

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of NovoRapid. This scientific discussion has been updated until 1 September 2004. For information on changes after this date please refer to module 8B

1 Introduction

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

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

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

This application seeks marketing authorisation for insulin aspart (IAsp), a human insulin analogue, for the treatment of patients with diabetes mellitus.

Insulin aspart is a rapid-acting human insulin analogue produced by recombinant DNA technology. Insulin aspart differs from human insulin in that proline in position B 28 of the insulin B-chain is replaced by aspartic acid.

Insulin aspart (IAsp) has been developed for use as rapid-acting insulin in a meal-related regimen for the treatment of insulin requiring diabetes. The goal was to provide diabetic patients with a fast-acting insulin with a more physiological pharmacokinetic profile that allows doctors and patients to intensify mealtime insulin treatment without increasing the risk of hypoglycaemic or other adverse events.

2 Part II: Chemical, pharmaceutical and biological aspects

Composition

The composition of NovoRapid is given in Table 1.

Table 1. Composition of NovoRapid

Ingredient
Insulin aspart
Glycerol
Phenol
Metacresol
Zinc (as chloride)
Disodium Phosphate Dihydrate
Sodium Chloride
Sodium Hydroxide
Hydrochloric acid
Water for injections

NovoRapid is presented in vials (NovoRapid), cartridges (NovoRapid Penfill) and in multidose disposable pre-filled syringes (NovoRapid NovoLet, NovoRapid FlexPen and NovoRapid InnoLet).

Active substance

Development Genetics

Insulin aspart is produced from a protein, which is expressed by a gene incorporated into a plasmid. *Saccharomyces cerevisiae* is used as host strain. The production and characterisation of the production strain have been adequately described.

Cell bank system

The cell bank system consists of an Initial Cell Culture (ICC), a Master Cell Bank (MCB) and a Working Cell Bank (WCB). The preparation and storage of the cell bank system has been adequately described.

Production of active substance

The production of the active substance via two intermediate products has been adequately described. It involves the following process steps: propagation, fermentation, recovery and purification.

The applicant has developed a new process (NN2000) for the manufacture of the active substance employing a changed expression system of the same host organism *Saccharomyces cerevisiae* as used with an optimised recovery and purification steps. The new clone, YAK1214, and the currently approved yJB155 cell clone have been established from the same parental cell line, but using different expression vector constructs.

The current process will be replaced by the new process (NN2000).

Specification

An acceptable active substance specification has been proposed. The analytical methods have been described and sufficiently validated.

Other ingredients

The excipients used are described in Ph.Eur., except for Zinc (as chloride), sodium hydroxide and hydrochloric acid, which are manufactured from chemical agents conforming to Ph. Eur.

Product development and finished product

The components and their concentrations have been chosen with regard to stability of the active substance molecule in solution as well as to isotonicity and anti-microbial preservation of the product. A comprehensive development pharmaceuticals section has been presented in which the choice of composition for a neutral soluble preparation of rapid acting insulin analogue, insulin aspart is justified.

Studies have been presented showing that the NovoLet, FlexPen and InnoLet pen injector fulfils the dose accuracy tolerance limits defined in ISO/DIS 11608 "Pen-injector for medical use – Part I: Requirements and test methods".

The rationale for the manufacturing process has also been comprehensively discussed. The (identical) manufacturing formulations are presented for vial and Penfill 3ml products.

The NovoLet, FlexPen and InnoLet are manufactured by assembling the Penfill cartridge and pen injector parts.

The validation studies performed show satisfying performance of the aseptic process and closure of the container.

Finished product stability

Testing has been carried out in accordance with the finished product specification.

Overall it may be concluded that a shelf-life at 2-8°C, as indicated in the SPC, is acceptable.

Manufacturing facilities

The active substance is manufactured by Novo Nordisk A/S. The site of manufacture is:

- Hallas Allé, 4400 Kalundborg, Denmark.

Manufacture of the finished dosage form takes place at the production sites:

- Novo Nordisk A/S, Novo Allé, 2800 Bagsvaerd, Denmark
- Novo Nordisk Pharmaceutique S.A., 45, Avenue d'Orléans, F-28002 Chartres, France.

Assembly of pre-filled syringes takes place in:

- Novo Nordisk A/S, Hallas Allé, 4400 Kalundborg, Denmark
- Novo Nordisk A/S, Brennung Park, 3400 Hilleroed, Denmark
- Novo Nordisk Pharmaceutique S.A., 45, Avenue d'Orléans, F-28002 Chartres, France.

A valid manufacturing licence covering these sites has been updated on 9 July 2003 by the Danish Medicines Agency.

GMP inspection status

There were no major issues relating to manufacture of the finished product, therefore a product specific inspection was not considered to be necessary by the CHMP. An inspection of the active substance manufacturing site was also not considered to be necessary. Batch release for all EU member states is performed by Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark or Novo Nordisk Pharmaceutique S.A., 45, Avenue d'Orléans, F-28002 Chartres, France.

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.

3. Part III: Toxicopharmacological aspects

Pharmacodynamics

Related to the proposed indication

Receptor binding. Data from human insulin (HI) receptor binding assays using soluble HI receptors with and without the 36 bp exon11 insert and hepatoma (HepG2) cells, showed an affinity essentially similar (92-100%) to that of HI. There were also no significant differences in receptor dissociation rate constants relative to HI in CHO cells overexpressing the HI receptor and in human HepG2; $81 \pm 8\%$ and $112 \pm 14\%$ (SEM), respectively.

Data from IGF-1 human receptor binding assays revealed a relative affinity of insulin aspart (IAsp) for the soluble human IGF-1 receptor(s) of 132% (relative EC_{50} values) compared with HI, while the corresponding figure in human HepG2 cells was 69%.

Tyrosine kinase activation. Studies on the activation of tyrosine kinase associated with partly purified soluble receptors (insulin and IGF-1) from HepG2 cells showed a relative activity compared to HI of 204% with a confidence interval of 118-353%. Additional data were submitted showing relative tyrosine kinase activation of 100 and 93% in two batches of IAsp. These assays were conducted using partly purified rat skeletal muscle cells. In another newly performed study using CHO cells overexpressing the human insulin receptor, a relative potency to HI of 107% was obtained.

