SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Actrapid. 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 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 ß 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 has been obtained for the treatment of patients with diabetes mellitus

The active substance of Actrapid is human insulin manufactured by recombinant DNA technology in Saccharomyces cerevisiae. The formulation is designed for fast/rapid onset of action.

Actrapid is intended for marketing in dose strengths of 40 IU/ml and 100 IU/ml and 6 different presentations, as follows:

Actrapid 40 IU/ml, 10ml vial
Actrapid 100 IU/ml, 10ml vial
Actrapid Penfill 100 IU/ml, 3ml
Actrapid InnoLet 100 IU/ml, 3ml
Actrapid NovoLet 100 IU/ml, 3ml
Actrapid FlexPen 100 IU/ml, 3ml

The Penfill presentation is a cartridge that is designed to be inserted in a durable device. The cartridges should only be used with devices and needles that are compatible with the Penfill products.

The InnoLet presentation is a multi-dose pre-filled pen delivering a maximum of 50 units per dose in increments of 1 unit. The device is equipped with an *end-of-content* mechanism that ensures that the adjusted dose does not exceed the remaining content of the 3 ml cartridge after multiple use. The device is targeted for use by geriatric patients with impaired dexterity and/or vision.

The NovoLet presentation is a multidose pre-filled pen delivering 2-78 units per dose in increments of 2 units.

The FlexPen presentation is also a multidose pre-filled pen delivering 1-60 units per dose in increments of 1 unit. For patients, the FlexPen device represents an improvement over the NovoLet device in terms of automatic zeroing and delivery of dose in single unit increments.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The formulation, designed for fast onset of action, is a neutral solution containing Human insulin (rDNA) as active ingredient and agents for functions as follows: zinc (stabilising), glycerol (isotonic) and metacresol (preservative).

Actrapid is presented in 10 ml vials, 3 ml cartridges (Penfill) and in multidose pre-filled pens (InnoLet, NovoLet and FlexPen). Two strengths exist in vial presentations: 100 IU/ml and 40 IU/ml. Only one strength exists in the other presentations: 100 IU/ml. All 100 IU/ml presentations have identical compositions.

The 10 ml vial is a glass container with a laminated rubber stopper (disc) and snap-off cap. The glass container is produced from type I Ph.Eur. colourless glass.

The Penfill cartridges consist of a 3 ml type I Ph.Eur., colourless glass cartridge sealed with a laminated rubber stopper and a rubber plunger.

InnoLet, NovoLet and FlexPen are multidose pre-filled pens made of a plastic injector device fitted with 3 ml Penfill cartridges.

Active substance

The active substance of Actrapid, 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 amino acid chain insulin precursor attached to a pre-pro leader region of the yeast mating factor (MFα1) gene. The plasmid is constructed based on the yeast 2μ plasmid.

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 that human insulin rDNA has been manufactured by the applicant 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 ingredients conform to Ph.Eur. apart from metacresol (no monograph in Ph.Eur.), which conforms to USP.

Product development and finished product

Development Pharmaceutics

The Actrapid formulation is a sterile multi dose neutral aqueous solution. It is produced in two strengths (100 IU/ml and 40 IU/ml) as explained under

Composition.

Like for other insulin products, components with the purpose of assuring appropriate isotonic, preservative and stabilizing properties have been added.

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 1960's. The present formulation was developed in connection with the switchover from animal to semi synthetic human insulin in the early 1980's and fine-tuned in the late 1980's with an improved antimicrobial preservative efficacy system. There have been no changes to the formulation since then.

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 product is prepared by mixing a number of solutions. The solutions are sterile filtered into a filling tank. Filling occurs in a grade A zone and vials and cartridges are inspected individually by manual or automated inspection. Pen injector products are assembled thereafter.

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 the product, 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 various Actrapid products manufactured at various approved sites and in different batch sizes. Available data show a consistent, well-controlled manufacturing process.

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

- 1999:0854 Insulin Preparations, Injectable
- 1997:0834 Insulin Injection, Soluble

In addition to monograph tests the products are tested by in-house methods for identity and content of preservative and for dose accuracy (pre-filled injector products only).

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, presentations and production sites for Actrapid.

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, and L-threonine and trypsin used in the purification process to convert human insulin precursor to human insulin methyl ester.

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.

L-threonine is sourced from avian feathers and porcine gelatine and trypsin from porcine pancreas.

The risk of transmission of TSE from Actrapid 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 is 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 Part III: Toxico-pharmacological aspects

The preclinical evaluation of the present product is based on the documentation for the active ingredient; insulin human (rDNA). The programme includes recent studies performed with the insulin analogue insulin aspart. In several of these studies, were insulin human (rDNA) 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 bromsulphtalein-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	$t_{½}$ (min)	122	121	57	23
	C_{max} (pM)	102	122	2871	18000
	T_{max} (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_{max}, 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_1 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 that 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 β-cells. Although the rate of β-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 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.

Clinical pharmacology

Seven different studies are supporting the pharmacodynamics of Actrapid. Four of those were conducted in healthy subjects, two studies in type 1 diabetics (including one performed in children/adolescents) and one trial has been conducted in type 2 diabetics patients. These studies are recent studies performed with the rapid acting insulin analogue insulin aspart in which Actrapid, human insulin was used as a comparator (see table 3 below).

Table 3: Clinical pharmacology trials

Studies	Population (Number of subjects)	Design	Objectives
022, 023, 026 and 027 – clamp trials	**Healthy volunteers** 022: 25 subjects 023: 24 subjects 026: 20 subjects 027: 20 subjects.	Randomised, double blind 2 period cross-over (022 and 023) 6-period cross-over (026) Parallel group (027).	022: To compare the plasma profile of rapid acting insulin aspart with that of human insulin (i.e. Actrapid) 023: To compare the pharmacokinetics and pharmacodynamic response to a single dose of rapid acting insulin aspart with that of Actrapid, human insulin by means of euglycaemic clamp. 026: To compare the pharmacokinetic profiles and the pharmacodynamic response to single doses of rapid acting insulin aspart and Actrapid,human insulin injected SC using three different injection sites during an euglycaemic clamp. To compare these profiles with profiles of Actrapid, human insulin injected at the same sites. 027: Primary: To investigate the intra-subject variation in the time action profile after four independent injections with either rapid acting insulin aspart or Actrapid, human insulin. Secondary: To investigate inter-subject variations.
024 and 043 – children and adolescents	**Type 1 diabetic patients** 024: 24 subjects. 043: 18 subjects.	Randomised double blind 3-period cross-over (024). Randomised double blind 2-period cross-over meal test (043).	024:To compare the postprandial serum glucose profile of rapid acting insulin aspart when given at time t=0 min. to the postprandial plasma glucose profile of Actrapid, human insulin when give at time t=0 min and t=30 min in relation to the standard meal. 043: Primary: To compare the pharmacokinetics of rapid acting insulin aspart with Actrapid, human insulin in paediatric type 1 diabetic subjects to verify that the pharmacokinetic differences observed in adults also apply to children. Secondary: To compare the postprandial serum glucose profiles of rapid acting insulin aspart with those of Actrapid.
030	**Type 2 diabetic patients** 25 subjects.	Randomised double blind 3-period cross-over.	To compare the postprandial serum glucose profile of rapid acting insulin aspart when given at time t=0 min to the postprandial plasma glucose profile of Actrapid, insulin human when given at time t=0min and t=30 min in relation to the standard meal.

