SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Insuman. This scientific discussion has been updated until 1 May 2002. For information on changes after this date please refer to module 8B.

1. Introduction

Insuman is recombinant human insulin (Insulin HGT) produced by r-DNA technology. The structure and activity are identical as compared to the semi-synthetic human insulin products (produced by enzymatic conversion of porcine insulin) currently marketed in several countries, but the manufacturing process of the active ingredient differs. Recombinant DNA technology offers an efficient alternative manufacturing procedure to that used for semi-synthetic insulins, which are dependent upon a constant supply of porcine pancreas.

The Recombinant human insulin molecule consists of two chains interconnected by two disulfide bonds and has a molecular weight of 5,808. It is derived from *Escherichia coli K 12* bacteria as a chimeric product in the form of a fusion protein and modified chemically and enzymatically during downstream processing.

Insuman, annex II application of Commission regulation (EC) No 542/95, as amended under the centralised procedure, was submitted in order to introduce a second generation of recombinant human insulin (insulin HR 1799 or insulin HPR).

This centralised application, from Hoechst Marion Roussel Deutschland GmbH (Germany) differs from the first generation recombinant human insulin (insulin HGT) in its manufacturing process. The modified manufacturing process avoids the use of cyanogen chloride, sulfitolysis and urea in high amounts during stream down streamprocessing (*dominus technicus*).

Insulin HPR is manufactured from a protein produced by a K12 strain of *Escherichia coli* that has been genetically modified with a corresponding recombinant plasmid.

The first generation insulin HGT was approved for marketing in February 1997, but the company does not intend to market this product. Instead, a Marketing Authorisation has been sought for the second generation recombinant human insulin HPR.

Insuman (insulin HPR) is indicated for the treatment of diabetes mellitus and, like the previous insulin HGT, is presented as 6 different preparations depending on the ratio short/prolonged duration of action: Insuman Rapid, Comb 50, Comb 25, Comb 15, Basal, Infusat. The Rapid formulation contains the regular, unmodified insulin, while the Basal one is an insulin suspension with delayed absorption. Insuman Comb contains fixed combinations of these two formulations. Insuman Infusat is a formulation for pump infusion. For all presentations, except Infusat, two dosage forms were developed: recombinant human insulin with 40 IU/ml and with 100 IU/ml.

Except for Insuman Infusat, Insuman is presented in vials and in cartridges for use in reusable injection pens ("OptiPen"). Insuman Infusat is insulin for use in an insulin pump and is presented in vials and cartridges. Insuman Rapid, Comb 15, Comb 25, Comb 50 and Basal are also presented in pre-filled disposable injection pens under the name Insuman OptiSet with strength of 100 IU/ml. The total content of a pen corresponds to 300 IU human insulin. The colour code indicated on the cartridges dosage knob matches the colour code on the labelling of the cartridge and of the outer carton.

On two occasions (12 May 1995, 15 May 1996) the applicant requested scientific advice from the CPMP on the sufficiency to perform a reduced clinical program. The CPMP emphasised that "in order to demonstrate that the two recombinant human insulins have the same characteristics, the company should conduct intensive comparative studies on physico-chemical characterisation. Evidence should be provided that the two r-h-insulins produced with different means have the same quality in terms of both impurities and characteristics of the active compound. On basis of comparative pharmacodynamic and pharmacokinetic studies, the company will have to demonstrate that similar biologic activity and similar pharmacokinetic parameters can support identical therapeutic activity.

Furthermore, the company should provide information on the level of antigenicity of the different types of insulin. Provided that the results obtained with proper studies are satisfactory, a reduced clinical package of information can be considered."

