

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Monotard. 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.

This application seeks marketing authorisation for human insulin for the treatment of patients with diabetes mellitus. The active substance of Monotard is human insulin manufactured by recombinant DNA technology in *Saccharomyces cerevisiae*. The formulation is a neutral suspension designed for long duration of action.

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

Monotard 40 IU/ml, 10ml vial  
Monotard 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) and amorphous insulin at neutral pH. The ratio of crystalline to amorphous insulin is 7:3. The formulation contains the following agents for functions as follows: zinc (protracting agent – stabilizes the crystals and amorphous insulin), sodium chloride (isotonic), sodium acetate (buffer) and methyl para-hydroxybenzoate (preservative).

Monotard 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 isoprene/bromobutyl 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 Monotard, insulin human (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 storage temperature.

#### **Other ingredients**

All excipients comply with Ph.Eur. specifications.

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

##### *Development Pharmaceutics*

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*

Crystalline and amorphous fractions are prepared separately. The amorphous fraction is then transferred to the crystalline fraction resulting in a formulated bulk.

#### Crystalline fraction

Insulin and buffer solutions are made separately and sterilized by filtration before mixing. The mixture is then seeded with insulin microcrystals and allowed to crystallise. After crystallisation sterile solutions containing zinc, preservative and base are combined with the sterile crystal suspension to form the crystalline fraction.

#### Amorphous fraction

Solutions containing preservative, insulin and buffer are prepared separately and combined with stirring. The resultant solution is sterile filtered into a pressure tank and sterile filtered zinc solution added resulting in the formation of an amorphous precipitate of insulin.

#### Formulated bulk

The amorphous fraction is transferred into the filling tank holding the crystalline fraction, and the mixed formulated bulk is filled aseptically 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 Monotard products manufactured at the approved sites and in different batch sizes. Available data show a consistent, well-controlled manufacturing process.

Monotard complies with the requirements of the following Ph.Eur. Monographs:

01/2002:0854 Insulin Preparations, Injectable

1999:0837 Insulin Zinc Injectable Suspension

In addition to monograph tests the products are tested by in-house methods for crystal size, identity 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 each presentation. All batches comply with their respective specifications.

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

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

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 crystalline fraction. L-threonine is sourced from avian feathers and porcine gelatine, trypsin from porcine pancreas, and bovine insulin from bovine pancreas.

Peptidase 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 Monotard 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**

Monotard is a neutral suspension of the intermediate acting amorphous (30%) and the long acting crystalline (70%) human insulin. The addition of zinc provides the basis of the protracting principle. The preclinical evaluation of the present product is based on the documentation for the active ingredient insulin human. The programme includes recent studies performed with the insulin analogue insulin aspart. In several of these studies, insulin human was used as a reference substance.

#### **Pharmacodynamics**

- **Primary pharmacology programme.**

The programme includes studies performed in the eighties demonstrating the similarity between insulin human and semi-synthetic insulin human, later studies supplementing above studies and recent studies where insulin human 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.