It was concluded that the presented information on receptor affinities, dissociation rates and tyrosine kinase activation provided evidence that there were no relevant differences between IAsp and human insulin.

Glucose lowering effect. IAsp showed similar plasma glucose lowering effect in diabetic mice to human insulin (HI) at a subcutaneous dose of 1 U/kg. IAsp was also effective in lowering plasma glucose in healthy rats.

The biological potency of IAsp was determined against the first international HI standard (WHO 83/500) using the blood glucose lowering effect in mice as endpoint. The molar potency was not statistically significantly different from that of HI. When using the blood sugar assay in rabbits according to the USP, a similar potency to that obtained in the mouse assay (Ph Eur) was observed. In mouse free fat cells, the stimulation of lipogenesis did not differ between IAsp and HI, lending further support to similar molar potency of these two insulins.

In healthy pigs, IAsp gave an earlier onset and an earlier decline in glucose lowering effect compared with that of HI.

General Pharmacodynamics

A number of studies of adequate design comparing IAsp with HI were conducted in order to investigate potential effects on the central nervous, autonomic, cardiovascular and respiratory system. The observed effects induced by IAsp did not qualitatively or quantitatively differ from those obtained with HI at equal dosing.

Data on the mitogenic activity of IAsp relative to HI and the insulin analogue AspB10 as obtained in human MCF-7 cells and in CHO K1 cells was presented. The results in CHO K1 cells were essentially similar to those of HI whereas the mitogenic activity of IAsp in MCF-7 cells indicated differences to HI. Subsequent analysis indicated lower activity than initially calculated but the analysis also showed that the results in MCF-7 cells were not sufficiently robust for proper assessment. Newly performed studies using human osteosarcoma B10 cells revealed essentially similar response of IAsp and HI. A summary table of available mitogenicity data comparing IAsp with HI, insulin lispro and/or AspB10 is given in Table 2.

Table 2. Mitogenic potential (relative EC50 values to HI) of IAsp, insulin lispro and AspB10 as determined in various cell systems; 95% confidence intervals or SEM are given.

	IAsp	Insulin lispro	B10 analogue
MCF-revised*	1.2 (0.9-1.6)	n.d.	n.a.
CHO-K1**	0.94 (.76-1.38)	1.0 (0.8-1.4)	6.6 (5.3-8.3)
HOSC/B10***	0.58 ± 0.22	0.66 ± 0.21	15.1 ± 0.6
HMEC****	n.d.	0.89 ± 0.1	3.4 ± 0.4

* Revised Study T-17; S-phase percentage used as endpoint.

** Chinese Hamster Ovary K1 cells; ³H-thymidine used as endpoint.

*** Trub (new study, March 99); Human Osteosarcoma cells B10, ³H-thymidine as endpoint.

**** Slieker et al 1997; Human Mammary Epithelial Cells; cell number used as endpoint.

Data presented by the applicant indicated that the relative numbers of insulin and IGF-1 receptors were essentially similar in CHO-K1, human osteosarcoma B10 and human mammary epithelial (HMEC) cells. It was concluded that sufficient information had been provided to demonstrate no relevant differences in mitogenic potency between IAsp, insulin lispro and native insulin.

Pharmacokinetics

The pharmacokinetics were investigated in rats, dogs and pigs following single s.c. and i.v. injection, as well as after repeated s.c. administration in rats and dogs. HI was used as comparator in many of the studies. The PK data after single s.c. dosing in rats and dogs are shown in Table 3.

Table 3. Comparative basic PK-parameters of IAsp and HI after s.c. injection

Parameter	Man (0.1 U/kg)		Dog (1 U/kg)		Rat (6 U/kg)	
	IAsp	HI	IAsp	HI	IAsp	HI
$t_{1/2}$ (min)	76	122	67	57	22	23
C_{max} (pM)	246	102	3146	2871	1700	1800
T_{max} (min)	52	145	46	60	15	15
Cl (l · min/kg)	0.02	0.02	0.06	0.05	0.04	0.06

Plasma pharmacokinetics of repeated s.c. administered IAsp (twice daily for 7 days) were assessed in rat (up to 6 U/kg) and dog (up to 1.0 U/kg). There were no apparent change in plasma profile level between day 1 and day 7, and a dose-proportional increase in AUC was evident in both species.

Single and Repeated Dose Toxicity

Single subcutaneous and intravenous injections of IAsp were well tolerated by rodents (mice and rats) and dogs. Only few animals showed signs of hypoglycaemia even at very high doses given systemically. Acute deaths in mice were considered to be due to hypoglycaemia.

Repeated dose toxicity studies were performed in Sprague-Dawley rats and beagle dogs with subcutaneous administration of up to 52 weeks duration. In the pivotal 52-week study in dogs, daily dose levels of 0.5, 1, and 2 U/kg were given bid; another group of dogs was given 2 U/kg/day of HI. Despite careful management between food intake and treatment hypoglycaemic episodes occurred in high dose animals and the dose level was therefore reduced to 1 U/kg/day from week 29 onwards.

No significant antibody titres were detected and the only toxicity findings observed were those related to hypoglycaemia.

In the two 52-week studies performed in Sprague-Dawley rats (T12 and T13), deaths occurred especially in high dose animals in both HI and IAsp treated animals. The cause of deaths was considered to be the result from hypoglycaemia despite food access *ad libitum*.

The primary pharmacological effect of IAsp, i.e. p-glucose depression, appeared to be maintained throughout the treatment periods of up to 52 weeks. Fasted p-glucose appeared to increase over time in a dose-related manner. Antibody determination revealed significant immunological response against IAsp as well as HI (only in the 52-week studies). The antibodies detected did not appear to neutralise the primary effect of IAsp or HI.

Other findings in the study T12 were elevated p-triglyceride levels, increased incidence of focal seminiferous epithelial atrophy in high dose males, and increased incidence of subcutaneous masses in the mammary gland region.