2. Chemical, pharmaceutical and biological aspects

The documentation submitted for part II of the Annex II application (Insuman, insulin HR 1799 or insulin HPR) contains a revision of the sections on production and control of starting material active substance, packaging material of the active substance, stability tests on active substance and virological safety. With regard to the finished products (parts IIA, IIB, IIC.2, IIC. 3, IIE, IIF), cross-reference was made to Insuman centrally authorised in 1997, procedure number EMEA/H/C/119, and a brief summary is provided in this section. In 2000 Part II of the dossier was updated to take into account the change from the previous source (insulin HGT) to the new source of active ingredient (insulin HR1799). In addition minor changes to the manufacturing process were introduced. These changes did not modify the quality of Insuman.

Part II of the dossier of HR 1799 is well documented and the data provided demonstrates that the production process for HR 1799 is well controlled and that consistency in this process is achieved. Furthermore, the company has conducted intensive comparative studies using state-of-the-art techniques on the physico-chemical characteristics of insulin HR1799, insulin HGT and insulin ET (semi-synthetic insulin). These studies indicate that the structure of these insulins is indistinguishable within the accuracy of the measurements. The impurity profile of insulin HR 1799 is comparable to insulin HGT, with the exception of pre-HR 1799 in insulin HR 1799 (≤ 0.1 % of total protein). The evaluation of the immunogenicity of insulin HR 1799 is considered a clinical topic.

The applicant has overall responded in a satisfactory way to the major objection and minor points related to part II during the assessment of the dossier. Additionally some tests will be included in specifications of the active substance and the applicant will present the test results as follow-up measures.

As a condition to the marketing authorisation, the applicant made the commitment to further optimise the sensitivity of an appropriate routine test for residual *E. coli* proteins in the specifications, and to submit within an agreed timeframe, description and validation batch results on a full-scale level. A validated test was presented in November 1998.

The shelf life proposed for the active substance is 24 months. Stability results covering the complete re-test period were presented post-approval.

With regard to the finished product, the approved shelf life of 2 years was granted on the basis of stability data obtained with the previous insulin HGT. Results from stability studies performed on insulin HR1799 have not been presented. The MAH indicated that stability studies according to ICH guidelines have been initiated on the first marketed (full-scale) batches of all products containing insulin HR1799. The MAH will present 6 months stability data in June 2000 together with a comparison with the stability data obtained with products containing insulin HGT.

Brief summary on the cross referred information on the pharmaceutical data is hereto provided

Composition of the medicinal product Insuman is presented as solution for injection or suspension for injection in six different injectable formulations (table I below), activity profiles varying from rapid to intermediate. Insuman Rapid contains regular unmodified insulin. Insuman Basal is an insulin suspension (crystalline insulin) with delayed absorption whereas Insulin Comb contains fixed combinations (three different combinations) of these two formulations. Insuman Infusat is a formulation for pump infusion. Five of these formulations will be produced in two strengths; 40 IU/ml and 100 IU/ml. Insuman Infusat is presented only in one strength; 100 IU/ml.

Table I: Insuman formulations

CODE	TRADE NAME	INSULIN TYPE	STRENGTH, CONTAINER
HOE 31 HPR	Insuman Rapid	regular, short action 100 % dissolved insulin	100 IU/ml in vials 100 IU/ml in cartridges for OptiPen 40 IU/ml in vials
HOE 36 HPR	Insuman Basal	basal, prolonged action 100% crystalline insulin	100 IU/ml in vials 100 IU/ml in cartridges for OptiPen 40 IU/ml in vials
HOE 32 HPR	Insuman Comb 15	intermediate, 15% dissolved insulin 85% crystalline insulin	100 IU/ml, vials 100 IU/ml, cartridges for OptiPen 40 IU/ml, vials
HOE 33 HPR	Insuman Comb 25	intermediate, 25% dissolved insulin 75% crystalline insulin	100 IU/ml, vials 100 IU/ml, cartridges for OptiPen 40 IU/ml, vials
HOE 34 HPR	Insuman Comb 50	intermediate, 50% dissolved insulin 50% crystalline insulin	100 IU/ml, vials 100 IU/ml, cartridges for OptiPen 40 IU/ml, vials
HOE 21 PPR	Insuman Infusat	regular, for use in insulin infusion system, 100 % dissolved insulin	100 IU/ml, vials 100 IU/ml, cartridges

