SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Novomix. 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 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 I diabetic patients will eventually need 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. Especially in patients with significant residual endogenous insulin production, insulin requirements may be acceptably provided by a premixed insulin formulation containing both soluble and intermediate acting insulin, usually given twice daily.

Although this regimen does not offer optimal glycaemic control, patient compliance may be better for this simpler regimen than for the multiple injections regimens.

This application seeks marketing authorisation for biphasic insulin aspart 30 (BIAsp 30), which contains 30% soluble insulin aspart (IAsp) and 70% insulin aspart protamine crystals. Insulin aspart is a human insulin analogue produced by recombinant DNA technology, which differs from human insulin in that proline in position B 28 of the insulin B-chain is replaced by aspartic acid. A soluble formulation of IAsp (NovoRapid) was authorised under the centralised procedure on 7 September 1999.

BIAsp 30 has been developed to provide diabetic patients with the convenience of a premixed insulin which can be administered immediately before a meal or soon after a meal. The soluble fraction exerts rapid absorption reaching high insulin plasma concentrations after administration while the protamine bound fraction of IAsp has retarded absorption and provides the patient with a low insulin release during the day.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The composition of NovoMix 30 is listed below.

Insulin aspart
Mannitol
Phenol
Metacresol
Zinc (as chloride)
Sodium chloride
Disodium phosphate dihydrate
Protamine sulphate
Sodium hydroxide
Hydrochloric acid
Water for injections

NovoMix 30 is presented in cartridges (NovoMix 30 Penfill) and in multidose disposable pre-filled syringes (NovoMix 30 NovoLet and FlexPen).

Active substance

The INN name of the active substance is insulin aspart.

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

All excipients comply with Ph.Eur. specifications apart from metacresol which is USP standard .

Product development and finished product

Development pharmaceutics

A comprehensive development pharmaceutics section has been presented in which the choice of composition for a neutral premixed formulation of 30% soluble insulin and 70% protamine-crystallised insulin aspart is justified. Novo Nordisk has concentrated on excipients, which are well known and are currently used in their human insulin product range marketed in the EU.

The rationale for the manufacturing process has also been comprehensively discussed.

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

The product should be stored at 2-8 °C to prevent degradation during long term storage and is also shown sensitive to light and freezing.

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 and Novo Nordisk Pharmaceutique S.A. F-28002 Chartres France.

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

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.

Validation of the process

Process validation for NovoMix 30 is mainly based on the applicant's experience with their existing biphasic human insulin product range. The batch size, formulation, preparation steps and processing limits are identical for Penfill, NovoLet and FlexPen NovoMix 30 products.

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.

TSE risk assessment

No animal derived raw materials have been used directly in the production of the active substance or the finished product. The requirements of EMEA/410/01 are met.

Virus risk assessment

The risk of transmission of viruses is negligible as no primary animal or human sourced materials have been used in the preparation of either active substance or finished product.

Discussion on chemical, pharmaceutical and biological aspects

The quality of the product has in all essential parts been acceptably documented. The requirements of the relevant directives and guidelines are met. The pharmaceutical portions of the SPC, package insert and product labels are supported by the information provided in the dossier.

3. Part III: Toxico-pharmacological aspects

NovoMix 30 comprises only one pharmacodynamically active substance, insulin aspart, which has already been approved under the centralised procedure (NovoRapid), and the known substance protamine, already widely used to modify the release characteristics of insulins. Therefore, the preclinical evaluation has been concentrated on confirming the pharmacodynamic and pharmacokinetic properties of BIAsp 30, and on studies of its local and systemic toxicity.

Pharmacodynamics

Several studies have been done in animals, especially the pig, because subcutaneous injection in that species provides an adequate model for man. As anticipated from its known actions, BIAsp 30 resulted in a glucose lowering effect upon subcutaneous injection in the pig. The effect occurred more rapidly than after injection of biphasic human insulin (BHI). The presence of the insulin-aspart-protamine complex prolonged the glucose lowering effect.

It can be concluded that BIAsp 30 has the intended altered release characteristics when administered subcutaneously, as shown by the onset and time course of its glucose lowering effect.

No formal investigation of the receptor binding and other specific pharmacodynamic actions of BIAsp 30 were performed because those properties have already been well proven for IAsp.

Pharmacokinetics

Various studies based on assay of plasma levels of insulin released from subcutaneous injections of BIAsp 30 and IAsp in the pig were performed. Release from the injection site has been demonstrated by following the disappearance of radioactivity with an external gamma counter after subcutaneous administration of ^{125}I-tyrosine labelled insulin aspart. The specific biological activity of the radio-labelled insulin aspart was proven by showing its glucose lowering effect.

A single dose pharmacokinetic study in rats was conducted. Measured parameters, C_{max}, AUC, MRT, $t_{1/2}$ and t_{max} suggested linear pharmacokinetics.

The disposition, metabolism and excretion of BIAsp 30 have not been examined because those aspects of insulin aspart are already known and protamine is a long-established component of NPH insulin in clinical use.