A statistical analysis (time-to-tumour method according to Peto et al.; incidental/non-incidental classification) of the data coming from both non-survivals and survivals revealed statistically significant increase in the incidence of all mammary gland tumours combined (fibroadenoma, adenoma and adenocarcinoma) and benign mammary tumours alone in IAsp female rats dosed 200 U/kg/day (~ 100-200 times maximum clinical dose) in comparison with that of the control group; see Table 4. There were no statistically significant differences when the incidence of mammary tumours in the 200 U/kg/day group was compared with that in the HI reference group (p=0.062).

In the T13 study (non-GLP) in female Sprague-Dawley rats, no significant differences in incidence of mammary tumours were reported between the controls and rats treated with 200 U/kg/day of IAsp (Table 4). There were no statistically significant differences when the incidence of mammary tumours in the high dose group was compared with that in the HI reference group (p=0.52).

A Peto analysis on the combined incidence of mammary tumours in high dose animals of the two 52-week studies in Sprague-Dawley (T-12 and T-13) indicated that the tumourigenicity of IAsp was not different from human insulin (p=0.29).

Table 4 summarises the statistically significant findings relative to control with respect to mammary tumors in female Sprague-Dawley rats in the performed 52-week toxicity studies on IAsp (T12 and T13). For comparison results are also shown from a previously performed study on insulin Asp B10 (B10 analogue), which was previously identified as being significantly different from human insulin

(Dideriksen/Huntington). Furthermore results from an additional 52-week female Sprague-Dawley rat study with human insulin (NVO104) are shown. In the study, HI showed a significantly increased incidence of mammary tumours in female rats dosed with 150 U/kg/day (reduced to 75 /kg/day at week 40) compared to controls, see Table 4. The incidence of adenocarcinomas was also significantly elevated at this dose level. No statistically significant differences compared to controls were found at the lower dose level of 60 U/kg/day (reduced to 30 U/kg/day at week 40).

Table 4. Overall outcome of 52-week toxicity studies conducted with human insulin and insulin analogues in female Sprague Dawley rats. Statistically significant differences relative to controls as regards benign tumors (B), malignant tumors (M), all tumors combined (C). n.s. indicates no statistically significant increase in mammary tumors compared to controls.

Dose U/kg/d	Human insulin			B10 analogue			IAsp analogue		
	60	150	200	12.5	50	200	10	50	200
Dideriksen/ Huntington			n.s.	B	M	B/M			
NVO104	n.s.	M/C							
T13			B/C			B/C			n.s.
T12			n.s.				n.s.	n.s.	B/C

It is concluded that both HI and IAsp have the capability to produce mammary tumours in the Sprague-Dawley rat upon prolonged exposure at supraphysiological doses (approximately 100 times the human exposure). The relevance of results generated at such high doses/exposures as well as the ethics of conducting long-term studies at doses, which produce 50% mortality within one year, was questioned. Although the design of the 52-week studies with IAsp can be criticised, it was concluded that the results obtained in studies with a similar background incidence of benign and malignant mammary tumours did not indicate any significant or relevant difference in tumourigenic potential between IAsp and HI. The overall evidence from in vitro and in vivo data thus suggests that the mammary tumours observed are not relevant for the proposed therapeutic use of IAsp.

Toxicity to Reproduction

Toxicity to reproduction was investigated with conventional designs in Sprague-Dawley rats and rabbits following subcutaneous administration. Reference groups of animals treated with HI were included in all the three separate studies. In rats, IAsp had no direct effect on fertility or embryo-foetal development. Findings observed were secondary to treatment-induced hypoglycaemia and were similar to those observed with HI.

Genotoxicity and carcinogenicity

The ability of IAsp to induce gene mutations in bacteria and mammalian cells and chromosomal aberrations in vitro and in vivo was investigated. Tests of primary DNA damage in vitro was also conducted. IAsp showed no potential for mutagenicity or clastogenicity in the standard battery of genotoxicity tests in the presence and absence of rat liver S9 fraction.

No carcinogenicity study was performed and this was accepted in view of the tumour findings in the 52-week repeat dose toxicity studies in rats, see above.

Environmental risk assessment

The applicant considers that the protein nature of IAsp and its very close similarity to marketed insulins, with their ready degradation, do not suggest any environmental risk. Neither do the containers and devices constitute any hazard to the environment. This argumentation was considered reasonable.

Overall conclusion on toxico-pharmacological aspects

The submitted documentation is in accordance with a full application for a new active substance. Insulin aspart from two different manufacturing processes was used in the preclinical studies. The change was implemented between phase I/II and III clinical trials. Batches produced by the old and new processes were compared in single dose toxicity studies as well as in a 4-week repeated dose study in rats; no differences in toxicity were observed.

Information was provided showing the expected pharmacodynamics of this modified insulin. Toxicities related to the exaggerated pharmacological response were seen in all repeated dose studies. A list of questions covering human epidemiology, *in vitro* and *in vivo* experiments related to the mitogenic and tumourigenic activity of IAsp in relation to HI formed the basis for discussions. It was concluded that the *in vitro* and *in vivo* data provided did not indicate any significant or relevant difference in mitogenic or tumourigenic potential between IAsp and human insulin.

4. Part IV: Clinical aspects

Clinical Pharmacology

Pharmacodynamics

The pharmacodynamic response to IAsp administered s.c. was investigated in:

- healthy subjects in three euglycaemic clamp trials
- diabetic subjects in four trials:
 - two in Type 1 male diabetic adults
 - one in Type 2 diabetic adults
 - one in Type 1 diabetic children and adolescents

Healthy subjects

The results from trials in healthy subjects supported the conclusion that IAsp has a faster onset and a shorter duration of action compared with HI. When injected s.c. into the abdominal wall, the onset of action of IAsp occurred from 10 minutes of injection, and maximum effect was exerted between 1 to 3 hours post injection. Based on $t_{AUC\%}$, the duration of action of IAsp was estimated at 3 to 5 hours.

Type 1 diabetic adults

In Type 1 diabetic subjects the postprandial serum glucose profiles were compared following a single 0.15 U/kg dose of IAsp just before a standard meal, or of HI just before or 30 minutes before a standard meal. The subjects were clamped from the evening before trial product administration in order to obtain a blood glucose concentration of 5 to 8 mmol/L. Postprandial glucose excursion was lower for IAsp than for both HI treatments. The duration of action of IAsp ranged between subjects from 3 to 5 hours, which was shorter than that for HI. C_{max} for serum glucose was significantly lower for IAsp compared with HI_{0min} , but not with HI_{30min} .