The composition of the six formulations differs in relationship to the excipients. Insuman Rapid contains m-Cresol as preservative, sodium hydrogen phosphate as buffering agent, glycerol for ensuring isotonicity, hydrochloric acid to dissolve human insulin and finally, sodium hydroxide for adjusting pH. Insuman Basal and Comb formulations include in addition phenol as preservative, protamine sulphate as a crystallising agent and zinc chloride, which acts as a promotor of the complex formulation. The special characteristics for Insuman Infusat are obtained by using non-ionic surfactant poloxamer 171 as stabilising agent. The product contains also zinc, which has an additional stabilising effect. Phenol is used as an antimicrobial preservative, trometamol as a buffering agent, glycerol for ensuring isotonicity and hydrochloric acid for dissolution.

Insuman Rapid, Basal and Comb are presented in 5- or 10-ml vials or in 3-ml cartridges. Insuman Infusat is packaged in 10-ml vials or 3 15-ml cartridges. The glass complies with type I glass (Ph.Eur.) and the rubber with type I rubber closures (Ph.Eur.). The packaging material can be regarded as suitable for its intended use.

Clinical studies have been performed with 3-ml cartridges of the 100 IU/ml formulations, which are identical to the formulations to be marketed.

There is no need for submission of product development studies, as the composition of these products is based on the present formulations for insulin semi-synthetic products.

Method of preparation

Preparation and filling are performed under aseptic conditions. Insulin is dissolved and mixed with an aqueous solution of the excipients to obtain a soluble insulin preparation. Crystalline insulin is prepared by dissolving insulin and mixing with solutions of the excipients dissolved at an appropriate pH to crystallise insulin. The bulk solutions are sterilised by filtration.

Appropriate sterilisation methods for the equipment, glass vials, etc. are used. The method of preparation as well as the packaging is adequately validated.

Control of starting materials

Active ingredient

Active ingredient specifications comply with the Ph. Eur. and USP. Additional tests are carried out according to the methods developed by the company. All tests are validated.

Development genetics

The assembly of the production strain has been described. The genetic information cloned into the vector used for the production of Insulin HGT has been described in its key elements.

Three different plasmids were used as source material for the construction of the expression vector.

The nucleotide sequence of the coding region of the fusion protein, the promotor and the junctions between the individual plasmids were confirmed by DNA sequencing. A complete DNA sequence has been provided.

Seed bank system

Sufficient details on the preparation and storage of the master cell bank (MCB) and working cell banks (WCB) are provided. All these seed banks were tested for identity, growth rate, viability, microbial contamination, plasmid retention.

Also the protocol for the preparation of a subsequent new working cell bank from the master cell bank is given. Concerning the stability, the company has provided reassurance that the cell bank systems are periodically tested for cell viability and genotypic and phenotypic stability.

Fermentation and harvesting

The fermentation process is performed in a closed system and has been adequately described. Details of description of the process, equipment used etc. have been provided.

Downstream modification and purification

The downstream processing of the fusion protein to human insulin is a sequence of modification and purification steps. Certain steps are specifically designed to remove specific contaminants.

All the steps are well validated and sufficient in-process controls are performed.

Characterisation

Evidence of the structure of insulin was adequately provided by using several techniques (mass spectroscopy, protein sequencing and H-NMR).

Process validation and batch analysis

The full-scale process has been adequately validated and the data from production runs are provided.

Batch analysis of batches produced on production scale and the batches used for the pre-clinical and clinical studies have been provided. The data demonstrate sufficiently the consistency of the production and the purification process.

Other ingredients

The excipients used are described in Ph.Eur., USP or USP/NF.