Toxicity testing

The studies have been limited to systemic single dose and local toxicity of BIAsp 30 in view of the information already available about its separate components and the programme of completed toxicity tests on IAsp.

A study in rats using aged and fresh preparations of BIAsp 30 was conducted and showed results comparable to existing insulin preparations.

Local tolerance

Several different formulations of insulin aspart-protamine were tested in pigs in comparison with marketed preparations (Protaphane HM, Pen Mix 30 HM).

Immunogenicity

The immunogenicity of fresh and aged BI~~a~~Asp 30 was examined in comparison to other insulins, whose immunogenic properties have been established over years of manufacture and supply.

The results showed:

- no difference in immunogenicity between fresh and aged BIAsp 30.
- no difference in immunogenicity between fresh BIAsp 30 and either Protaphane MC or Ultralente Insulin.
- Protaphane MC resulted in lower antibody levels than the aged BIAsp 30.

The studies show that the immunogenicity of BIAsp 30 lies within the range of that of marketed preparations of porcine and bovine insulin.

Other toxicity tests

No other formal tests have been done. The lack of repeated dose studies, genotoxicity testing, carcinogenicity and reproduction tests, or further pharmacokinetic investigations is justified by the fact that insulin aspart has already been approved as a human medicine, and because protamine sulphate has been safely used for many years in preparations of biphasic insulins for human use.

Overall conclusion on toxico-pharmacological aspects

The pharmacology and toxicology of the active ingredient, insulin aspart, has already been characterized. There are no new issues related to the active component per se or to the components included except those that can be derived from the change in the pharmacokinetic profile. Relevant aspects of the pharmacological profile have been discussed in the assessment for IAsp (NovoRapid).

Additional studies showed that the glucose-lowering effects were, as expected, more rapid and pronounced with increasing admixture of soluble insulin aspart.

The results and conclusions from previous toxicity studies may also be considered valid for the present formulation. Additional pharmacokinetic studies using single-dose administration were in line with that plasma levels with the new formulation were covered in a 52-week rat toxicity study of IAsp.

Thus, the dose and exposure in previous studies also seems to cover the present change in formulation and the more sustained pharmacokinetic profile.

Immunogenicity of fresh and aged BiAsp, tested in rabbits, indicated that the compound had comparable immunogenic potential with respect to bovine and porcine insulin.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

The pharmacodynamic profile of BIAsp 30, which has been studied in healthy volunteers using a euglycaemic clamp model and in patients with type 2 diabetes, is characterised by a more rapid onset of action following subcutaneous injection, compared with biphasic human insulin 30 (BHI 30). Furthermore, a more intense glucose lowering effect during the first six hours after injection could be observed. Some effect of BIAsp 30 remained after 24 hours, but the glucose lowering effect of BIAsp 30 was less than that of BHI 30 during the later part of the 24-hour period of study. In type 2 diabetics, dosed with BIAsp 30 or BHI 30 immediately before breakfast and dinner, BIAsp 30 had a quicker onset of action, resulting in enhanced prandial control around those meals when the insulin was given, but resulted in inferior lunchtime control.

Pharmacokinetics

With regard to the pharmacokinetic profile of BIAsp 30, the soluble part of BIAsp 30 is rapidly absorbed and reaches maximum concentration about 60 minutes after dose in healthy volunteers and at about 95 minutes in type 2 diabetic patients. The absorption is significantly faster than that of the soluble part of biphasic human insulin (BHI 30). Both C_{max} and AUC reflecting the soluble part of the dose ($AUC_{0\text{-}90min}$ in healthy volunteers and $AUC_{0\text{-}2h}$ in patients) were higher for BIAsp 30 than for BHI 30. Judged by the terminal half-life ($t_{½}$) and area under the insulin concentration curve from 6 to 24 hours ($AUC_{6\text{-}24h}$), the absorption rate and bioavailability of the protamine bound fraction of BIAsp 30 were similar to those of BHI 30. Thus, there is a difference in pharmacokinetic profile between the soluble part of BIAsp 30 and BHI 30 while the pharmacokinetics of the protracted part of BIAsp 30 and BHI 30 is similar. There was no difference in bioavailability between BIAsp 30 and BHI 30. In one study in type 2 diabetic patients receiving administration immediately before breakfast and dinner, the insulin profile appears improved after breakfast and dinner but not after lunch where insulin levels were slightly lower for BIAsp 30 compared with BHI 30. Terminal half-life was similar in healthy subjects and type 2 diabetic patients. The pharmacokinetic parameters for the soluble fraction of BIAsp 30 are similar to those previously observed for IAsp.

The effect of various injection sites on the absorption of BIAsp 30 has not been investigated and a corresponding statement has been included in the SPC.

Pharmacokinetics of BIAsp 30 have been studied in type 2 diabetic patients, but not in type 1 diabetic patients. However, IAsp showed similar pharmacokinetics in healthy volunteers and Type 1 diabetic patients, and no differences between these populations are expected for BIAsp 30.

Special populations

The effect of hepatic function, renal function, age, gender and race was not studied.