Pharmacodynamics in healthy subjects

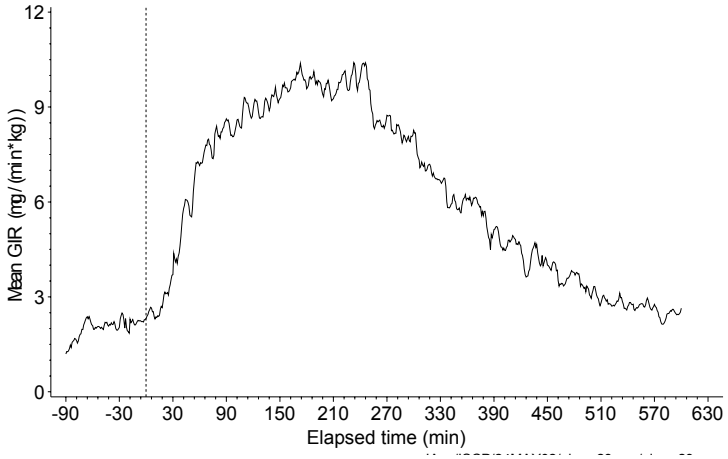
The study **ANA/DCD/022/UK** (also denoted by 022/UK) was aimed at comparing the plasma insulin profile of a single dose of rapid acting insulin aspart with that of Actrapid, insulin human in healthy volunteers. Plasma glucose, plasma insulin and C-peptide profiles after a single dose of 0.1 U/kg of rapid acting insulin aspart and Actrapid, insulin human injected subcutaneously in the abdominal wall were compared in 24 healthy male subjects. Other endpoints were the mean residence time for insulin (denoted by $MRT_{(ins)}$), the area under the serum glucose concentration to time curve denoted by $AUC_{(BG)}$, the

maximum change from baseline to minimum concentration $\Delta C_{min(BG)}$ and $T_{min(BG)}$ derived from plasma glucose profiles in an interval from 0-480 minutes, as well as $C_{max(ins)}$, $T_{max(ins)}$, and $AUC_{(ins)}$ [respectively highest insulin(s) concentration measured in the plasma, the time when this highest concentration was observed and the area under the plasma insulin(s) concentration-time curve] derived from the serum insulin profiles in an interval from 0-480 minutes.

The results of the study show that $AUC_{(BG)}$ was 435.8 (131.4) min.mmmol/l, $\Delta Cmin_{(BG)}$ was 1.4 (0.4) mmol/l and $T_{min(BG)}$ was 226.4 (119.6) min.

The study **023/D** is a two period double-blind randomised cross-over trial to compare the pharmacodynamic response to a single dose of rapid acting insulin aspart with that of Actrapid, insulin human in healthy volunteers during a euglycaemic clamp. The pharmacodynamic response to a single dose of 0.2 U/kg insulin aspart and Actrapid, insulin human respectively, injected SC in the abdominal wall, was compared in 24 male healthy subjects. The primary endpoints, derived from the glucose infusion rate in the interval 0-600 minutes (glucose infusion rates profile) were AUC_{GIR}, GIR_{max}, T_{GIRmax}, $T_{AUC½}$ (time to half of the area under the glucose concentration-time curve, it reflects the median of the integrated glucose infusion rate profile). The secondary endpoints i.e. the area under the concentration-time curve (AUC_{ins}), the highest concentration observed in the plasma (C_{max}) and the time when it was observed (T_{max}), and the mean residence time (MRT) were derived from serum insulin profiles in the interval 0-600 minutes. The primary glucose endpoints were the following (expressed in means with SD in brackets) for Actrapid AUC_{GIR} 3.7 (0.7) g/kg, GIR_{max} 12.1 (2.6) mg/(min x kg), T_{GIRmax} 180.8 (56.8) min, $T_{AUC½}$ 235.9 (23.4) min. Based on $T_{AUC½}$, the duration of action for Actrapid is approximately 8 hours. The maximum effect was obtained 3 hours after the injection.

Figure 1: Mean glucose infusion rates profiles for Actrapid, insulin human.



Study **026/US** was a six-period double-blind randomised cross-over trial aimed at comparing the action profile of rapid acting insulin aspart in healthy subjects using different injection sites during an euglycaemic clamp, and to compare rapid acting insulin aspart profiles with profiles of Actrapid, insulin human.

The primary efficacy endpoints were derived from the glucose infusion rates profiles in the time interval from 0-600 minutes. The primary efficacy endpoints were AUC_{GIR}, GIR_{max}, T_{GIRmax} and $T_{AUC½}$. The secondary endpoints were derived from the insulin profiles in the time interval 0-600 minutes: AUC_{ins}, C_{max}, T_{max}, and the mean residence time (MRT).

Table 4: The pharmacodynamic parameters for Actrapid, insulin human are displayed in the table below.

Injection site	Deltoid	Abdomen	Thigh
AUC (mg)	204519 (56189)	192010 (47896)	205773 (53704)
GIRmax (mg/min)	736 (243)	708 (204)	720 (229)
Tmax(min)	192 (51)	173 (62)	193 (60)
$T_{AUC½}$ (min)	243 (37)	235 (46)	243 (37)

Glucose infusion rates indicate a more rapid glucose lowering action when the insulin is injected in the abdomen than deltoid or thigh injection sites. The $T_{AUC½}$ and T_{max} after an injection in the abdomen were slightly shorter than after an injection in the deltoid or in the thigh. The total amount of glucose infused was less after an abdominal injection than for the other injection sites. The maximum glucose infusion rate was lower for abdomen than the other injection sites.

Study **026/US** was conducted in healthy volunteers but the results of the study can be extrapolated to the type 1 diabetic patients according to published studies (such comparison between SC injection in the abdomen or in the thigh has been published in "Effects of the anatomical region used for insulin injections on glycaemia in type 1 diabetes subjects. Bantle *et al.*, Diabetes care 1993; **16**(12):1592-7; and in the comparison between a subcutaneous injection in the abdomen or in thigh and intramuscular injection in thigh has also been done (see "Impact of injection sites for soluble insulin on glycaemic control in type 1 diabetic patients treated with a multiple insulin injection regimen. Henriksen *et al.*, Diabetologia 1993; **36**: 752-8"). As type 2 diabetic patients usually have a higher body mass index and a thicker subcutaneous tissue, especially thicker abdominal wall, this could explain why the absorption may be different.