Control test on the finished product

It is shown that the finished medicinal product meets the Ph.Eur. specifications. Apart from the Ph.Eur. Tests, specifications are included for appearance, high molecular weight proteins, preservatives, bacterial endotoxins, and, if applicable, resuspendability, sedimentation. Batch analyses data indicate an acceptable batch consistency.

Insuman OptiSet (disposable injection pen)

The data provided in support of the application for the disposable injection pen satisfactorily addressed concerns with respect to the performance of the injection device and in particular the dose accuracy. In the absence of regulatory guidance, the current draft ISO/DIS 11608 “Insulin Syringes and Medicine Pen-injectors” was taken into account for testing the performance of the pen with respect to dose accuracy and resistance to impact (free fall test). In addition dose accuracy was evaluated on three batches of the disposable pen filled with Insuman Rapid. An HPLC investigation of dose accuracy was also performed on pens filled with Insuman Basal.

Stability testing on the assembled device containing the cartridge was not performed. Given that the injection pens contain previously approved cartridges, the device as such does not influence the

quality of the insulin used in the disposable pen. The shelf life and storage directions for the disposable pen are the same as for the single cartridges, i.e. 2 years at 2°C to 8°C. As for the reusable pens ("OptiPen"), the disposable pens may be kept up to four weeks once in use when stored not above 25°C. The MAH will, however, perform stability testing on the assembled injection device containing the cartridge in order to evaluate dose accuracy after storage over the complete shelf life and report results on an ongoing basis.

3. Toxico-pharmacological aspects

The format and the presentation of the pre-clinical data are considered acceptable and the studies were performed under GLPs.

However, a consequence of the novel production process is that the final product contains ≤ 0.1 % of a insulin like by-product protein, pre-HR 1799, which was described as a partly processed pre-pro-insulin, in which the normal B-chain is extended at its amino-terminus by 10 residues of the fusion peptide. The most significant toxico-pharmacological, and of course also clinical aspect of this insulin-like by-product is the assessment of its immunogenicity. Some pre-clinical data are available in the dossier; this issue is further addressed under chapter 4. *Overview of Part IV of the dossier: clinical aspects.*

There were no major objections or questions with regard to the presented data for the authorisation of Insuman, insulin HR 1799.

Brief summary on the cross-referred information on the pre-clinical data is hereto provided

The pre-clinical data provided for the authorisation of Insuman, insulin HGT is summarised as follow:

Pharmacodynamics

Related to the proposed indication

The blood glucose lowering effect of Insuman formulations were indistinguishable from that of semi-synthetic human insulin preparations after subcutaneous administration in rats, dogs and rabbits. In the rat and dog studies, a statistically significant difference in depot effect between three preparations has been demonstrated.

Safety

The general cardiovascular pharmacodynamics of Insulin HGT was studied in anaesthetised dogs. The observed and expected cardiovascular effects were shown to be due to induced hypoglycemia.

The additional administration of other drugs may potentiate or attenuate the effect of insulin on blood glucose concentrations. There is considerable experience of this in the clinic. It was therefore considered not necessary or appropriate to perform additional experiments in animals.

Pharmacokinetics

No pharmacokinetic studies were performed in laboratory animals. This information is considered not to be necessary for the products at hand.

Toxicology

Single dose toxicity

Single dose toxicity was studied in Wistar rats. The animals were observed for three weeks for signs of toxicity. No signs of toxicity occurred.

Repeated dose toxicity

Repeated dose toxicity has not been studied. The low level of impurities in the recombinant insulin preparations and the biological and chemical identity of the drug to natural insulin are considered to be valid arguments for the chosen strategy.

Reproduction studies

Reproduction studies have not been performed. It is known from the literature that insulin-induced hypoglycaemia provokes birth defects in mice, rats and rabbits. In addition, it is well known that diabetic hyperglycaemia causes congenital malformations and increased neonatal mortality. Because of the complexity of this problem and the identity of recombinant and semi-synthetic insulin, the arguments put forward are considered to be acceptable.