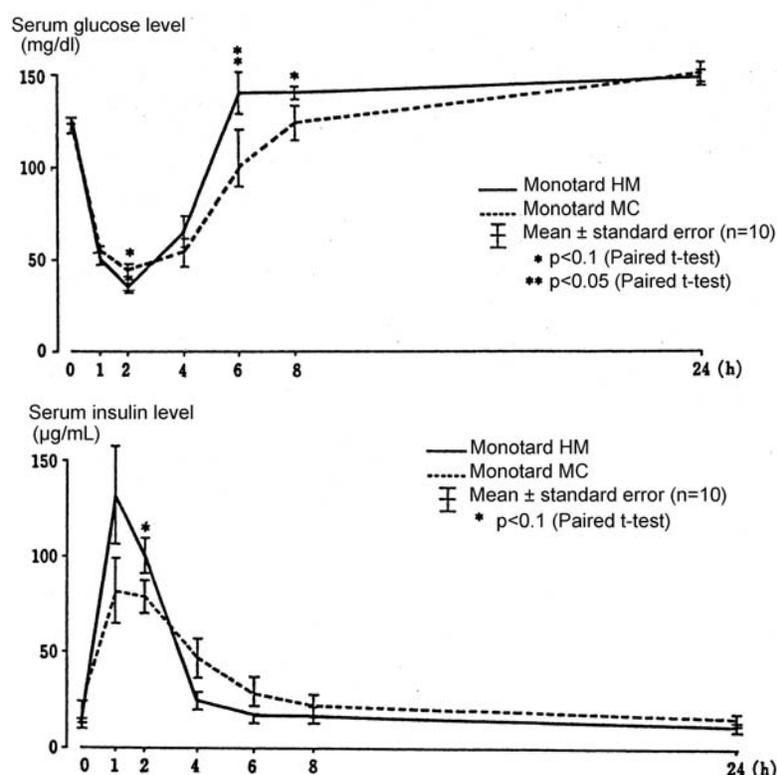
### **Pharmacokinetics**

No specific pharmacokinetic studies on zinc insulin human have been carried out. The semi-synthetic Monotard® has been compared to other insulin products in a standard crossover design (British Pharm., 1980). Monotard preparations showed a significant prolonged hypoglycaemic effect compared to pork insulin MC. There were no significant difference between the product Monotard containing the human insulin and the product Monotard containing the porcine insulin.

In a recent study, semi-synthetic insulin and zinc suspended semi-synthetic insulin were compared with their porcine MC counterparts (Nonaka *et al.*, 1997). Groups of six male fasted rabbits received a subcutaneous injection (0.5 U/kg) of either insulin human, Monotard HM or the corresponding porcine insulin MC product. After dosing with insulin human, blood was sampled at a shorter schedule; therefore the results were not statistically comparable with Monotard.

The serum glucose profile of Monotard HM versus Monotard MC (see Figure 1 below) resembles the above study until 6 hours except from a small significant difference after 2 hours in the later study ( $p < 0.1$ ). A significant difference between 6 and 8 hours after dosing has been found ( $p < 0.05$  and  $p < 0.1$ ). However an ANOVA did not show any difference between the products. Except from a low significant difference after 2 hours ( $p > 0.1$ ), the RIA and  $\Delta$ RIA values of serum insulin after administration of either HM and MC products were similar (see Figure 1 below). There were no overall significant differences between the two Monotard products when serum insulin levels were analysed using ANOVA. Some basic pharmacokinetic parameters were calculated and listed in Table 2 below.

**Figure 1: Serum levels of glucose and insulin after injection of Monotard (semi-synthetic insulin) compared to Monotard MC in the Rabbit.**



Some basic pharmacokinetic parameters were calculated and listed in Table 2 below.

**Table 2: Pharmacokinetic parameters**

Parameter	Monotard		Fast acting insulin human (rDNA)			
	Man	Rabbit (3) 0.5 U/kg	Man 022/UK 0.1 U/kg	Rabbit (3) 0.5 U/kg	Dog NN 960548 1U/kg	Rat NN 960550 6U/kg
$t_{1/2}$ (min)	540 <sup>(1)</sup>	512	122	144	57	23
$C_{max}$ (pM)	-	874	102	761	2871	18000
$t_{max}$ (min)	180 <sup>(2)</sup>	90	145	60	60	15

<sup>(1)</sup> Hildebrandt *et al.* 1984.

<sup>(2)</sup> Bilo *et al.* 1987.

<sup>(3)</sup> Nonaka *et al.* 1997.

## **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 insulin semi-synthetic 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.

No specific studies on the immunogenicity of administration of zinc insulins to laboratory animals have been carried out. However Monotard, insulin human, is based on the highly purified mono component insulin human and hence expected to have a very low immunogenic potential.

- **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 original studies for primary and secondary pharmacodynamics was to demonstrate the similarity between the new insulin human and marketed semi synthetic insulin. Effects seen in the original and newer 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.

No specific safety pharmacology studies on Monotard have been carried out. Effects seen in the original and newer safety pharmacology studies on insulin human can all be related to hypoglycaemia.

No specific studies were conducted on toxicity of Monotard, as the active component is insulin human. The toxic effects seen in the single dose and repeated dose toxicity studies of insulin human 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. 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-acting or 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 (intermediate) long-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 (intermediate) long-acting insulins or mixtures of fast-acting and (intermediate) long-acting insulins. Although this regimen may not offer optimal glycaemic control, patient compliance is generally 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

### **Clinical pharmacology**

Four pharmacodynamic and pharmacokinetic studies (Table 3) have been listed as important references by the clinical expert: three in healthy subjects and one in type 1 diabetic patients. The last study is primarily a pharmacokinetic study.