Study **027/D** is a parallel randomised double-blind trial to investigate the intra-subject and inter-subject variations in action profiles after injection with rapid acting insulin aspart or Actrapid during a euglycaemic clamp. Four independent doses (0.2 U/kg) of either insulin aspart or Actrapid, insulin human were given in this euglycaemic clamp trial subcutaneously into the abdominal wall to 18 healthy male subjects. The primary endpoints derived from the glucose infusion rate and secondary endpoints were related to insulin in the time interval 0-600 minutes. Intra-subject variability and inter-subject variability were determined.

There is a considerable inter-subject variation of absorption and action characteristics of all known insulin preparations in normal subjects, and in particular in diabetic patients with different degrees of lipodystrophy. Moreover the most important in the daily clinical practice is the predictability of absorption and action characteristics of insulin from day-to-day in the individual patient, rather than the absolute predictability of absorption and action profile of the insulin preparation when administered to a patient. Therefore the intra-subject variability should preferably have been investigated in diabetic patients instead in healthy subjects.

Table 5: Pharmacodynamic parameters measured in healthy subjects [studies ANA/DCD/023/D, 026/USA and 027/D]. The medians (1st to 3rd quartile) are displayed for $T_{AUC½}$ and T_{GIRmax}.

Trial[a]	Actrapid N	AUC_{GIR} (g/kg)	GIR_{max} (mg/min kg)	$t_{AUC½}$	t_{GIRmax} (min)
023/D	24	3.7 (0.7)	12.1 (2.6)	237 (222-249)	182 (144-235)
026/USA	19	2.5 (0.6)	9.4 (2.7)	230 (209-273)	168 (136-212)
027/D	37[b]	3.6 (0.8)	13.0 (3.1)	234 (219-259)	187 (163-222)

AUC_{GIR} and GIR values are mean (SD). $t_{AUC1/2}$ and t_{GIRmax} are median (1st to 3rd quartile)

[a] In all three trials, the dose was 0.2 U/kg administered s.c. into the abdominal wall.

[b] There were 10 patients in the treatment group; N represents the total number of insulin profiles for all the patients for the 4 dosing days.

Pharmacodynamics in type 1 diabetic patients

The study **ANA/DCD/024/UK** compared the effects on postprandial glycaemic excursion of rapid acting insulin aspart given immediately before a test meal, with the excursion obtained after administration of Actrapid, insulin human given immediately before or 30 minutes before a test meal in type 1 diabetic patients [*Note: Postprandial glucose excursion is calculated by subtracting a fasting blood glucose level from the after meal value at the one or two hour points. Post- meal blood glucose excursions should be around 1.7–2.2 mM*].

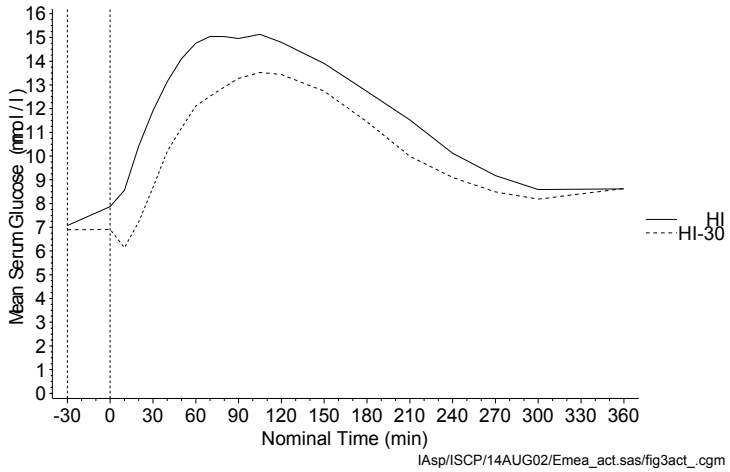
This trial compared the postprandial glycaemic excursions obtained after the injection of 0.15 U/kg insulin aspart immediately before a test meal to the effect obtained after a similar dose of insulin human given either immediately or 30 min before a standard test meal. Twenty two type 1 diabetic subjects were enrolled in the study. Blood glucose excursions were calculated and compared primarily over the period 0 to 240 min after the test meals. During this period, the total excursion of blood glucose denoted by $EXC_{(BG)}$ was lower after insulin human given 30 min prior to the meals. The $C_{max,\ glu}$ was lower when Actrapid was given 30 min before the meal and AUC_{ins} and C_{max}, ins were slightly higher when insulin human was administered 30 min before the meal.

The time when the maximum plasma insulin concentration was observed ($T_{max\ ins}$) was reached in half the time when Actrapid, insulin human was given 30 minutes before the meal compared to administration immediately before the meal. Therefore administration of Actrapid, insulin human 30 minutes before a meal is advantageous compared to administration of Actrapid, insulin human immediately before a meal with respect to postprandial blood glucose control. It has a lower maximum blood glucose concentration, which is consistent with a higher maximum insulin concentration, the maximum insulin concentration is reached faster.

Table 6: The main glucose pharmacodynamic data for the 0 to 240 minutes assessment period together with the main insulin pharmacokinetic data for the full 0 to 360 minutes study period are presented below.

EFFICACY RESULTS Primary blood glucose endpoint: Means (SD)			
	$EXC_{(BG)}$ (mmol/l x min)		
$Actrapid_{t=0(0-240min)}$	1311.36 (511.66)		
$Actrapid_{t=-30(0-240min)}$	1105.82 (571.35)		
Secondary blood glucose endpoints: Means (SD)			
	$C_{max(BG)}$ (mmol/l)	$C_{min(BG)}$ (mmol/l)	$T_{max(BG)}$ (min)
$Actrapid_{t=0(0-240min)}$	16.37 (3.37)	10.03 (3.53)	102.73 (49.90)
$Actrapid_{t=-30(0-240min)}$	14.45 (3.47)	9.10 (2.61)	121.14 (44.85)
Secondary insulin endpoints: Means (SD)			
	$AUC_{(ins)}$ (mU/l x min)	$MRT_{(ins)}$ (min)	
$Actrapid_{t=0(0-360min)}$	8820.64 (4932.83)	162.44 (18.76)	
$Actrapid_{t=-30(-30-330min)}$	9427.75 (4952.84)	122.55 (15.65)	
	$C_{max(ins)}$ (mU/l)	$T_{max(ins)}$ (min)	
$Actrapid_{t=0(0-360min)}$	35.86 (20.13)	100.68(44.86)	
$Actrapid_{t=-30(-30-330min)}$	39.89 (21.87)	55.23 61.79)	