Mutagenic potential

Mutagenicity testing is not required for recombinant human insulin because of its peptidic nature and well-characterised impurity profile.

Nevertheless the following tests were performed: Ames test and *E. coli* WP2 uvrA test. The tests were performed with or without addition of metabolic activator. Insulin HGT did not increase the number of revertant colonies above background. Appropriate positive controls were presented.

Carcinogenicity

No studies were performed. The arguments put forward were considered to be acceptable.

Local tolerance (e.g. phototoxicity, photosensitivity)

Local tolerance of s.c. injection of Insuman Rapid was tested in rabbits. No macroscopic or microscopic signs of local toxicity were observed.

Special toxicity studies

Immunotoxicity, the induction of anti-insulin antibodies, is discussed in the clinical assessment report (section 3.4).

Environmental risk assessment

Since natural human insulin is rapidly and completely degraded by enzymatic hydrolysis, the injected drug is no environmental risk factor.

4. Part IV: Clinical aspects

The clinical part of the dossier for the approval of Insuman (Insulin HPR or Insulin HG 1799) consists of 4 bioequivalence studies carried out studying the comparison of the biosynthetic human insulin from the applicant, Hoechst Marion Roussel GmbH, *versus* the corresponding recombinant human insulin manufactured by a competitor:

1. Study A1: Comparison of the pharmacodynamics and pharmacokinetics of HOE 31 HPR (Insuman Rapid, biosynthetic human insulin, applicant) and biosynthetic human insulin (human insulin fast acting, ATC code: A10AB01) using the euglycaemic clamp technique.
2. Study A2: Comparison of the pharmacodynamics and pharmacokinetics of HOE 35 HPR (human intermediate intermediate 30% dissolved insulin and 70% crystalline insulin, biosynthetic human insulin, applicant) and biosynthetic human insulin (human insulin intermediate acting combined with fast acting, ATC code: A10D01) by using the euglycaemic clamp technique.
3. Study A3: Comparison of the pharmacodynamics and pharmacokinetics of HOE 36 HPR (Insuman Basal, biosynthetic human insulin, applicant) and biosynthetic human insulin (human insulin intermediate acting, ATC code: A10C01) by using the euglycaemic clamp technique.
4. Study A4: Comparison of the pharmacodynamics and pharmacokinetics of HOE 31 HPR and HOE 31 HGT (Insuman Rapid, biosynthetic human insulins, applicant) and biosynthetic human insulin (human insulin fast acting, ATC code: A10AB01) by using the euglycaemic clamp technique.

In all these studies the euglycaemic clamp technique is used to compare the blood glucose lowering activity of biosynthetic human insulins from Hoechst Marion Roussel and the corresponding recombinant human insulins manufactured by a competitor. By adjustment of the glucose infusion rate

(GIR) the euglycaemic clamp technique allows blood glucose levels to be maintained at the individual fasting concentration in each subject after injection of insulin. The technique is widely used to demonstrate the time-action profiles of glucose-lowering drugs.

All four studies were carried out in accordance with GCP guidelines. In addition, these studies in healthy volunteers were carried out according to the CPMP guidelines regarding bioequivalence studies as far as study design, analytical procedures and statistical methods are concerned.

In study A1 the two insulin preparations compared well with regard to all variables calculated for the Glucose Infusion Rate (GIR) and the exogenous insulin serum concentrations. Based on these results it can be concluded that the two insulin preparations studied, i.e. HOE 31 HPR (Insuman Rapid, applicant) and human insulin fast acting from the competitor are bioequivalent.

For study A2 the two tested insulin preparations also compared well with regard to all variables calculated for GIR and the exogenous insulin serum concentrations. Based on these results one can conclude that the two insulin preparations studied, i.e. HOE 35 HPR (applicant) and human insulin intermediate acting combined with fast acting from the competitor are bioequivalent.