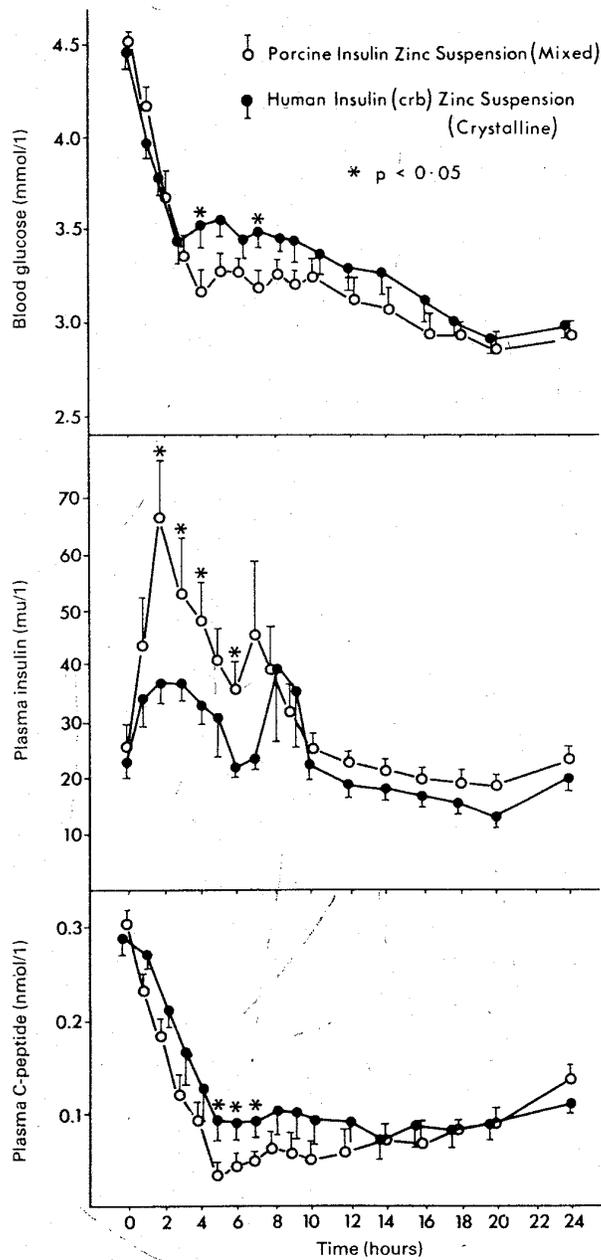
**Table 3: Clinical pharmacodynamic trials**

<b>Study</b>	<b>Population (Number of subjects)</b>	<b>Design</b>	<b>Dose regimens</b>
Frier <i>et al.</i> 1984	Healthy males (10 subjects)	Randomised, cross-over, single-dose, single-centre	One single dose of Monotard, human insulin zinc suspension crystalline 0.2 U/kg and Monotard MC (highly purified porcine insulin zinc suspension) 0.2 U/kg.
Bilo <i>et al.</i> 1987	Healthy males (8 subjects)	Randomised, cross-over, single-dose, single-centre	One single dose of human insulin NPH (3 different formulations), human insulin zinc (two different formulations). All doses 0.33 IU/kg.
Owens 1986	Healthy males (6 subjects)	Randomised, cross-over, single-dose, single-centre	Monotard (human insulin zinc) 0.1, 0.15 and 0.3 U/kg and porcine insulin zinc 0.1, 0.15 and 0.3 U/kg.
Hildebrandt <i>et al.</i> 1984	Male and female patients with insulin- dependent diabetes (9 subjects)	Single-dose, single-centre	125-I labelled Monotard (human insulin zinc) 6, 12, 24 and 36 U.

### **Pharmacodynamics in healthy subjects**

The first study (**Frier *et al.***) compared the pharmacodynamic and pharmacokinetic properties of human insulin zinc suspension crystalline and Monotard MC (highly purified porcine insulin zinc suspension). In a randomised cross-over study ten healthy non-obese fasting male subjects received a subcutaneous injection in the anterior abdominal wall of either insulin product. The dose was 0.2 U/kg. Blood glucose, plasma insulin and plasma C-peptide levels were obtained prior to drug administration and for a 24-hour period following injection.

