulin is the only way of optimising metabolic control. Insulin can be administered during pregnancy and lactation.

- **Interaction studies.**

No formal interaction studies have been performed. There are no literature reports of direct pharmacokinetic interactions between insulin and other products. The products which interfere with glucose metabolism through various mechanisms are well identified.

- **Conclusion on pharmacokinetic studies.**

Ultratard is a very long acting human insulin. It is a crystalline zinc suspension.

Onset of action is within about 5 h, and the peak effect is reached within 8-24 h. The duration of action is about 32 h.

The pharmacodynamic data correspond well with the pharmacokinetic results. No specific pharmacodynamic/kinetic data on Ultratard with regard to the effect of age, gender, ethnic origin, hepatic and renal impairment are available. Like with all subcutaneously injected insulins, the terminal elimination half-life is determined by absorption rather than elimination. The terminal elimination half-life of Ultratard has not been documented. The elimination half-life of intravenously administered human insulin is short (minutes). Human insulin is eliminated through degradation in various organs and tissues. There are no active metabolites. Numerous drugs interact with insulin on the dynamic level by affecting glucose metabolism. There are no known pharmacokinetic interactions with other products (different from insulin).

### **Clinical efficacy**

Main studies (phase III = therapeutic confirmatory trials).

These studies include four published studies performed in type 1 diabetic patients and two in type 2 diabetic patients.

*Studies performed in type 1 diabetic patients.*

- **Tunbridge et al. 1989.**

This study (**Tunbridge et al. 1989**) compared the effect of a long-acting human insulin and Ultratard administered in a twice-daily regimen, mixed with fast acting human insulin on fasting blood glucose. It was a 6-month double blind crossover study in 66 type 1 diabetes patients.

Fasting blood glucose obtained after the administration of Ultratard regimen was significantly lower than with the other long-acting human insulin regimen ( $6.6 \pm 0.8$  vs.  $8.2 \pm 0.5$  mmol/l) (no further significant differences between these two long-acting insulins were noted on the 8-point blood glucose profile). However a significant difference between the two insulins was not observed for those patients with fasting blood glucose previously over the median (patients enrolled in this study had previously been enrolled in a similar study comparing NPH insulin and the long-acting human insulin, see Tunbridge *et al.* 1989). Overall blood glucose control, fructosamine and HbA<sub>1c</sub> were similar for both treatments. The evening dose of Ultratard was slightly but significantly lower than the evening long-acting human insulin dose ( $14.9 \pm 0.8$  vs.  $15.5 \pm 0.8$  IU) confirming the lowering effect of Ultratard on fasting blood glucose. However, the incidence of serious hypoglycaemic effects was significantly higher with Ultratard compared to the long-acting human insulin, with the majority of nocturnal events occurring between 5 a.m. and breakfast.

- **Parillo et al. 1992.**

The prevention of early morning hyperglycaemia, assessed by fasting blood glucose was the main interest of this study. In a randomised cross-over trial with 6-week treatment periods ten patients with persistent fasting hyperglycaemia were studied (fasting blood glucose FBG > 10 mmol/l). These patients were treated with the basal bolus regimen with intermediate insulin as basal insulin. The basal bolus regimen was used, with either Ultratard or NPH insulin being the basal insulin. Fasting blood glucose were significantly lower with Ultratard compared to NPH insulin ( $6.26$  mmol/l  $\pm$   $0.88$  vs.  $10.82 \pm 4.27$  mmol/l). The other blood glucose values during the day were not different for the two treatments. Glycosylated haemoglobin (HbA<sub>1c</sub>) was similar for both treatments the same is true for insulin doses and hypoglycaemic reactions.

- **Mansell et al. 1992.**

In contrast Mansell *et al.* found that fasting blood glucose measurements were significantly lower for another NPH insulin (intermediate-acting human insulin) compared to Ultratard, despite lower doses used with the NPH insulin than Ultratard. This study was a randomised, cross-over study comparing NPH insulin and Ultratard as bedtime insulin (soluble human insulin administered to the meals) in 20 diabetic patients in 12 weeks periods. The remaining parameters (fructosamine, HbA<sub>1c</sub>, mean daily blood glucose concentrations) were similar with either insulin. It is noteworthy that the basal insulin was administered before the evening meal in the previous study (Parillo *et al.*) and at bedtime in this study (Mansell *et al.*). In addition, patients with morning hyperglycaemia were enrolled in the previous study (Parillo *et al.*).

- **Mellvig et al. 1990.**

Mellvig *et al.* compared a long-acting human insulin and Ultratard administered as basal insulin at bedtime in a basal bolus regimen in 15 diabetic adolescents aged from 12 to 19 years old. Three of the patients had already used the multiple injection regimen. The study had a double-blind cross-over design with each period lasting 3 months. The mean levels of fasting blood glucose were high (12.3 mmol/l for Ultratard and 10.8 mmol/l for the long-acting human insulin) on the other hand, HbA<sub>1c</sub> decreased significantly during the study period but no difference was found between the long-acting human insulin and Ultratard. The insulin dose tended to increase when the conventional regimen was replaced by the multiple injection regimen, patients weight increased as well. The basal insulin portion constituted approximately 40% of the daily insulin dose. The number of hypoglycaemic episodes was higher with the long-acting human insulin compared to Ultratard but the difference was not significant.

*Studies performed in type 2 diabetic patients.*

Two studies (**Mansell et al. 1992** and **Holman et al. 1987**) suggest the addition of long-acting insulin such as Ultratard to oral hypoglycaemic treatment when glycaemic control is not satisfactory.

Discussion on clinical efficacy

The treatment of diabetes mellitus with insulin has been established for many decades. It is a life saving treatment for patients with type 1 diabetes and is required by many patients with type 2 diabetes.