However, in study A3, bio-equivalence was not fully demonstrated between HOE 36 HPR applicant and human insulin intermediate acting, due to the well-known high intra-individual coefficients of variation of NPH.

After the assessment of the responses provided by the applicant, the slight differences between HOE 36 HPR (Hoechst Marion Roussel) and human insulin intermediate acting can be considered as clinically not relevant.

In the study A4 the three insulin preparations compared well with regard to all variables calculated for the Glucose Infusion Rate (GIR) and the exogenous insulin serum concentrations. Based on these results, it can be concluded that the three insulin preparations studied, i.e. HOE 31 HPR and HOE 31 HGT (both from Hoechst Marion Roussel) and human insulin fast acting are mutually bioequivalent.

The results from studies A1 to A4 based on both the pharmacodynamic effect and pharmacokinetic profile, indicate that the 3 insulin formulations, Insuman Rapid (insulin HPR 1799), Insuman Rapid (insulin HGT) and another fast acting insulin have comparable benefit/risk profiles when administered intravenously. Based on this assessment a new route of administration (intravenous use) was added for Insuman Rapid for treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

For Insuman Infusat (HOE 21 PPR 100 IU/ml), a solution of regular insulin for i.v. infusion, bio-equivalence studies are not required according to the EU guidelines. The applicant intends to submit a variation application in order to claim for this route of administration.

For Insuman Comb 15 (HOE 32 HPR), Insuman Comb 25 (HOE 33 HPR) and Insuman Comb 50 (HOE 34 HPR) no bio-equivalence studies were presented.

Furthermore, no studies are included in the dossier dealing with product immunogenicity in humans. Chemically, a new insulin like by-product was found (pre-HR 1799), although in low concentrations. Some pre-clinical data are available in the dossier, but these data are insufficient to assess the lack of immunogenicity in humans. The applicant agreed to provide the human data on immunogenicity during the post-marketing phase.

In a number of Member States of the EU, Insuman will be replacing semi-synthetic human insulin produced by enzymic modification of porcine insulin. In three Member States (Austria, France and Ireland), the tradename Insuman is already used for the marketed semi-synthetic human insulin products. During its July 1997 meeting, CPMP raised concerns about possible confusion caused by the use of the same tradename. In September 1997, the company provided CPMP with information on how they would manage the changeover. Following this reassurance, the use of the same tradename was accepted by CPMP. The company has committed itself to the following activities for the launch of recombinant human insulin in Austria, France and Ireland:

- The change from semi-synthetic to recombinant human insulin will be discussed together with wholesalers, pharmacists, diabetes associations, opinion-leaders, patients' groups and nurses.
- An information campaign will be started prior the launch.

- There will be a new HMR design of packages at the launch of the recombinant human insulins. This will exclude the risk of mixing up.

In the other Member States where these semi-synthetic human insulins are marketed (Germany, Finland, Netherlands, Portugal and Sweden), a different tradename is used. The company had requested permission from the European Commission to indicate after the name on the German labelling "previously known as H-Insulin Hoechst". This proposal was legally acceptable to the Commission provided it was for a limited period of one year. However, CPMP had concerns that such a statement would be misleading since the semi-synthetic and recombinant human insulins are comparable from a quality, safety and efficacy point of view, but they are not identical. In addition, it was considered that the equivalent information should be given on the labelling in all Member States where these semi-synthetic human insulins are marketed.

It was concluded that the following condition would be applied to the Marketing Authorisation:

In Member States where Hoechst Marion Roussel Deutschland GmbH or any entities belonging to the same industrial pharmaceutical group as Hoechst Marion Roussel Deutschland GmbH hold Marketing Authorisations for semi-synthetic insulins, each blue box will clearly state that such recombinant human insulin (Insuman) replaces the corresponding semi-synthetic insulin. Each statement should clearly indicate the tradename of the product replaced by such recombinant human insulin (Insuman). Such statement should not be used for a period of time exceeding one year from the date of placing on the market of the first batch of the recombinant human insulin (Insuman).