Type 1 diabetic children and adolescents

In Type 1 diabetic children (aged 6 to 12 years) and adolescents (aged 13 to 17 years) pharmacodynamics were compared following a single 0.15 U/kg dose of either IAsp or HI just before a meal. IAsp tended to reduce glucose excursions compared with HI during the 4-hour post-dosing period, otherwise no differences were observed.

Type 2 diabetic subjects

In Type 2 diabetic subjects postprandial serum glucose profiles were determined following a single 0.15 U/kg dose of IAsp just before a standard meal, or of HI just before (HI_{0min}) or 30 minutes before (HI_{30min}) a standard meal. The subjects were clamped overnight in order to obtain a morning serum glucose in the range of 5 to 8 mmol/l. Postprandial glucose excursions and maximal postprandial glucose values were lower with IAsp than with HI_{0min} .

Pharmacokinetics

The pharmacokinetics of IAsp have been studied in healthy volunteers, Type 1 and Type 2 diabetic patients and in Type 1 diabetic children and adolescents.

Absorption

IAsp is rapidly absorbed after subcutaneous administration. Maximum concentration of IAsp was reached 40 to 50 min after dose, which is approximately 1 hour earlier than for HI. C_{max} for IAsp was approximately twice that for HI.

The pharmacokinetics have not been studied after multiple-dose or long-term administration.

Elimination

Clearance was estimated to be 1.22 ± 0.32 l/h/kg. The half-life has not been determined after i.v. injection. The terminal half-life of s.c. administered insulin is absorption rate limited and was 102 min. The insulin concentration returned to baseline more rapidly for IAsp than for HI.

Metabolism and excretion

The metabolites of IAsp are assumed to be natural amino acids and peptides that are subsequently incorporated into host proteins or metabolised, as with HI.

Target population

The pharmacokinetics profile of IAsp were compared with those of HI in Type 1 and Type 2 diabetic patients. The trials were performed with test meals after an overnight insulin infusion to ensure similar basal glucose levels in the morning. The pharmacokinetics of IAsp 0.15 U/kg bw given s.c. immediately before a meal were compared with HI given 30 minutes before a meal or immediately before a meal.

The pharmacokinetics in Type 1 diabetic patients were found to be similar to that of healthy volunteers. The insulin concentrations increased rapidly and reached a C_{max} that was twice as high as that for HI, and t_{max} was about 40-60 min earlier than for HI. The concentrations returned to baseline earlier than those for HI, about 4 to 6 hours after dose.

In Type 2 diabetic patients the IAsp concentration was determined with an IAsp specific ELISA. Thus, no comparison with pharmacokinetics of HI was made. AUC was of the same magnitude in Type 2 patients as in Type 1 patients, but C_{max} was 30% lower in Type 2 patients and t_{max} was reached about 20 minutes later than in Type 1 patients. This might partly be due to a thicker subcutaneous fat layer in Type 2 patients, which could decrease the absorption rate. In subjects with body mass index (BMI) <26 median t_{max} was 50 min compared with 70 min in patients with BMI ≥ 26 . C_{max} was also higher in normal Type 2 patients compared with obese patients, 68.3 ± 41.4 and 51.8 ± 39.2 mU/l, respectively. The clinical relevance of these differences in Type 2 diabetic patients was considered to be small, but stresses the importance of individual titration.

The pharmacokinetics were studied in 18 Type 1 diabetic children and adolescents aged 6-17 years after s.c. administration of a single dose of 0.15 U/kg IAsp or HI in two different periods. The data were analysed both for all children together and for the age groups 6-12 and 13-17 years. The pharmacokinetics in paediatrics differed from adults, in that higher C_{max} and AUC were observed in paediatrics, but similar t_{max} and MRT. Similar differences between paediatrics and adults were also seen for HI.

Special populations

The pharmacokinetics have not been studied in elderly or patients with liver or kidney impairment.

Clinical efficacy

The efficacy of IAsp has been studied in 4 controlled clinical trials in patients with Type 1 and Type 2 diabetes. They are summarised in Table 5. In all studies one or two daily injections of intermediate acting insulin (NPH) were combined with short acting insulin (IAsp or HI) before each meal.

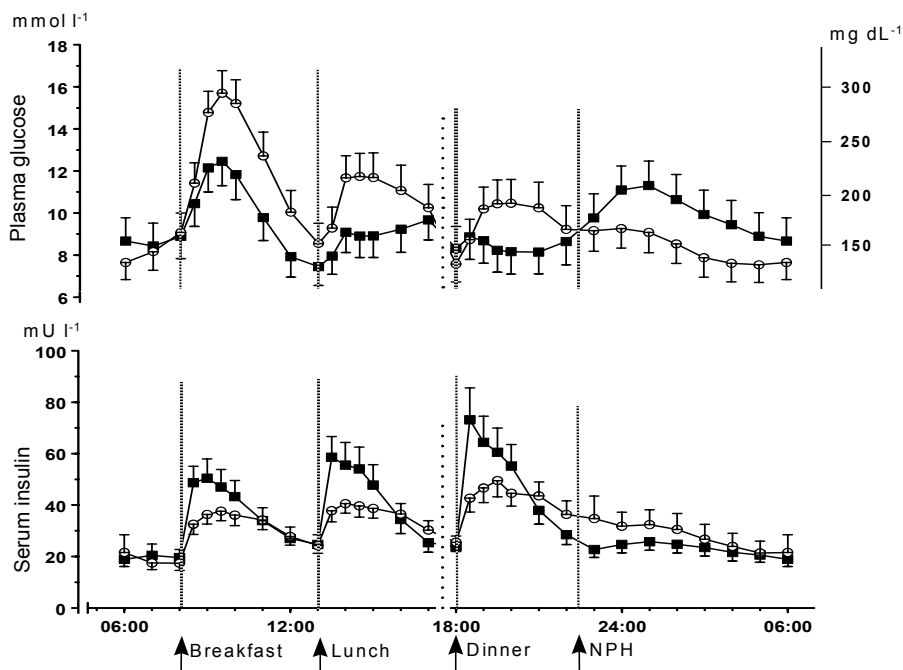
Table 5. Overview of Controlled Clinical Trials