**Figure 2: Mean (SEM) blood glucose, plasma insulin and plasma C-peptide following injection of either human insulin zinc suspension crystalline or highly purified porcine insulin zinc suspension (e.g. Monotard MC).**



The decrease in blood glucose was similar from 0 to 3 hours, but at 4 and 7 hours, blood glucose was significantly lower after porcine insulin injection. The nadir occurred at 20 hours, and the blood glucose had not returned to baseline at 24 hours. With regard to plasma C-peptide, nadir was reached at 5 hours for both insulin types. Mean concentrations were significantly lower following porcine insulin injection at several time points. It appears from the figures that the blood glucose lowering effects are quite similar. The hypoglycaemic action starts within 1-2 hours and lasts for at least 24 hours.

In this study, the porcine insulin zinc suspension (Monotard MC) was not compared with the equivalent human insulin Monotard, but with a human insulin zinc suspension product which is entirely crystalline in its formulation.

The second study (**Bilo *et al.***) investigated the pharmacodynamic and the pharmacokinetic properties of five different intermediate-long acting human insulins. Eight healthy non-obese, fasting male subjects received a subcutaneous injection in the front of the thigh with the five insulin products in random order. The dose administered to these subjects was 0.33 U/kg. For each subject the injections were separated by at least one week. Blood glucose levels were maintained at fasting level for an 8-hour period by a manual euglycaemic clamp, to prevent endogenous insulin secretion. Blood glucose, plasma insulin and plasma C-peptide levels were obtained prior to drug administration and for the 8-hour period following injection.

The mean plasma C-peptide remained below fasting concentrations. The glucose requirement from 0-2 hours was statistically significantly higher after administration of the NPH insulins compared to the zinc insulins (including Monotard, insulin human). Due to the short observation time, the duration of action could not be assessed. From this study it appears that the NPH insulin types have a more pronounced action during the first hours after injection than the zinc insulin types.

The third study (**Owens**) compared the pharmacodynamic properties of two products (Monotard) containing respectively porcine and human insulin in six healthy male patients. All subjects were given three doses of each insulin type on different days. The doses were 0.1, 0.15 and 0.3 U/kg given as subcutaneous injections in the anterior abdominal wall. The study also included a control day with no treatment. Blood glucose, plasma insulin and plasma C-peptide levels were obtained prior to drug administration and for 11 hours following injection. Both insulin types resulted in a hypoglycaemic response that started within the first 1-2 hours and reached maximum after about 4 hours. For the rest of the 11-hour study period, the response remained stable for the 0.15 and 0.3 U/kg dose levels, and there was only a moderate recovery towards normoglycaemia for the 0.1 U/kg dose.

From this study it seems that the maximum effect is reached about 4 hours after injection. In the only study where subjects were monitored over a period of 24h (Frier *et al.*), neither blood glucose nor C-peptide had returned to baseline levels at 24h.

#### Pharmacokinetics

Pharmacokinetic data were obtained from the four studies performed in young healthy subjects and insulin-dependent diabetic patients (see table 3).

- **Absorption and bioavailability**

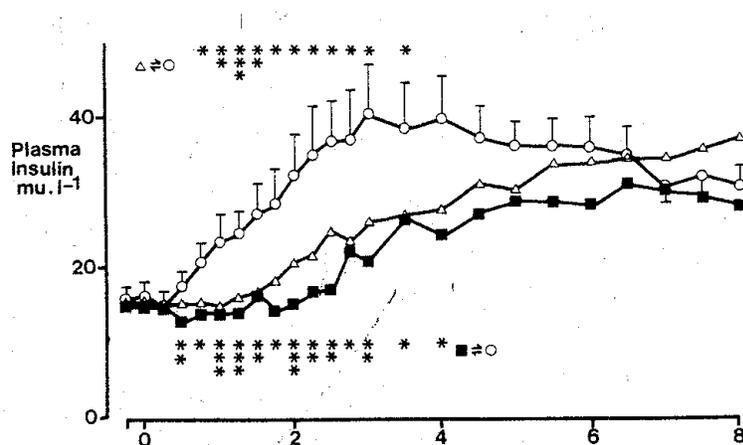
Hildebrandt *et al.* studied the absorption of Monotard, insulin human, at different dose levels in nine insulin-dependent diabetic patients with a mean age of 40.7 years. The doses were 6, 12, 24 and 36 U administered subcutaneously in each subject on four consecutive days, alternating between the thighs. The insulin used was 125-I labelled. The disappearance from the subcutaneous depot was measured externally by gamma counters.