Brief summary on the cross referred information on the clinical data is hereto provided

The applicant dossier is cross-referred to the clinical data presented for the approval of Insuman (Insulin HGT)

Pharmacodynamics and pharmacokinetics

Pharmacodynamics and pharmacokinetics studies were performed in volunteers after single administration of one of the Insuman preparations. A total of five Phase I studies were submitted. In these studies, five different biosynthetic formulations were compared to those of the corresponding semi-synthetic insulins. Insulin was injected subcutaneously.

In all studies the pharmacodynamic action of insulin was assessed using the euglycaemic clamp technique. There were no statistically differences between biosynthetic and semi-synthetic insulins. However, high variation in all parameters was observed due to well-known variation in absorption from the injection site and method of euglycaemic clamp technique. As conclusion, no significant differences in the pharmacodynamic values were found.

The results indicated that variability in the pharmacokinetic parameters is high. Single noted differences are of no therapeutic relevance.

Clinical efficacy

In order to assess the clinical efficacy of Insuman, two phase III trials (B1-B2) were performed involving a total 611 patients with either type I or type II diabetes mellitus.

B1 study was a multi-centre parallel-group study. Men and woman of ages 18-70 were enrolled in the study. Patients were stratified either to a free combination of NPH (crystalline, basal) with or without regular insulin or to a fixed combination Insuman Comb 25. Patients were randomised to either biosynthetic or semi-synthetic insulin preparations in each group. A total of 288 patients were treated daily with biosynthetic insulin for a range of 2-266 (median of 176) days and 289 patients were treated daily with semi-synthetic insulin for a range of 2-247 (median of 176) days. There was a strong association between stratified regimen and type I diabetes.

B2 was a small multi-centre open non-controlled trial including 34 patients. Men and women aged 18-65 years suffering type I diabetes mellitus were included in the study. Patients received continuous infusion of biosynthetic human pump insulin designed for use in an external insulin pump. The duration of treatment was 12 weeks.

Glycated hemoglobin and hypoglycaemia were chosen as primary efficacy parameters.

Results in B1 study show that both biosynthetic and semi-synthetic insulin gave similar lowering of glycated hemoglobin levels until week 12 of the study. Thereafter the levels remained constant during the second half of the study. There is no significant difference between biosynthetic and semi-synthetic insulins during the 24-week study. Subgroups analyses performed with different factors (age, sex, type of diabetes, pre-study treatment with insulin, presence of diabetic late complications) show that there were no special areas of concern for patients in these subgroups with respect to % glycated haemoglobin. In all treatments the level of glycated haemoglobin was less than optimal.

In study B2 at endpoint no significant increase (0.2%) of glycated haemoglobin was measured. In this study the patients had a better metabolic control at baseline compared to the B1 study. The reason for this was the fact that most of the patients had already been treated with insulin pump when the study started.

The difference between mild, moderate and severe hypoglycaemia episodes was investigated by using the criteria of the American Diabetes Association.

With regard to the study B1, the tables (II and III) show the distribution of hypoglycaemic episodes separated by intensity after 10 weeks of treatment and during the entire study. After 10 week treatment more than 40% patients both semi-synthetic and biosynthetic group experienced hypoglycaemic episodes. No statistically significant difference between these two groups was seen.