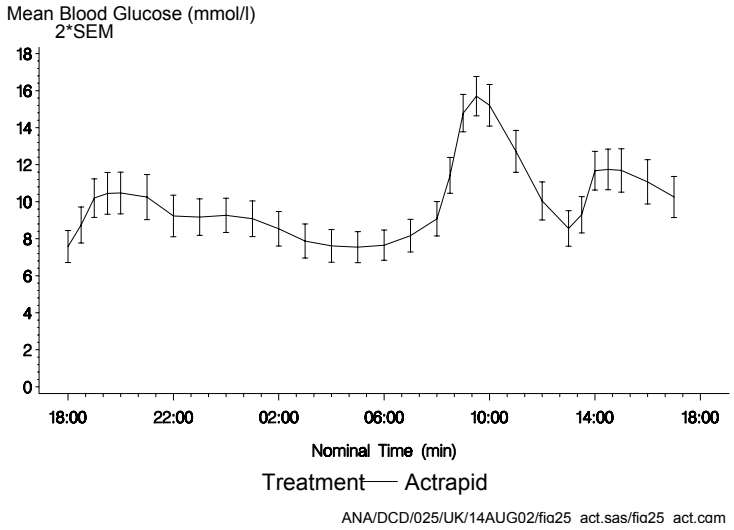
Figure 2: Mean glucose and insulin profiles during the full 0 to 360 minutes study periods. (HI = Actrapid, insulin human)



The study **025/UK** compared the metabolic control obtained with rapid acting insulin aspart, with the metabolic control obtained with Actrapid, insulin human in type 1 diabetic patients. One hundred and four adult patients with type 1 diabetes for at least 2 years and a HBA1c <9% were randomised in the study, 90 of them completed the trial. The treatment periods lasted 4 weeks each. Primary efficacy endpoint was fructosamine. Secondary endpoints were 23-hour in-patient plasma glucose profiles at the end of each treatment period, weekly 8-point blood glucose profiles, ratio of bolus to basal insulin. The safety profile was assessed with the incidence of hypoglycaemia.

The study demonstrated that the mean fructosamine levels after treatment with Actrapid, insulin human were (3.82 mM (0.56)).

Figure 3: 23 hour Mean Blood Glucose Profiles

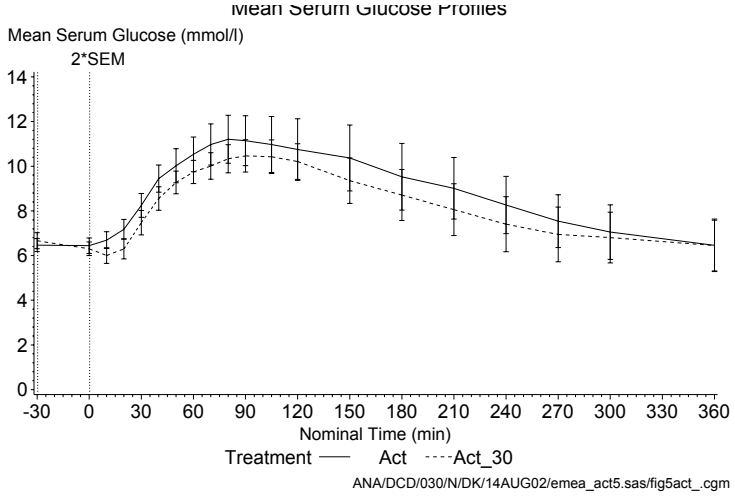


Pharmacodynamics in type 2 diabetic patients

Study **030/DK/N** compared the effects on postprandial glycaemic excursions of Actrapid given immediately before or 30 minutes and insulin aspart before a test meal in insulin treated type 2 diabetic patients.

Twenty-two subjects with type 2 diabetes were enrolled in this study. Euglycaemic clamps were performed overnight before each of the 3 study days. The primary endpoint was the glucose excursions determined during the period from 0 to 360 minutes after the insulin injections.

Figure 4: The mean serum glucose profiles shown below were observed with different treatments: Actrapid, insulin human administered either immediately before or 30 minutes before a test meal.



The mean glucose excursion measured with Actrapid, insulin human administered 30 minutes before the meal was 868 mmol/l x min (standard deviation = 374). The mean maximum glucose concentration for Actrapid, insulin human administered 30 minutes before the meal was (11.1 ± 1.8 mmol/l), it was slightly higher when Actrapid, insulin human was administered immediately before the test meal (12.0 ± 2.4 mmol/l). Mean C_{min} was comparable for the two treatments (6.3, and 6.6 mmol/l).

Overall, The blood glucose excursions in study 030/DK/N in type 2 diabetic patients appeared to be lower compared to the ones in type 1 diabetic patients as observed in study 024/UK. In both studies, the injection of Actrapid, insulin human 30 minutes before a meal was more favourable regarding the blood glucose excursions compared to injection immediately before the test meal.

The studies conducted in healthy volunteers, type 1 and type 2 diabetic patients mainly by using the euglycaemic clamp technique, confirm the glucose lowering action of Actrapid, insulin human. The studies performed in healthy subjects confirmed the time to onset, the duration of action and the time of the maximum effect. From the studies in diabetic subjects it can be concluded that the administration of insulin human 30 minutes before a meal (instead of directly before the meal) is more favourable as regards the total excursions of blood glucose concentrations.

Pharmacokinetics

- **Absorption and bioavailability**

Actrapid, insulin human and rapid acting insulin aspart were given subcutaneously at 0.1 U/kg in study 022/UK and 0.2 U/kg in studies 023/D and 027/D.

Table 7: The pharmacokinetics properties of insulin human have been explored in studies 022/UK, 023/D, and 027/D in healthy subjects (see tables, standard deviations from the means are indicated in brackets).

	C_{max} (mU/l)	T_{max} (min)[a]	MRT (min)	AUC (mU/lxh)[b]
022/UK	17.5 (4.3)	120 (15-360)	217 (30.3)	77.8 (13.9)
023/D	55.2 (8.5)	120 (30-270)	238 (21.7)	303 (31.7)
027/UK	46.5 (9.5)	150 (30-420)	240 (25.5)	251 (35)

a. median (range)
b: 0-8h in 022/UK, in the other studies 0-10h

The median T_{max} for Actrapid, insulin human was 120 min. Absorption from three different injection sites (abdomen, deltoid and thigh) was evaluated in study 026/USA and the absorption was found to be faster from the abdominal wall than after an injection in deltoid whereas the slowest absorption was observed after an administration in the thigh.

Table 8: Absorption from three different injection sites (abdomen, deltoid and thigh) from study 26/USA

Injection site	*Deltoid*	*Abdomen*	*Thigh*
AUC (pmol x min/l)	47013 (10469)	47362 (11881)	44171 (5294)
C_{max} (pmol/l)	220 (99)	227 (93)	188 (71)
T_{max}(min)	103 (74)	110 (64)	124 (75)
MRT (min)	198 (44)	186 (43)	198 (48)

- **Distribution**

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

- **Elimination**

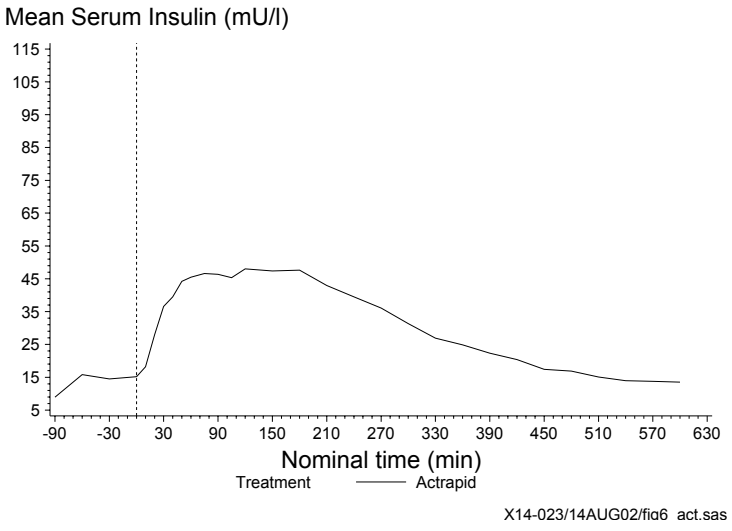
Metabolism

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 Actrapid, insulin human is 220 minutes.