A dose-dependent absorption was found with significantly decreasing absorption rates of increasing doses. The times for half of the initial activity to disappear were 9.0 h (6 U), 8.9 h (12 U), 10.9 h (24 U) and 14.8 h (36 U).

A biphasic pattern was seen in the insulin concentration-time profile for both porcine zinc insulin (Monotard MC) and the human zinc insulin in the study performed by Frier *et al.*. In the second study (Bilo *et al.*) insulin levels were measured following injection of five different insulins. After Monotard, insulin human, injection insulin levels were observed to increase about two hours after injection (Figure 3).

Figure 3:

Plasma insulin concentrations Monotard insulin human ( $\Delta$ ) (From Bilo et al.)#



Owens measured the plasma insulin levels reached after the administration of human zinc insulin (Monotard, insulin human) and porcine zinc insulin (Monotard MC). At the two lower dose levels, maximum insulin concentrations were seen 2.5-5 h after injection, followed by a gradual fall over the remaining period. At the high dose level, insulin levels reached a plateau about three hours after injection and started to fall only at the end of the study period.

- **Distribution**

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

- **Elimination**

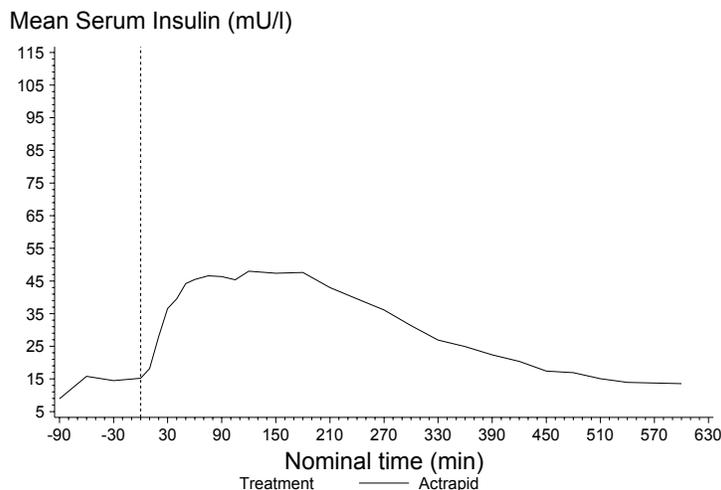
*Metabolism*

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*

The terminal half-life of insulin following a subcutaneous administration is determined by the rate of absorption from the subcutaneous tissue since the half-life in the blood stream is very short (only a few minutes). The mean terminal half-life for insulin human is 220 minutes.

Figure 4: Pharmacokinetic profile of Actrapid, insulin human



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- **Pharmacokinetics in the target population**

*Diabetic patients*

In study **024/UK** the pharmacokinetic profile of insulin human in type 1 diabetic patients was shown to be similar to the pharmacokinetic profile in healthy volunteers.

When insulin human was injected 30 minutes before a meal  $T_{max}$  was 80 minutes whereas it was reached after 97 minutes when insulin human was administered at mealttime. The maximum concentration ( $C_{max}$ ) was 36 mU/l when injected at meal and 39.9 mU/l when injected 30 minutes before meal. The half-lives for insulin human measured after the different times of administration were equal to 169 and 193 minutes respectively.

- **Pharmacokinetics in special population**

*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.

*Pharmacokinetics in children.*

No specific study performed with Monotard has been conducted in children.

- **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.

It is well established that phosphate-buffered insulin types should never be mixed with Monotard. In such case, the phosphate precipitates the zinc liberating the zinc insulin to the free form (White *et al.*, 1991 and others). This physicochemical interaction may induce severe hypoglycaemic episodes.

Finally, **Klauser *et al.* 1988** studied the pharmacodynamics effects and pharmacokinetics parameters observed after the injection of different types of insulin, either injected separately or mixed in the same injection. Eight type 1 diabetic patients received four different subcutaneously injected preparations of human insulin: Monotard and insulin human (soluble fast-acting human insulin) as separate injections, Monotard and insulin human as mixture, NPH-insulin and insulin human as separate injections, and NPH-insulin and insulin human as mixture. The dose administered was 0.4 U/kg (two thirds intermediate- or long-acting and one third fast-acting insulin).