Trial ID/Trial Population/	Design ^a	Duration/Treatment Dose	Primary Efficacy Variable	Secondary Efficacy Variables and Other Variables
Phase II (Type 1 Diabetes)				
<u>ANA/DCD/025/UK</u> Well-controlled male patients Mean age 34 years Mean duration of diab 15 yrs Randomised n=104 Completers n=90	Double-blind Crossover	4 weeks on IAsp + 4 weeks on HI Dosage was adjusted on an individual basis.	Fructosamine	Derived from 23-hour serum glucose (SG) profiles: - ΔAUC - C _{max} and C _{min} 8-point blood glucose (BG) profiles Insulin: meal-related/basal ratio Incidence of hypoglycaemia
Phase III (Type 1 Diabetes)				
<u>ANA/DCD/035/EU^{b,c}</u> Male and female patients M/F 55%/45% Mean age 38 years Mean duration of diab 15 yrs Randomised Iasp/HI 708/367	Open-label Parallel-group	6 months Dosage was adjusted according to local practise	HbA _{1c}	Derived from 8-point BG-profiles: - prandial increments - variability Insulin: - meal-related/basal ratio - total daily dose Incidence of hypoglycaemia Insulin antibodies
<u>ANA/DCD/036/USA^{d,e}</u> Male and female patients M/F 51%/49% Mean age 40 years Mean duration of diab 15 yrs Randomised Iasp/HI 597/287	Open-label Parallel-group	6 months Dosage was adjusted according to local practise	HbA _{1c}	Derived from 8-point BG-profiles: - prandial increments - variability Insulin: - meal-related/basal ratio - total daily dose Incidence of hypoglycaemia Insulin antibodies
Phase III (Type 2 Diabetes)				
<u>ANA/DCD/037/USA</u> Male and female patients M/F 62%/38% Mean age 57 years Mean duration of diab 13 yrs Randomised Iasp/HI 91/91	Open-label Parallel-group	6 months	HbA _{1c}	Derived from 8-point BG-profiles: - prandial increments - variability Insulin: - meal-related/basal ratio - total daily dose Incidence of hypoglycaemia Insulin antibodies

- a All trials were designed as multi-centre, randomised, active-controlled trials
- b EU = D,DK,N,S,SF,UK
- c Subjects completing the trial were invited to participate in a 2.5 year extension trial
- d The trial was also conducted in Canada
- e Subjects completing the trial were invited to participate in a 6 month extension trial

The phase II trial, 025/ UK, was designed to evaluate short-term safety and efficacy of IAsp compared with HI given immediately before meals in Type 1 diabetic subjects under strict glucose regulation. Serum fructosamine was the primary endpoint at the end of each 4-week treatment period. Enrolled patients were mainly Caucasian (96%), aged between 30 and 50 years (mean 34.3 years), with a mean BMI of 25.5 kg/m². They had a mean duration of diabetes of nearly 15 years and a mean baseline HbA_{1c} of 7.1%. Regarding the primary variable, fructosamine levels at the end of each treatment period, no differences between treatments were observed. The 23-hour Plasma Glucose Profiles and Serum Insulin Profiles are illustrated in Figure 1.

Figure 1. Mean 23-hour Plasma Glucose and Serum Insulin Profiles at the End of Treatment Period. Mean \pm 2 SE (filled squares are IAsp, open circles are HI).



The baseline corrected plasma glucose excursions (Δ AUC) outside the normal range (defined as 4mmol/l to 7mmol/l), were smaller with IAsp, compared with HI. The maximum plasma glucose concentrations after breakfast (C_{\max} Morning) and lunch (C_{\max} Afternoon) were lower with IAsp than with HI. During the same intervals, the minimum postprandial glucose levels (C_{\min}) were also significantly lower with IAsp. Hypoglycaemia was classified in minor (the patients dealt with the episode themselves), and major episodes (the patient required third party help). During four weeks of treatment, a total of 16 patients reported 20 major hypoglycaemic episodes with IAsp and 24 patients reported 44 major episodes with HI ($p=0.002$). The incidence of major hypoglycaemic episodes during the last two weeks of each treatment period was assessed separately to avoid possible carry-over effects. A total of nine patients had 11 major hypoglycaemic episodes while on IAsp, compared with 15 patients with 22 major episodes while on HI ($p=0.04$).

The three phase III trials were essentially identical in design. All three were 6-month multicentre, open label, parallel group trials, designed to evaluate the efficacy and safety of IAsp compared with HI in type 1 (035/EU and 036/USA) and type 2 diabetic subjects (037/USA). In these trials IAsp, given immediately before meals was studied against HI administered 30 minutes before meals, as part of a basal-bolus regimen with one or two daily injections of NPH as the basal insulin component. Enrolled patients were required to have been treated with HI in any treatment regimen for at least 12 months. Therapeutic response was primarily evaluated by measurements of HbA_{1c}. The secondary and other efficacy variables are presented in Table 11. The trials excluded patients anticipated to be severely insulin resistant, or to exhibit poor compliance, as well as those with poor function of organ systems involved in drug/glucose metabolism. The demographic and baseline characteristics were similar in the European trial and the US trial, with the exception of the number of daily injections of basal insulin at baseline. In 035/EU, 60% of subjects took one basal injection while the remaining 40% took two injections daily. In 036/USA, more than 95% of subjects took only one basal insulin injection daily.

HbA_{1c} after 6 months

Mean HbA_{1c} after 6 months was slightly, but significantly lower for type I diabetic patients treated with IAsp compared with HI in trials 036/USA, 035/EU (difference between treatment groups in mean HbA_{1c} at 6 months being 0.12 and 0.15 percentage point, respectively).

In Type 2 diabetic patients, no significant differences were observed, but according to preplanned criteria, non-inferiority of IAsp to HI was documented.