Figure 5: Pharmacokinetic profile of Actrapid, insulin human



- **Pharmacokinetics in the target population**

Adult with type 1 diabetes

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

When Actrapid was injected 30 minutes before a meal T_{max} was 80 minutes whereas it was reached after 97 minutes when it was administered at mealtime. 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 Actrapid measured after the different times of administration were equal to 169 and 193 minutes respectively.

Children with type 1 diabetes.

Study **043/DK** compared the pharmacokinetics of rapid acting insulin aspart and Actrapid, insulin human in children with type 1 diabetes. This study was a single centre randomised double-blind cross-over trial.

Eighteen subjects were included half aged between 6 and 12 years old and half between 13 and 17 years old. The insulin was administered subcutaneously into the abdominal wall immediately before breakfast at 0.15IU/kg for both rapid acting insulin aspart and Actrapid, insulin human.

The different pharmacokinetic parameters measured in this study were the maximum insulin plasma concentration $C_{max(ins)}$, the time when it was reached $T_{max(ins)}$, and the areas under the concentration-time curve measured at different time intervals $AUC_{0\text{-}5h\ (ins)}$, $EXC_{0\text{-}4h(glu)}$. Other parameters included total baseline corrected glucose excursion.

Table 9: Pharmacokinetic parameters of Actrapid, insulin human when administered to children. The mean values are given with standard deviation to the means indicated in brackets.

Parameters	6-12 years (n=9)	13-17 years (n=9)	All
$C_{max(ins)}$ (mU/l)	59 (16)	82 (40)	70 (32)
$AUC_{0\text{-}5h\ (ins)}$ (mU/l x h)	179 (69)	313 (186)	246 (153)
$T_{max(ins)}$ (min)	77 (28)	99 (48)	88 (40)
$AUC_{0\text{-}\infty(ins)}$ mU x h/l)	275 (139)	612 (451)	444 (367)
$T_{½(ins)}$ (h)	3.0 (1.4)	4.0 (2.4)	3.5 (2.0)
MRT_{ins} (min)	129 (16)	141 (13)	135 (38)

The highest insulin concentration observed in plasma $C_{max(ins)}$ appeared to be higher in adolescents than in the age group 6-12 years. In addition this parameter $C_{max(ins)}$ appeared to be higher in diabetic children (both age groups) than in adult with type 1 diabetes patients (see results of study **024/UK**). The area under the plasma insulin concentration-time measured between 0 and 4 hours $AUC_{ins(0\text{-}4h)}$ appeared to be higher in adolescents compared to adults (study **024/UK**). The half-life of insulin in pediatric patients equals to 3-4 hours differed from the half-life measured in adults (2-3 hours).

- **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.**

The fact that the maximum plasma concentration is reached within 1.5-2 hours after SC administration is supported by the results from the studies conducted in healthy volunteers. Absorption is different dependent on the injection sites and is fastest from the abdomen and slowest from the thigh.

No formal distribution studies were performed with Actrapid, insulin human. It is established that human insulin is not bound to plasma proteins unless circulating insulin antibodies are present.

Metabolism of Actrapid, insulin human was not formally investigated as well. From previously published data it is known that insulin human is degraded by various proteases. The degradation products are not active. Presumably, these degradation products are broken down into amino acids.

The half-life after subcutaneous injection is determined by the absorption which is subject to an important inter-and intra-individual variation.

The applicant has not submitted any data on the pharmacokinetics in patients with impaired renal/hepatic function. Renal and hepatic impairment may reduce insulin degradation and thus reduce insulin requirements.

Clinical efficacy

Main study (phase III = therapeutic confirmatory trials).

Table 10: Phase III trials

Studies	Population (Number of patients)	Design	Objectives
035/EU	Type 1 diabetic patients (1070 patients enrolled in the study – 708 received rapid acting insulin aspart and 362 received Actrapid, insulin human).	Six-month multicentre multinational randomised parallel open-labelled	Compare the efficacy and safety of rapid acting insulin aspart and Actrapid, insulin human on glycaemic control as measured by HbA1c in type 1 diabetic subjects
036/US	Type 1 diabetic patients (884 patients enrolled in the trial – 597 received rapid acting insulin aspart and 287 Actrapid, insulin human).	Six-month multicentre randomised parallel open-label study	Compare the efficacy and the safety profile of rapid acting insulin aspart and Actrapid, insulin human in a multiple-injection regimen in patients with type 1 diabetes
037/US	Type 2 diabetic patients (182 patients were randomised, 91 to each treatment group).	Six-month multicentre randomised parallel open-label study.	Compare the efficacy and the safety profile of rapid acting insulin aspart and Actrapid, insulin human in a multiple injection.

These studies include two 6-months multi-centres and open-labelled active-controlled trials performed in type 1 diabetic patients and one 6-months multicentre and open-labelled active-controlled trial performed in type 2 diabetic patients.

Studies performed in type 1 diabetic patients.

- **Study 035/EU**

Study **035/EU** was a six-month multicentre multinational randomised parallel open-labelled study comparing the efficacy and safety of rapid acting insulin aspart and Actrapid, insulin human on glycaemic control as measured by HbA_{1c} in type 1 diabetic subjects.

2. Description of the study

This study was a randomised open label parallel groups study. In addition to the comparison of effects of rapid acting insulin aspart with Actrapid, insulin human on the glycaemic control, the secondary objectives were the comparison of rapid acting insulin aspart with Actrapid, insulin human on 8-point blood glucose profiles after 6 months of treatment.

The safety profiles of the two insulins were assessed with the incidence of hypoglycaemic episodes and adverse reactions during 6 months of treatment. Other biological parameters were also monitored.

The duration of the treatment phase was 6 months. Patients included were required to have a type 1 diabetes duration of at least 24 months, currently treated with insulin human in any treatment regimen for at least 12 months. Finally, the patients enrolled in the study had the following characteristics: age ≥18 years, with a body mass index (BMI) ≤ 35 kg/m2 and an HBA_{1c} ≤11.0%.