After administration of the insulins, euglycaemia was maintained by infusion of glucose. The glucose infusion rate was significantly lower following administration of Monotard and fast-acting insulin human as mixture compared with the same insulins given as separate injections. The same applied to the free insulin levels. There were no statistically significant differences between the two NPH-insulin/insulin human injection procedures. Other authors have found similar results (e.g. Olsson *et al.* 1987 and Heine *et al.* 1984).

- **Conclusion on pharmacokinetic studies.**

Monotard is a long-acting human insulin. It is a zinc suspension, which consists of a mixture of amorphous (30%) and crystalline (70%) particles. The documentation of the time aspects of the pharmacodynamics of Monotard is quite sparse. Onset of action is within 2½ h, and the peak effect is reached after about 4 hours or later. The duration of action is poorly documented, but probably about 24h.

No specific pharmacodynamic/kinetic data concerning Monotard are available with regard to the effect of age, gender, ethnic origin, hepatic and renal impairment. Like with all subcutaneously injected insulins, the terminal elimination half-life is determined by absorption rather than elimination. The terminal elimination half-life of Monotard 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. An important physicochemical incompatibility exists with phosphate-buffered insulin types. These products should never be mixed with Monotard as the phosphate will precipitate the zinc in Monotard liberating the zinc insulin to the free form. In addition, mixing Monotard with fast-acting soluble human insulin may decrease the rate of absorption of the fast-acting insulin.

### **Clinical efficacy**

Main study (phase III = therapeutic confirmatory trials).

*Studies performed in type 1 diabetic patients.*

- **Renner et al. unpublished.**

The first study (**Renner et al. unpublished**) was a double-blind randomised multicentre cross-over trial. This study was aimed at comparing the effect on nocturnal glucose regulation of a bedtime injection of Monotard with the effect observed with a porcine zinc insulin in type 1 diabetes patients on intensified insulin therapy (with NPH insulin failure). The treatment periods lasted 3 weeks each.

The primary efficacy parameters were fasting blood glucose values (FBG) and area under the blood glucose concentration-time curve (AUC) between 10 p.m. and 8 a.m. It had been planned to include 68 patients into the trial, 101 were randomised, 71 were evaluable for efficacy.

As regards fasting blood glucose, a significant difference was noted between the treatment groups ( $p < 0.001$ ). A lower fasting blood glucose ( $162 \text{ mg/dl} \pm 72$ ) has been achieved after a treatment with the porcine zinc insulin group as compared to the human zinc insulin group ( $207 \text{ mg/dl} \pm 83$ ). With regards to areas under the nocturnal blood glucose concentration-time curve an advantage for the porcine insulin was observed. The frequency of hypoglycaemic reactions and daily insulin doses were similar. Adverse events occurred with a slightly lower frequency with Monotard.

- **Tunnbridge et al. 1989.**

The second study (**Tunnbridge et al. 1989**) compared the effect of Monotard and a long-acting protracted insulin (a formulation consisting of a suspension of crystalline (rhombohedral) insulin at neutral pH) 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 the long-acting protracted insulin regimen was significantly lower than with the Monotard 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 Monotard, see Tunnbridge et al. 1989 below). Overall blood glucose control, fructosamine and HbA<sub>1c</sub> were similar for both treatments. The evening dose of the long-acting protracted insulin was slightly but significantly lower than the evening Monotard dose ( $14.9 \pm 0.8$  vs.  $15.5 \pm 0.8$  IU) confirming the lowering effect of the long-acting protracted insulin on fasting blood glucose. However, the incidence of serious hypoglycaemic effects was significantly higher with the long-acting protracted insulin compared to Monotard, with the majority of nocturnal events occurring between 5 a.m. and breakfast.

- **Tunnbridge et al. 1989.**

Another double-blind randomised cross-over study by **Tunnbridge et al. 1989** compared the metabolic control achieved after a twice daily administration of insulin NPH or Monotard given together with fast-acting soluble human insulin. Eighty-nine patients participated in the study (82 completed it). Each of the two treatment periods lasted 5 months.

Fasting blood glucose did not differ between the two regimens; neither did blood glucose concentrations at any time point. In addition HbA<sub>1c</sub>, fructosamine, insulin dose and frequency of hypoglycaemia were similar for both treatments.