Table II: After 10 weeks

	No. OF PATIENTS (%)					
	MILD		**MODERATE**		**SEVERE**	
No of Episodes	**HGT* (n=267)**	**H** (N=268)**	**HGT (n=267)**	**H (n=268)**	**HGT (n=267)**	**H (n=268)**
≥ 1	86 (32%)	78 (29%)	50 (19%)	45 (17%)	3 (1%)	6 (2%)
>3	29 (11%)	29 (11%)	9 (3%)	12 (4%)	0	0
> 9	15 (6%)	15 (6%)	3 (1%)	5 (2%)	0	0

Note: For 1 HGT and 3 H patients, recorded episodes did not specify intensity.
HGT* = biosynthetic insulin
H** = semi-synthetic insulin

Table III: During entire study

	No. OF PATIENTS (%)					
	MILD		**MODERATE**		**SEVERE**	
No of Episodes	**HGT (n=288)**	**H (N=289)**	**HGT (n=288)**	**H (n=289)**	**HGT (n=288)**	**H (n=289)**
≥ 1	118 (41%)	103 (36%)	78 (27%)	64 (22%)	7 (2%)	11 (4%)
>3	53 (18%)	47 (16%)	18 (6%)	23 (8%)	1	0
> 9	21 (7%)	24 (8%)	4 (1%)	8 (3%)	0	0

Note: For 3 HGT and 6 H patients, recorded episodes did not specify intensity.

In study B2, 19 patients out of 34 experienced at least one hypoglycemic episode per month. Most patients had had pump insulin before the study and all patients had had mild hypoglycemic episodes during the previous year. The patients who experienced severe and frequent episodes in the pre-study were also those who had greater hypoglycemic scores during the study. None of severe episodes led to

a serious adverse event or to a withdrawal. Frequency and severity of hypoglycemic episodes are in line with published data and clinical experience.

Clinical safety

Apart from routine analysis of adverse events and blood chemistry and hematology, IgG antibodies to insulin and antibodies to *E. coli* peptides were measured.

As in all studies with human insulin, the immunogenicity is quite low. In study B1 at the endpoint, 4 biosynthetic treated patients and 5 semi-synthetic treated patients had elevated IgG antibodies, that were not present at baseline. In study B2 IgG antibodies were detected in one patient, but they were present already at start. After 24 weeks of the study B1, antibodies to *E. coli* peptides decreased in both semi-synthetic and biosynthetic insulin treated groups. The elevated activity at baseline is explained by a cross reaction to antibody of previous *E. coli* infection.

Regarding the adverse events in study B1, the overall frequency both for biosynthetic and semi-synthetic insulin treated patients was 45%. Infection, usually a common cold (including fever, bronchitis, rhinitis, upper respiratory infections etc.) was the most frequently occurring adverse event in the biosynthetic insulin treated patients. None of them could be specially related to the insulin treatment. As in all insulin studies, some patients reported moderate reactions at injection site. Serious adverse events occurred in 8% biosynthetic and 10% semi-synthetic treated patients. In the biosynthetic insulin treated group infection and myocardial infarction were the most frequently recorded serious adverse events. In 4 patients the serious adverse events were considered to be possibly related to the study. In this study 3 patients, all in the biosynthetic group, died. Two of these had both a history of cardiovascular disease. The cause for the first death was ventricular fibrillation and for the second it was suspected to be arrhythmia or coronaropathy. The third patient died of acute diabetic ketoacidosis. The insulin does obviously not cause the death of this patient.

In study B2 the overall frequency of adverse events was 53% where infection was seen as the most common adverse event. Diabetic ketoacidosis occurred in one patient. This was likely to be due to a technical pump incident and more related to the pump and not to the insulin used. No deaths occurred in this study. One patient was withdrawn from the study because of recurrence of skin allergy to the plastic catheter used in the pump, which is a classical adverse event in insulin pump therapy and obviously unrelated to the type of insulin used in the system.

Postmarketing experience

No new concern regarding the safety of Insuman have been raised following assessment of postmarketing experience.

5. Overall risk/benefit analysis

The CPMP, on the basis of the overall benefit/risk ratio, considers that Insuman showed a satisfactory safety profile and adequate evidence of efficacy.

The Marketing Authorisation Holder has been requested to submit additional chemical-pharmaceutical and clinical information on this medicinal product. All additional studies will be carefully assessed and the results will be reviewed by the CPMP.