Patients with impaired hepatic or renal function, cardiac disease, uncontrolled hypertension, recurrent severe hypoglycaemia, active proliferative retinopathy and patients with a need of a total insulin dose of ≥1.4 IU/kg were not included in this study.

3. Primary endpoints/assays

The primary and secondary endpoints were described above. Secondary endpoints derived from the 8-point BG profiles after 6 months of treatment were the prandial blood glucose increment after 3 meals (evaluated as the difference between pre-and post-meal blood glucose values averaged over the 3 meals) and the variability of the 8-point blood glucose profile (the standard deviation of the blood glucose values at the 8 time points).

4. Statistical analysis

The trial was aimed at demonstrating a non-inferior efficacy of rapid acting insulin aspart as compared to Actrapid, insulin human.

5. Study population

A total of 1070 patients were randomised in the study (362 received Actrapid, insulin human). The safety data have been obtained from 1065 patients who received the study medications. A total of 1047 patients defined the intent to treat population (described in ICH E9 as being the patients who were followed-up, assessed and the data analysed irrespective of their compliance to the planned course of treatment) (of these 349 received Actrapid, insulin human). Finally 1006 patients constituted the per protocol population (defined in ICH E9 as being the patients who complied sufficiently with the protocol to ensure that the data obtained with these patients reflected the effects of treatment) 332 were in the group Actrapid, insulin human). A total of 27 subjects withdrew during treatment with Actrapid.

The treatment groups were comparable with respect to age, gender, race, weight, and body mass index (BMI) and smoking status of the patients enrolled in the study. This was also the case with respect to baseline characteristics (duration of diabetes, HBA_{1c}, number of daily basal injections). The mean doses of insulin human and insulin aspart were similar at baseline, as well as were the mean doses of basal insulin.

6. Efficacy results

HbA_{1c} levels remained relatively stable over the 6 months treatment with Actrapid, insulin human.

Table 11: Results from study 035/EU

	(Actrapid)		
	N	**Mean**	**(SEM)**
HbA_{1c} (%)	346	8.00	(0.04)
Prandial BG Increment (mmol/l)	329	1.69	(0.12)
BG Variability (mmol/l)	315	2.84	(0.07)
Meal: basal Ratio	345	1.58	(0.03)
Total Insulin (U/kg)	348	0.69	(0.01)

All adjusted for baseline value and centre

- **Study 036/US**

Study **036/US** was a six-month multicentre randomised parallel open-label study aimed at comparing the efficacy and the safety profile of rapid acting insulin aspart and Actrapid, insulin human in a multiple-injection regimen in patients with type 1 diabetes.

1. Description of the study

The design of this study was identical to the design of the previous study.

A total of 884 subjects were randomised in this trial (287 to Actrapid, insulin human). The intent to treat (ITT) population consisted of 279 in the insulin human treatment group. The per protocol (PP) population included a total of 257 patients for Actrapid, insulin human. A total of 24 subjects (8.4%) withdrew while on Actrapid. The rates of discontinuation due to the occurrence of adverse effects or lack of efficacy were low and were comparable for both treatments.

Exactly like in the previous study the populations selected in the treatment groups were comparable (the criteria used to performed this comparison were identical to those used in study 035/EU).

2. Efficacy results

HbA_{1c} levels remained relatively stable over the 6 months treatment with Actrapid, insulin human.

Table 12: Results from study 036/US

	(Actrapid)		
	N	**Mean**	**(SEM)**
HbA1c (%)	278	7.93	(0.05)
Prandial BG increment (mmol/l)	259	1.58	(0.16)
BG variability (mmol/l)	253	3.31	(0.09)
Meal: basal ratio	273	1.86	(0.05)
Total insulin (IU/kg)	277	0.69	(0.01)

All end points adjusted for baseline value and centre-ITT analyses

The doses of meal related insulin remained almost constant over the treatment period. The mean basal insulin doses increased slightly from 0.25 IU/kg at baseline and at 3 months to 0.27 IU/kg at 6 months.

Studies performed in type 2 diabetic patients.

- **Study 037/US**

Study **037/US** was six-month multicentre randomised parallel open-label study. It was aimed at comparing the efficacy and the safety profile of rapid acting insulin aspart and Actrapid, insulin human in a multiple injection regimen in subjects with type 2 diabetes.

1. Description of the study

The design of this trial was the same as the 2 phase III trials in type 1 diabetic patients. The randomisation ratio was identical for rapid acting insulin aspart and for Actrapid, insulin human. The endpoints used to assess the clinical efficacy of the two products as well as the statistical methodology were identical.

2. *Study population*

A total of 182 subjects were randomised, 91 subjects to each of the 2 treatment groups. All of these were exposed to study drug. The intent to treat population (ITT) consisted of 177 patients 87 received the treatment with Actrapid, insulin human). The per protocol population (PP) included 156 patients (78 in each treatment group). A total of 9 (9.9%) subjects withdrew while receiving Actrapid, insulin human. Three patients withdrew due to an adverse event (myocardial infarction, colon carcinoma, cerebrovascular disorder) 1 due to ineffective therapy, 1 due to non-compliance and 4 due to other (unspecified) reasons.

Table 13: Results from study 037/US

		(Actrapid)	
	N	**Mean**	**(SEM)**
HbA_{1c} (%)	86	7.82	(0.10)
Prandial			
BG Increment (mmol/l)	82	1.32	(0.20)
BG Variability (mmol/l)	80	2.78	(0.14)
Mealrelated/ Basal Insulin Ratio	87	2.01	(0.11)
Total Insulin (IU/kg)	87	0.70	(0.02)

All adjusted for baseline value and centre, (ITT population)

HbA1c levels remained relatively stable over the 6 months treatment with Actrapid, insulin human.

- **Intravenous use of fast acting insulin for the treatment of the acute complications of diabetes or acute concurrent conditions.**

Severe hyperglycaemia in non-diabetic patients, including blood glucose levels in the diabetic range, detected in stress situations as infections, trauma, surgery and other catabolic conditions, is according to WHO criteria of diabetes mellitus not diagnostic for diabetes. A recent review of 15 studies revealed a strong association between stress induced hyperglycaemia in diabetic as well as non-diabetic patients with myocardial infarction, and an increased risk of in-hospital mortality and morbidity, suggesting that glucose is an important risk factor for morbidity and mortality after myocardial infarction also in non diabetic patients (The Lancet 355: 773-78, 2000). It should be emphasised that these studies are observational studies, from which it cannot be concluded that reversal of the hyperglycaemia improves clinical outcome.

Likewise, another recent published observational study of 2030 patients admitted to general wards in-hospital revealed association between hyperglycemia and poor clinical outcome and mortality among patients with known diabetes as well as in patients without known diabetes (J Clin Endocrinol Metab 87: 978-82,2002).