- **Mellvig et al. 1990.**

A fourth study (**Mellvig et al. 1990**) compared the metabolic control and the glucose profiles obtained after the administration of Monotard or a long-acting protracted insulin administered as basal insulin at bedtime in a basal bolus regimen in 15 diabetic adolescents aged 12-19. 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 (10.8mmol/l for Monotard) but on the other hand, HbA<sub>1c</sub> decreased significantly during the study period. The insulin dose tended to increase when the conventional regimen was replaced by the multiple injections regimen, and 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 Monotard in comparison with the long acting protracted insulin (but the difference was not found to be significant).

- **Martina et al. 1989.**

A final study performed in type 1 diabetic patients (**Martina et al. 1989**) compared the metabolic control obtained after a treatment with a long-acting protracted insulin and Monotard. Sixteen type 1 diabetic patients were given either the long-acting protracted insulin or Monotard at bedtime and human insulin at lunch and dinner. The insulin injection regimen was adjusted for the Italian meal pattern with high caloric intake at lunch and at dinner. After a treatment period of 8 weeks with either the long acting protracted insulin or Monotard as basal insulin the subjects were switched over to the other basal insulin treatment for another 8 weeks. No differences between the treatments were revealed for blood glucose profiles, fructosamine, HbA<sub>1c</sub>, and insulin dose. No safety data are reported in this publication.

*Studies performed in type 2 diabetic patients.*

**Sane et al. 1992** investigated in an open uncontrolled study the 1 year metabolic control obtained after the administration of either Monotard or a long acting protracted insulin in combination to oral hypoglycaemic agents in type 2 diabetic patients. Seventeen type 2 diabetes patients poorly controlled on oral therapy have been enrolled in the study. The endpoints used in this study to assess the metabolic control were fasting blood glucose, diurnal blood glucose and HbA<sub>1c</sub>. Metabolic control was significantly improved with both Monotard and the long-acting protracted insulin at 3 and 12 months of therapy (the difference was not found to be significant). No severe hypoglycaemic episodes occurred.

#### 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 issue resulting in a relatively slow absorption. Fast/rapid-acting insulin human may be given intravenously (e.g. in diabetic ketoacidosis) and intramuscularly but is predominantly administered subcutaneously. Monotard 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.)

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 publications support the efficacy of Monotard both regarding the use in a conventional twice daily regimen as well as its use as basal insulin in the basal bolus regimen and confirm its pharmacokinetic properties.

### **Clinical safety**

The data concerning the safety profile of Monotard have been obtained from the published efficacy studies mainly including data on Monotard containing semi-synthetic human insulin, which was marketed until 1988 and from periodic safety reports concerning Monotard containing insulin human (rDNA) 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. Two periodic safety update reports (PSURs) covering the period from March 1993 to end of June 2000 have been assessed.

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.

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

During the reporting period, 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 Monotard 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 active constituent of Monotard is insulin human manufactured by recombinant DNA technology. Monotard is a neutral suspension of the intermediate acting amorphous (30%) and the long acting crystalline (70%) human insulin. Newer studies support the conclusion from the original ones that insulin human and insulin semi-synthetic have identical blood sugar lowering effect. No specific safety studies on zinc insulin human were carried out. Effects seen in the original and newer safety pharmacology studies on insulin human can all be related to hypoglycaemia.

There was no conduct of specific toxicology studies for Monotard, the studies reported are those for insulin human. The toxic effects seen in the single dose and repeated dose toxicity studies were attributed to the hypoglycaemic activity. 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. 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. 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**

Monotard is a long-acting human insulin. 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 regime (one or two injections of NPH insulin covering basal insulin requirements in combination with 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 fast-acting soluble insulin. Monotard has been authorised for many years and its use is well-established. The provided publications support of the efficacy of Monotard both regarding the use in a conventional twice daily regimen as well as its use as basal insulin in the basal bolus regimen and confirm its pharmacokinetic properties.

### **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 summary of product characteristics. The most frequent adverse reactions are hypo-or hyperglycaemia. The safety profile of Insulatard is well characterised and acceptable.

### **Benefit/risk assessment**

Based on the submitted documentation on pharmacodynamic, pharmacokinetic and clinical data as well as the well-established use of Monotard, the efficacy and safety of Monotard 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 Monotard in the treatment of diabetes mellitus was favourable.