8-point BG (Blood Glucose) profiles

In Type 1 diabetic patients, mean postprandial BG levels at 6 months were significantly lower in the IAsp group compared with the HI group after all three meals. There was no treatment difference between pre- and postprandial BG levels or bedtime and night-time BG levels in Type 2 diabetic subjects. Analysis of mean prandial increments for the three main meals and the within subject variability (= standard deviation) in the mean 8-point BG profile after 6 months of treatment was performed for each of the phase III trials. The mean prandial BG increments (mean difference between pre meal and post meal BG values) were significantly lower in Type 1 diabetic subjects treated with IAsp compared with HI. Despite lower postprandial BG levels with IAsp, the within-subject variability in BG over the day did not differ between treatments in either trial. There was no difference between IAsp and HI treatment with respect to the mean prandial increase in BG levels or the within subject variability in BG in Type 2 diabetic subjects. Twelve-month data (036ext/USA) on glycaemic control were available in 467 patients on IAsp, compared with 208 on HI. The significant benefit of IAsp on mean HbA_{1c}, seen at six months, was maintained over 12 months (difference HI – IAsp: 0.14 percentage point, 95% C.I: 0.00;0.27) as was the slightly better postprandial glucose control with IAsp, compared with HI.

Hypoglycaemia versus Metabolic Control

In the phase III trials, hypoglycaemia was classified in the same way as in the Phase II trial 025/UK. Overall, no relevant differences between treatment groups were noted regarding the incidence of hypoglycaemic events. To evaluate whether there was any difference between treatments with regard to glycaemic control achieved and the incidence of hypoglycaemic episodes, HbA_{1c} levels were compared between patients in both treatment groups with the same frequency of major episodes and minor episodes. There was a significant treatment difference observed in HbA_{1c} in Type 1 diabetic patients regardless of the frequency of major episodes in both trials. The majority of Type 2 diabetic subjects did not have any major hypoglycaemic episodes during the six months of treatment with either IAsp or HI. After adjusting for the rate of major and minor hypoglycaemic episodes, the differences in HbA_{1c} between treatments remained significant in Type 1 diabetic subjects. Thus, Type 1 diabetic subjects with similar risk of having major or minor hypoglycaemic episodes had, on average, significantly better glycaemic control with IAsp.

Insulin doses

The mean dose of basal insulin after six months of treatment was significantly higher in Type 1 diabetic subjects treated with IAsp compared to HI (p=0.0002). The mean dose of basal insulin was on average 7.4% higher in the IAsp group than in the HI group in 036/USA, and 10.3% higher in the IAsp group than in the HI group in 035/EU. There was no difference between IAsp and HI treatment with respect to mean meal-related insulin dose after 6 months of treatment. When the estimates of the IAsp-HI differences in HbA_{1c} were adjusted for differences in basal insulin dosing at baseline and after 6 months, HbA_{1c} with IAsp treatment was still significantly lower than with HI treatment in Type 1 diabetic patients in both trials. At 12 months, mean basal insulin doses were identical between treatments and mean daily doses of IAsp and HI remained essentially constant over the entire treatment period.

No differences in meal-related or basal insulin dose were observed between treatment in Type 2 diabetic subjects.

Insulin Antibodies

Insulin antibodies were categorised into three groups according to their insulin binding ability: HI specific - only binding to HI; IAsp Specific - only binding to IAsp; cross-reacting antibodies - capable of binding to both HI and IAsp. Antibodies were measured by means of a radioimmunoassay (RIA) at baseline and three months (036/USA and 037/USA), and after six months (all Phase III trials). Twelve-month data were later submitted for 464 patients on IAsp and 201 patients on HI (036ext/USA).

HI and IAsp specific antibodies were absent in the majority of subjects. After six months of treatment, cross-reacting antibody titres were consistently higher than at baseline in the IAsp group, and similar or lower than at baseline in the HI group. Beyond 6 months, mean antibody titres decreased and at 12 months had returned to baseline levels. At this timepoint, change in cross-reactive antibodies did not differ significantly between treatments.

When tested at 6 months, there was no significant correlation between the percentage of antibodies (antibody titres) and the metabolic control or insulin doses reached during the studies.

Clinical safety

Patient exposure

The cumulative number of subjects who were exposed to at least one dose of IAsp and/or HI in the controlled trials is presented by duration of exposure in Table 6.

Table 6. Cumulative Number of Diabetic Subjects Exposed to IAsp and HI by 5 August 1998 – All Phase III Trials.

	Type 1 Diabetics ^b		Type 2 Diabetics ^c	
	IAsp N	HI N	IAsp N	HI N
Number of Subjects Exposed	1303	644	91	91
Duration of Exposure ^a				
= 1 month	1290	631	90	89
= 2 months	1270	623	89	88
= 3 months	1261	614	89	86
= 4 months	1246	608	89	85
= 5 months	1236	602	88	84
= 12 months ^d	870	447		

a. one month = 30 days

b. 036/USA and 036ext/USA combined, and 035/EU and 050/EU, combined.

c. 037/USA.

d. Includes limited safety data for 050/EU not presently included in the integrated database.

A total of 1,303 Type 1 diabetic subjects and 91 Type 2 diabetic subjects were exposed to IAsp during the phase III development program. Due to the fact that monthly intervals between visits in the trial were not rigidly defined, not all subjects who completed 036ext/USA were treated for 12 x 30 days. Thus, a total of 49 subjects in the IAsp group and 20 in the HI group are not included in the category for ≥ 12 months.

Adverse events and serious adverse events/deaths

Four deaths have been reported in the world-wide IAsp development programme up until 1 December 1998, only one of these subjects was exposed to IAsp. Three of the deaths occurred in the phase III trials (035/EU, 037/USA and 050/EU) and one occurred in a phase IIIb trial. All four deaths were evaluated by investigators as being unlikely related to the trial products. There were no new deaths reported in either of the extension trials.

The overall incidence of withdrawals due to AEs during the IAsp Clinical Development Programme was low. In the phase III trials, less than 1% of Type 1 diabetic subjects in either treatment group withdrew due to AEs. The AEs leading to withdrawals in both treatment groups are considered typical of the patient population studied (Table 7). There were no AE-related withdrawals reported for Type 2 diabetic subjects in the IAsp group.