In the Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction (DIGAMI) study hyperglycaemic patients with myocardial infarction were randomised to intensified insulin therapy with insulin-glucose infusion followed by multi dose insulin regime or routine anti diabetic therapy (J Am Coll Cardiol 26:57-65, 1995). Intensified insulin therapy improved long term prognosis in these patients. The study population comprised known diabetics as well as 10% unknown diabetics or stress induced hyperglycaemic patients. Whether the conclusion drawn from the study also applies to non-diabetic stress induced hyperglycaemic patients was not revealed.

A meta-analysis of all properly randomised trials of infusion of glucose-insulin-potassium (GIK) in patients with myocardial infarction, involving about 2000 patients, showed a reduction in mortality of 28% in patients receiving this therapy (Circulation 96:1152-56, 1997). Later, another randomised (not blinded) pilot study of 407 patients with myocardial infarction revealed a 66% reduction in the relative in-hospital mortality in patients receiving high-dose GIK therapy compared to the control group (Circulation 98: 2227-2234, 1998). There were, however, no differences in glucose levels between the groups and the study was not designed to reduce plasma glucose. Nevertheless these findings suggest that metabolic modulations with GIK infusion after myocardial infarction are highly beneficial.

In a newly published study from van den Berghe *et al.* (N Engl J Med 345:1359-67, 2001) the question whether normalisation of blood glucose levels with intensive insulin therapy in critically ill patients with hyperglycaemia improves prognosis, was addressed. The study was a randomised prospective controlled study including 1548 patients (2500 patients was planned to be enrolled, but the study was terminated prematurely after 12 month). The study population comprised critically ill patients admitted to a surgical intensive care unit (ICU). Only surgical patients were studied, two thirds of the patients were cardiac surgical patients needing mechanically ventilatory assistance and 13% of the study population had a history of diabetes. The patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose in the level 4.4 – 6.1 mmol/l) or to conventional treatment (insulin infusion when blood glucose exceeded 12 mmol/l). Primary outcome measure was death from any cause during intensive care. Secondary outcomes include death in hospital, number of days in hospital, number of days in ICU, need for ventilatory support, renal replacement therapy or other support and markers of infection and inflammation.

At 12 month the ICU mortality was 4.6% in the intervention group compared to 8% in the conventionally treated group, yielding a significant risk reduction in mortality of 42 %. Similarly, the in-hospital mortality was significantly reduced in the intervention group (risk reduction of 34 % compared to control group). The significant effect on mortality appeared only in patients treated more than 5 days therapy in ICU. Also, morbidity was reduced in the intervention group compared to the conventionally treated group. Intensive insulin therapy reduced the duration of admission in the ICU, length of requirement of ventilatory support and renal replacement therapy. Also episodes of septicaemia were significantly reduced in this group.

Hypoglycaemia defined as blood glucose of 2.2 mmol/ or less occurred in 39 in the intervention group and in 6 patients in the control group. No instances of convulsions or haemodynamic deterioration were observed.

Although these results seem convincing, criticism can be raised. With respect to the interpretation and conclusion of this study a major concern is that the study was not blinded and was carried out in a single intensive care unit. Furthermore, the study population represent a highly selected group of intensive care patients (major surgery). These patients are not directly comparable with patients admitted to common intensive care units, where patients suffering from different non-surgical disorders comprise a considerable fraction. Therefore, although the results of this study are of great interest and may have important implications for the treatment of stress induced non-diabetic hyperglycaemia, interpretation and generalisation of the results should be done with caution.

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. Insulin human may be given intravenously (e.g. in diabetic ketoacidosis) and intramuscularly but is predominantly administered subcutaneously. 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 assessment of efficacy of Actrapid is based on previously reported studies comparing Actrapid, insulin human and rapid acting insulin aspart. These studies are uncontrolled as far as the efficacy of Actrapid is concerned. The absence of controlled trials is acceptable as it would be unethical to perform a placebo controlled study and since insulin (especially fast acting insulin) is the mainstay in treatment of diabetes. The data obtained from uncontrolled studies from the studies performed with rapid acting insulin aspart does however provide evidence of the long-term efficacy of insulin human.

In three open-label, 6-month treatment studies in type 1 and 2 diabetes patients, comparing the efficacy of rapid acting insulin aspart with Actrapid, insulin human a total of 2136 patients were randomised. Seven hundred and forty patients received a treatment with Actrapid. Patients were moderately well controlled at baseline In studies 036/US and 035/EU the mean HbA_{1c} at baseline was equal to 7.87% [the standard deviations were respectively 1.25 and 1.6 in studies 036/US and 035/EU]. The mean HbA_{1c} was equal to 7.83% (1.08) in study 037/EU. The duration of the diabetes was long-standing in all trials, with an average of 15-16 years for the type 1 diabetic patients and 13 years in the type 2 patients. Patients with major secondary complications were, however, excluded. Recommended injection sites were abdomen for the meal-related insulin and thigh for basal insulin.

The present studies demonstrate that acceptable glycaemic control can be maintained with Actrapid as meal-time related bolus injections in combination with long-acting insulins.

Existing data from intervention studies in diabetic patients have shown that intensive insulin treatment of hyperglycemia improve long-term prognosis in patients with myocardial infarction. Furthermore a range of observational studies in non-diabetic hyperglycaemic patients strongly indicate that blood glucose represent a significant risk factor for mortality and morbidity after myocardial infarction. Furthermore, accumulating data suggests that GIK infusion in non-diabetic patients with myocardial infarction is beneficial. Also very recent data suggests but does not prove that maintenance of normoglycemia in non-diabetic critically ill patients, improve survival and reduce risk of infections. In conclusion, from a strict regulatory perspective the present data, although very suggestive, does not allow a firm conclusion on the benefit of treatment of stress induced hyperglycaemia in non-diabetic subjects and for that reason it is not considered appropriate to include this indication.

From a clinical perspective the distinction between stress induced hyperglycaemia in non-diabetics and diabetics is somewhat academic. During acute stress situations hyperglycemic patients with previous unknown diabetes may not be distinguished from non-diabetic patients with transitory hyperglycemia.

Thus most acutely ill patients with hyperglycaemia will receive insulin as diabetes cannot be ruled out until after the acute disease. This practical approach is considered covered by the simplified indication "treatment of diabetes".

Clinical safety

Patient exposure

A total of 644 patients with type 1 diabetes received Actrapid, insulin human. An additional 91 patients with type 2 diabetes received Actrapid, insulin human). Few subjects were excluded from the trials due to the occurrence of adverse events, five type 1 diabetic patients receiving Actrapid, insulin human (<1%) three (3%) type 2 diabetics receiving Actrapid, insulin human.

In addition, an important marketing experience with human insulins has been gathered. Since 1993 an estimated total of 25.35 million person years representing at least 6.5 million individual patients have been exposed to these human insulins (this estimate is based on the sales figures and assuming an average of 42 IU insulin per diabetic patient per day, see paragraph post-marketing experience below).

Discontinuation due to adverse events

The incidence of adverse events was low in studies performed in type 1 diabetic patients (studies 035/EU and 036/US).