It is not possible to mimic the physiological plasma insulin profiles; human insulin tends to self-associate in a hexameric form after injection into the subcutaneous tissue resulting in a relatively slow absorption. Fast-acting insulin human may be given intravenously (e.g. in diabetic ketoacidosis) and intramuscularly but is predominantly administered subcutaneously. Ultratard is for subcutaneous administration. No standard scheme of administration exists and doses to obtain an optimal glycaemic control vary individually. Several large studies have demonstrated that best results not only on glycaemic control but also on long-term microvascular complications are obtained in both type 1 and type 2 diabetic patients with intensified regimens, i.e. either with an insulin pump providing continuously subcutaneous insulin infusion or by injecting human insulin three or more times to the meals guided by frequent blood glucose monitoring in addition to a long- or very-long acting insulin injected once or twice daily covering the basal insulin requirements (see for further reference: The Diabetes control and complications trial research group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993, **329**:14-23 and UKPDS group: Intensive blood glucose-control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998.**352**:837-53.)

The addition of zinc ions in insulin preparations (such as in Ultratard) leads to a change in the pharmacokinetic properties. Therefore Ultratard is a very long-acting insulin which is usually injected once daily as basal insulin in the basal-bolus regimen. Injections of Ultratard as part of the conventional regimen, as monotherapy or in combination with oral hypoglycaemic agents in type 2 diabetes patients belong as well to the scope of its administration. The long acting effect of Ultratard was addressed in several publications (concerning both type 1 and type 2 diabetes patients) which support Ultratard efficacy.

**Clinical safety**

The data concerning the safety profile of Ultratard have been obtained from the published efficacy studies mainly including data on Ultratard containing semi-synthetic human insulin, which was marketed until 1988 and from periodic safety reports concerning insulin human (rDNA) zinc suspension preparation marketed since 1988.

Post-marketing experience

An extensive post-marketing experience (more than 31 million patient years of exposure) has been gathered with human insulin since 1988 when the first genetically engineered human insulin was

marketed and no new concern regarding the safety of human insulin have been raised following assessment of postmarketing experience.

The most common spontaneously reported reactions are hyper- and hypoglycaemia, injection site reaction and –pain, therapeutic response decreased, allergic reaction and rash or pruritus.

Since the report from Teuscher and Berger (Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. Lancet 1987, ii.382-5) there had been focus on diminished awareness of hypoglycaemia after changing from animal insulin to human insulin. A review of clinical and epidemiological studies prepared by the applicant could not support this hypothesis, neither could an update of this paper including literature research up to May 1997 could either.

Two changes have been made in the summary of product characteristics for safety reasons: a more detailed description of the symptoms of hypo- and hyperglycaemia and a more detailed description of possible generalised hypersensitivity reactions. Apart from these amendments, no regulatory or manufacturer actions have been taken for safety reasons.

#### Discussion on clinical safety

Based on the review of the safety data from the extensive post marketing experience, no new safety issue to be included in the product information was identified. The most frequent adverse reactions are hypo-or hyperglycaemia. The safety profile of Ultratard is well characterised.

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications

### **Preclinical pharmacology and toxicology**

The toxic effects seen in the single dose and repeated dose toxicity studies were attributed to the hypoglycaemic activity and thus an exaggerated pharmacological effect caused by the high doses of the insulin. Increased weight, depressed activity, convulsions and death were some of these effects. No specific studies were conducted on toxicity of Ultratard (containing the recombinant human insulin), as the active component is similar to Actrapid (containing the recombinant human insulin). An increase in the number of benign mammary adenomas and fibroadenomas has been shown in Sprague Dawley rats. In one 12 months study, there was a statistically significant increase of female animals bearing benign and malign mammary gland tumours at the highest dose. It is concluded that the increased incidence of mammary tumours seen in rats is probably caused by mitogenic and growth-promoting action via the insulin receptor, but is probably also related to the fact that Sprague Dawley rats are especially sensitive and were given large doses. It is concluded that newer studies conducted since the original marketing authorisation for insulin human support the older documentation and do not give reason for new safety concerns.

### **Efficacy**

The treatment of diabetes mellitus with insulin has been established for many decades. It is a life saving treatment for patients with type 1 diabetes and is required by many patients with type 2 diabetes

A number of different insulin regimens have been proposed for treatment of diabetes. It is generally accepted that the so-called basal-bolus insulin regimen (one or two injections of long-acting insulin covering basal insulin requirements in combination with generally three injections of fast-acting insulin to cover meal-related insulin requirements) generally yields the best glycaemic control in diabetes. However a number of patients, especially patients with type 2 diabetes can be adequately

regulated by twice daily injections of long acting insulin with or without concomitant injection of soluble insulin.

The addition of zinc ions in Ultratard leads to a change in the pharmacokinetic properties whereby Ultratard becomes a very long-acting, insulin which is usually injected once daily as basal insulin in the basal-bolus regimen. Injections of Ultratard as part of the conventional regimen, as monotherapy or in combination with oral hypoglycaemic agents in type 2 diabetes patients belong as well to the scope of its administration. The long acting effect of Ultratard was addressed in several publications (concerning both type 1 and type 2 diabetes patients) which support Ultratards expected efficacy.

### **Safety**

Based on the review of the safety data from the vast post marketing experience, no new safety issues were revealed that should be included in the present SmPC. The most frequent adverse reactions are hypo- or hyperglycaemia. The safety profile of Ultratard is well described and acceptable.

### **Benefit/risk assessment**

Based on the submitted documentation on pharmacodynamic, pharmacokinetic and clinical data as well as the well-established use of Ultratard, the efficacy and safety of Ultratard is considered adequately demonstrated.

### **Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Ultratard in the treatment of diabetes mellitus was favourable.