Table 7. Adverse Events Leading to Withdrawal IAsp and HI Treatment in the Phase III Trials 035/EU and 036/USA combined

Preferred Terms	Incidence of Events			
	Type 1 Diabetic Subjects		Type 2 Diabetic Subjects	
	IAsp	HI	IAsp	HI
Number of Subjects Exposed	1303	644	91	91
Number of subjects withdrawn due to AEs	9 (<1%)	5 (<1%)	0	3 (3%)
Angina pectoris		1		
Cerebrovascular disorder				1
Colon carcinoma				1
Coma hypoglycaemia	1			
Coronary artery disorder	1			
Fatigue	2			
Headache	1			
Hypoglycaemia		2		
Injury accidental	1			
Ketosis	1			
Larynx neoplasm malignant		1		
Myocardial infarction	1			1
Nausea	1			
Neuropathy		1		
Urticaria	1			
Weight increase	1			

Incidence of hypoglycaemia

A total of 592 major hypoglycaemic episodes were reported, mainly by Type 1 patients treated with IAsp in the phase III trials, compared with 317 major episodes in subjects treated with HI. The overall frequency distribution of major hypoglycaemic episodes in both Type 1 and Type 2 diabetic subjects was similar for IAsp and HI treatments. The overall rate of minor hypoglycaemic episodes was similar between treatments.

Relative Risk of Hypoglycaemic Episodes

The relative risk of having a major hypoglycaemic episode was estimated using the number of major hypoglycaemic episodes that occurred during each treatment as the endpoint. The estimated relative risk of major hypoglycaemic episodes, adjusted for the number of hypoglycaemic episodes during the run-in period, did not differ significantly from unity in either Type 1 or Type 2 diabetic patients.

There was no significant difference in the estimated risk of minor hypoglycaemic episodes between treatments in Type 1 diabetic subjects. For Type 2 diabetic subjects, the estimated risk of minor episodes was 15 % greater in the IAsp group than in the HI group, however, this difference was not significant.

Diurnal Distribution of Hypoglycaemia

The diurnal distribution of hypoglycaemic episodes during the treatment period was studied. Among Type 1 diabetics, there were trends to fewer major hypoglycaemic episodes in the IAsp group during the night (midnight - 8:00 a.m.). This was not consistent between the two Phase III trials, however. There were too few major episodes reported for Type 2 diabetic subjects to distinguish any pattern. There was a tendency for minor episodes to occur more frequently in the HI group from midnight to 4 a.m., compared with IAsp in both Type 1 and Type 2 diabetic patients.

The occurrence of major episodes in various time intervals after the last meal with short-acting insulin was generally distributed similarly for the IAsp group and the HI group. For both treatments, the proportion of subjects and the number of major hypoglycaemic episodes, peaked in the interval from 2 to 4 hours following a meal: 8% for the IAsp group versus 6% for the HI group. Three percent (3%) of the subjects in the IAsp group compared to 5% in the HI group had major hypoglycaemic episodes 4 to 6 hours after the meal when taking short-acting insulin before the meal.

Equally few major hypoglycaemic episodes occurred in both treatment groups (less than 1% of Type 1 diabetic subjects) at 0-1 hour following injection.

Laboratory findings

Laboratory adverse events of potential relevance were limited to the development of IAsp-HI cross-reactive antibodies.

Conclusions on clinical efficacy and safety

Pharmacological trials documented IAsp to have a more rapid onset and shorter duration of action, compared with HI. There were no indications of differences in glucose-lowering potency between HI and IAsp.

Clinical efficacy and safety was studied mainly in three six-month trials that enrolled patients with long-standing type 1 and type 2 diabetes without major secondary complications.

In two trials in type 1 diabetic patients, IAsp showed statistically significant superiority, compared with HI, regarding the primary endpoint, mean HbA_{1c} at six months. The difference between IAsp and HI was small in both trials and of, at best, limited clinical relevance. Long-term data, available in a reasonable number of patients with type 1 diabetes indicate sustained efficacy of IAsp. In type 2 diabetic patients, treatment with IAsp was non-inferior to treatment with HI with respect to glycaemic control as measured by HbA_{1c} after 6 months of treatment.

In all trials in type 1 diabetic patients, postprandial blood glucose increments and mean maximal blood glucose levels were lower with IAsp, compared with HI. This is reasonably a reflection of the more rapid onset of action of IAsp. In type 2 diabetic patients, no significant relationships were observed between diurnal blood glucose variations and the type of meal insulin used.

In the only moderately well controlled populations studied, there was no consistent relationship between glycaemic control, measured as HbA_{1c} and the incidence of hypoglycaemia. The slightly superior effect of IAsp on glycaemic control in type 1 diabetic subjects was not achieved at the expense of an increased risk of major or minor hypoglycaemic episodes, which occurred with similar incidence and diurnal variation irrespective of the type of meal insulin used. In type 2 diabetics, hypoglycaemic episodes were relatively few and without obvious relationship to glycaemic control or type of insulin used. Apart from hypoglycaemia, no specific, reasonably treatment related, clinical adverse reactions were observed.

Laboratory adverse events were limited to the development of IAsp-HI cross-reactive antibodies, the mean titres of which increased significantly during the first six months of therapy in IAsp-treated, but not in HI-treated patients. After one year, antibody titres had returned to baseline levels and there were no differences between treatment groups. There is currently no indication of clinically relevant immunogenicity of IAsp.

From the trials performed, it is considered acceptably documented that a basal-bolus regimen including IAsp provides at least as good metabolic control, as when HI is used as the meal component, and that IAsp, in comparison with HI, does not increase the rate of severe hypoglycaemia, nor alters the warning symptoms of hypoglycaemia. The lack of documentation of efficacy and safety beyond 6 months in type 2 diabetes is noted as a deficiency, but is considered acceptably compensated for by the extended experience in type 1 diabetes. A comparative pharmacodynamic study vs. insulin lispro in diabetic patients could yield clinically valuable information and will be performed by the MAH as a post-marketing commitment.

5. Overall conclusions and benefit/risk assessment

Overall conclusions on quality, efficacy and safety and benefit/risk assessment

The quality of the product has in all essential parts been acceptably documented. The applicant has agreed to resolve remaining quality issues by providing additional data on an ongoing basis or within one year post marketing authorisation.