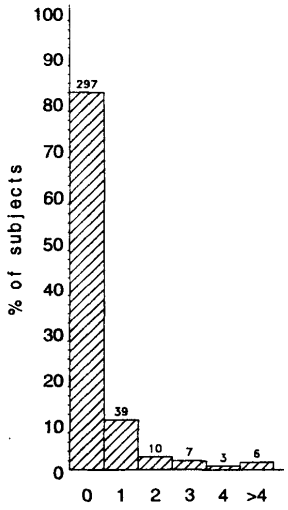
In study 037/US conducted in type 2 diabetic patients a total of 9 (9.9%) subjects withdrew while treated with Actrapid, insulin human. Of these 3 patients withdrew from the insulin human group due to an adverse event (myocardial infarction, colon carcinoma, cerebrovascular disorder).

Hypoglycaemic reactions

Studies performed in type 1 diabetic patients - Study 035/EU

The incidence of major hypoglycaemic episodes (defined as requiring intravenous glucose or glucagon) is shown below. The major hypoglycaemic episodes predominantly occurred in the early morning hours (0-4 a.m.).

Figure 6: Frequency of major hypoglycaemic episodes



Approximately 75% of the patients treated with insulin human experienced minor hypoglycaemic episodes

Study 036/US

Nineteen percent of subjects treated with Actrapid, insulin human experienced a major hypoglycaemic episode. Approximately 8% of these had more than 1 major hypoglycaemic episode in the treatment phase, often during the early morning hours (0-8 a.m.).

Eighty five percent of subjects in the human insulin group experienced a minor hypoglycaemic episode.

Studies performed in type 2 diabetic patients - Study 037/US

The proportion of patients receiving insulin human who experienced a major hypoglycaemic episode was approximately 5.5%. Minor hypoglycaemic episodes occurred in about 64% of the patients treated with human insulin. The mean rate of minor hypoglycaemic episodes was the highest in the afternoon.

Overall on these studies, major hypoglycaemic events occurred less frequently in type 2 diabetic patients.

Table 14: Frequencies of adverse events (AEs), serious adverse events (SAEs) and hypoglycaemic episodes observed in the clinical trials performed in type 1 (035/EU – 036/US) and type 2 (037/US) diabetic patients. In the table Actrapid, insulin human is denoted by HI.

	Type 1 diabetic subjects (studies 035/EU and 036/US are combined) HI (n=644)		**Type 2** diabetic subjects (study 037/US) HI (n=91)	
	N (%)		N (%)	
All AEs	468(73%)	1554	71 (78%)	221
SAEs	36 (6%)	41	7 (8%)	9
Hypoglycaemic episodes				
Major	120(19%)	309	5 (5%)	8
A		272	4	7
B		37	1	1
Minor		10647	58	677

Major A=requiring third party help
Major B=requiring i.v. glucose or glucagon treatment

Antibody formation

In study 035/EU Actrapid, insulin human specific antibodies were rare.

Other adverse events and serious adverse event/deaths observed in the clinical trials

The most frequent adverse events were upper respiratory tract infections (by more than 20% of patients in each treatment group), headache and accidental injuries (>10% of patients), pharyngitis, sinusitis, nausea, diarrhoea, and back pain (each of these reactions were observed in more than 5% of the patients). The most frequent serious adverse reactions in type 1 diabetic patients were related to glycaemic control, in type 2 patients the most frequent serious events were cardiovascular events, unlikely related to trial medication. No deaths occurred. There were no consistent trends or significant changes from baseline in laboratory tests.

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.

A total of 29 serious adverse reaction reports were classified as serious unlisted. Of these a total of three cases of toxic epidermal necrolysis/Stevens Johnson syndrome have been reported. As of 30 August 2000, a total of 6 cases of epidermal necrolysis/Stevens Johnson syndrome/erythema multiforme have been reported in association with Actrapid. In 5 of these cases concomitant medication provided a more likely explanation than insulin human.

In the last PSUR (1999-2000), the Company received 20 reports of impaired liver function (9 of these being serious). All these cases occurred in Japan. No reports on impaired liver function were received from other countries. Such reports have already been published (especially increased liver enzymes in patients with non-insulin dependant diabetes mellitus) and they are generally associated with overweight. According to evidence from three studies liver enzyme increases are most likely related to diabetes mellitus non insulin-dependent/treatment with oral antidiabetic agents but not to insulin. Many of the reports involved semisynthetic, - but not genetically engineered insulin. The hypothesis of an idiosyncratic reaction was ruled out by the Company since no other signs of hypersensitivity were observed and no eosinophile granulocytes were found in the biopsies.

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.

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 Actrapid is well characterised.

4. 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

Effects seen in the original and newer safety pharmacology studies can all be related to hypoglycaemia. 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. 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. There was no increase of mammary gland hyperplasia or tumours in the 12 months dog study.

There was no statistically significant difference between the immunogenicity in rabbits of insulin human rDNA and semi synthetic 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.

It is concluded that newer studies conducted do not give reason for new safety concerns.

Efficacy

The studies demonstrating pharmacodynamics and pharmacokinetics of Actrapid, insulin human are recent studies performed with the rapid acting insulin analogue insulin aspart with Actrapid, insulin human as comparator (in most cases). The studies conducted in healthy volunteers, type 1 and type 2 diabetic patients mainly by using the euglycaemic clamp technique, confirm the glucose lowering action of Actrapid. The studies performed in healthy subjects support the conclusions made in the SPC on the onset of action (within ½ hour), duration of action (approximately 7-8 hours) and the time of the maximum effect (within1.5-3.5 hours after injection).

The treatment of diabetes mellitus with fast-acting insulin preparations such as Actrapid has been established for many decades. It is a lifesaving treatment for patients with type 1 diabetes and is required by many patients with type 2 diabetes. 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.

The ”proof” of the efficacy of Actrapid, insulin human is based on previously reported studies comparing Actrapid, insulin human and insulin aspart. In essence these studies are uncontrolled as far as the efficacy of Actrapid is concerned. The lack of controlled trials is considered acceptable as it would be unethical to perform a placebo controlled study, and as insulin, especially fast acting insulin, is the mainstay in treatment of diabetes one can hardly imagine what should be chosen as active comparator. The “uncontrolled” data from the NovoRapid, insulin aspart studies does however provide evidence of the long-term efficacy of Actrapid, insulin human.

The present studies demonstrate that acceptable glycaemic control can be maintained with Actrapid as meal-time related bolus injections in combination with long-acting insulins.

Safety

An extensive post-marketing experience has been gained concerning human insulin. The post marketing information is collected in two PSURs, the first covering the period 1st March 1993 to 31th August 1998 and the second covering the period 1st September 1998 to 30th June 2000. The safety profile of Actrapid is well characterised and acceptable.

Benefit/risk assessment

Based on the submitted documentation pharmacodynamic and clinical data as well as the well-established use of fast acting human insulin, the efficacy and safety of Actrapid 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 Actrapid was favourable in the treatment of diabetes mellitus.