Following evaluation of the preclinical documentation, it was concluded that IAsp showed the expected effects of an insulin product both in terms of primary pharmacodynamic effects and toxicity.

With regard to the clinical documentation, it was concluded that IAsp has been acceptably documented as a fast-acting insulin that provides metabolic control comparable with that of soluble

human insulin when used as the meal component of a basal/bolus regimen in patients with diabetes mellitus. The safety profile of IAsp is considered comparable with that of soluble human insulin.

When considering the recommendations of use as defined in the SPC, the benefit/risk ratio was regarded to be positive for NovoRapid.

The Company has agreed to study the pharmacodynamic characteristics of IAsp in comparison with insulin lispro.

6. Post marketing experience

Comparative pharmacodynamic and pharmacokinetic study with insulin lispro

A trial was performed with the objective to compare the pharmacodynamic and the pharmacokinetic profiles of subcutaneously injected IAsp and insulin lispro. The pharmacodynamic effects in terms of blood glucose profiles are essentially similar with the two insulin analogues. Due to methodological difficulties, the specific insulin analogue levels could not be determined and, thus, a strict pharmacokinetic comparison is not possible. It can be noted, however, that the post injection, post-prandial profiles for total insulin concentrations (the sum of basal human insulin and insulin analogue levels) were similar for the two analogues.

Postprandial administration

The postprandial administration of IAsp was studied in a single-centre, double-blind, double-dummy, 4 period, crossover study performed in 20, young to middle-aged patients with type-1 diabetes compared with soluble HI. In randomised order, HI was tested at 15 minutes before a breakfast test meal and immediately before the meal. IAsp was given immediately before the meal or 15 minutes postprandially.

The administration of IAsp 15 minutes after a meal represents suboptimal use of the product but postprandial administered IAsp is not inferior to suboptimally/incorrectly used HI. Occasional postprandial use of fast-acting insulin may be practical and it does not create any substantial health concern. Therefore, a statement was included in section 4.2 to reflect that when necessary, NovoRapid can be given soon after a meal.

Continuous Subcutaneous Insulin Infusion (CSII)

A pump system employs an electronic pump that can be programmed to deliver IAsp continuously and as a bolus. From a clinical point of view, the results from two studies provided sufficient data to conclude that IAsp could be used for continuous subcutaneous infusion in compatible pump systems

One study was an open-label, single centre study, where 30 patients were randomised 2:1 to receive either IAsp or buffered HI by continuous subcutaneous infusion. The patients were treated for 6 weeks with infusion set changes every 48 hours. The last 7th week the patients used the same infusion set during the whole week. Insulin doses, efficacy of treatment, safety and pump compatibility were evaluated. In this small study there was an insignificant tendency for more pump flow obstructions in the IAsp group. However, the frequency of catheter changes was the same in the 2 groups. There was a tendency for a higher proportion of basal to bolus doses in the IAsp group. Otherwise, there were no differences in clinical outcome.

Another study was a multicentre, open-label study where 146 patients were randomised to IAsp, buffered human insulin or insulin lispro on a 2:2:1 basis and they were treated for 16 weeks. The within-patient blood glucose variability did not differ between the 3 groups.

The mean daily insulin doses (basal, bolus and total) remained unchanged for each treatment group. The study results supported the conclusion that IAsp given subcutaneously in a suitable pump system can maintain good glucose control over time. The number of adverse events did not differ from the expected, as compared to other insulin preparations approved for use in external pumps.

Hypoglycaemic episodes

A class-labelling statement for fast-acting insulins was introduced in the SPC and PL with the following wording “*A consequence of the pharmacodynamics of rapidly acting insulin analogues is*

that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin”.

In addition, the Product Information was updated to reflect a reduced incidence of nocturnal hypoglycaemia, compared with human insulin with the following statement: *“Clinical trials in patients with type 1 diabetes have demonstrated a reduced risk of nocturnal hypoglycaemia with IAsp compared with soluble human insulin. The risk of day-time hypoglycaemia was not significantly increase”.*

The data studying the incidence of major hypoglycaemic episodes included:

- -A double-blind, cross-over trial comparing IAsp and HI in a multi-dose regimen over 16-week study periods with intervening 4-week washout in type1 diabetic patients. The primary endpoint was incidence of major hypoglycaemic episodes.
- -An analysis of pooled data from two six-month, open label clinical trials in type1 diabetic patients, where IAsp was compared with HI in a basal/mealtime bolus regimen.

Intravenous administration

IV administration (bolus or infusion) of soluble human insulin (HI) is well-established therapy e.g. in situations of diabetic ketoacidosis and/or severe hyperglycaemia, during acute illness, and during and after surgery. The short-acting insulin analogues are specifically engineered to provide improved absorption kinetics after SC administration and cannot be expected to have any inherent benefit after IV administration, relative to human insulin. Nevertheless, the CHMP has accepted utility in principle for IV use of short-acting insulin analogues, e.g. for patients already established on such therapy or with ”insulin allergy”.

The experience with IV administration of IAsp is studied in to two pharmacodynamic trials. Although no clinical trial data have been provided in the intended target population, the documentation is considered sufficient to support the essential characteristics of glucodynamic response and autonomic and hormonal counter-regulation to hypoglycaemia after IV administration. In all these respects, IAsp could be considered equivalent to HI. Therefore, the SPC and PL were updated to reflect that *“NovoRapid may also be administered intravenously.”*

Updating the Undesirable effects sections in labelling.

Sections “Undesirable effects” in the SPC and ”Possible side effects” in the package leaflets have been revised and updated with the frequencies of adverse drug reactions from clinical trials as requested by CHMP. Diabetic retinopathy and painful neuropathy have been included as ADRs. Diabetic retinopathy and painful neuropathy are normal complications of diabetes mellitus and not related to insulin treatment. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy and temporary painful neuropathy.

Readability

Readability test have been performed on package leaflets of the Novo Nordisk insulin products and the results applied to the NovoRapid package leaflets. Based on the results from the readability tests CHMP has accepted to include an extra heading (*!What to do in an emergency”*) and a revised format for headings as compared to the QRD template.

Benefit/Risk assessment

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of NovoRapid is favourable in the treatment of patients with diabetes mellitus.