In conclusion, the pharmacokinetic data suggest that the soluble phase of BIAsp 30 is absorbed faster than the soluble phase of conventional BHI 30 while the absorption of the protamine bound phase is similar to that of conventional BHI 30. Compared with BHI 30, the insulin profile appears improved after breakfast and dinner but not after lunch.

Clinical efficacy

Only one confirmatory trial (**038/D,UK**) was presented in the application. This was a 12-week, open-label, active-controlled, randomised, parallel-group, multicentre, multinational trial, which is currently ongoing as a 21-month extension trial (**067/D,UK**). BIAsp 30 and BHI 30 were injected subcutaneously twice daily (before breakfast and dinner). BHI 30 was recommended to be injected

30 minutes before meals, while BIAsp 30 was recommended to be injected within 10 minutes before meals. The study randomised 294 patients (BIAsp 30, n=143; BHI 30, n=151). Of these, 291 were exposed to study drug. The ITT-population (defined as exposed patients with any efficacy data) numbered 279 (BIAsp 30, n=134; BHI 30, n=145). In excess of 90% of patients in both treatment arms completed more than 8 weeks on study drug. The PP population comprised 260 patients (BIAsp 30, n=124, BHI 30, n=136). Enrolled patients had a mean age of 55-58 years and a mean duration of diabetes of 15 years. Type 2 diabetes was present in 61-68% of patients in the two treatment groups. Metabolic control at baseline was very similar between groups (mean HbA_{1c} 8.2%).

The primary efficacy endpoint was HbA_{1c} after 12 weeks of treatment.

Secondary efficacy endpoints were derived from 8-point BG profiles after 12 weeks of treatment and included:

- prandial BG increment; defined as the mean difference between the BG value 90 minutes after the meal and the BG value just before the meal, over the three meals,
- BG range; defined as the range of the 8 BG values (minimum-maximum) for each subject,
- average of the 8 BG values for each subject.

The total daily dose of biphasic insulin was also evaluated.

Both for the ITT population and the PP population, protocol-specified non-inferiority was demonstrated. There was no statistically significant difference in response according to type of diabetes. Average blood glucose (mean of 8-point profiles) was similar between treatments, supporting the similarity of overall control indicated by HbA_{1c}. In both treatment arms, there was slight improvement in average metabolic control during the study period.

In correspondence with the findings in the pharmacodynamic trials, blood glucose control was better with BIAsp 30 after breakfast and dinner. Mean prandial blood glucose increments (average over three meals) at study endpoint were significantly lower on BIAsp 30. The blood glucose control, as assessed by 8-point profiles, was superior with BIAsp 30 compared to BHI 30 after breakfast and dinner. In this 3-month study, lunch time control did not differ significantly between treatments, in contrast to the findings in the smaller 2-week pharmacodynamics study described in the section Clinical Pharmacology. There was a trend to higher fasting blood glucose with BIAsp 30, compared with BHI 30.

In both study groups, the mean daily insulin dose increased somewhat during the study. At endpoint, the mean dose of biphasic insulin was statistically significantly higher in the BIAsp 30 treatment arm. The absolute difference was small, however, and clinically hardly relevant (0.03 IU/kg for total daily dose). Insulin antibodies were evaluated (see section "Clinical safety"), but did not correlate with insulin dose or metabolic control, when evaluated at 12 weeks of therapy.

Clinical safety

Hypoglycaemia

The overall incidences of hypoglycaemic episodes were similar between treatment groups. As would be expected, hypoglycaemia was more common in type 1 than in type 2 patients. There were no differences between treatment groups regarding the incidence of hypoglycaemic episodes over time on therapy.

Antibodies

The evaluation of the current application disclosed increased cross-reactive anti-insulin antibodies, the titres of which levelled off and decreased after the first 3-6 months of therapy, and which could not be correlated with insulin dose requirements or metabolic control. Long-term extension data from 52 weeks showed antibody levels that were still significantly increased with BIAsp 30, as compared with BHI 30. The relationship between titres of cross-reactive antibodies and long-term efficacy and safety of IAsp 30 will be reported post-marketing.

Other adverse events

No specific events with likely relationship to study drug were noted.

Conclusions on clinical efficacy and safety

Confirmatory clinical experience is limited to one 12-week trial, enrolling a mixed population of type 1 and type 2 diabetic patients. BIAsp 30, given immediately before breakfast and dinner was compared with BHI 30, recommended to be given 30 minutes before meals. Both insulins resulted in very similar overall metabolic control at study endpoint and non-inferiority of BIAsp 30 to BHI 30 was demonstrated according to acceptable criteria. This conclusion remained after adjustment for a small, but statistically significant increase in total daily insulin dose seen in the BIAsp 30 group. Eight-point blood glucose profiles indicated improved mean prandial control with BIAsp 30 after breakfast and dinner.

In the confirmatory trial, the overall incidences of hypoglycaemic episodes were similar between treatment groups. As would be expected, hypoglycaemia was more common in type 1 than in type 2 patients. There were no differences between treatment groups regarding the incidence of major nocturnal hypoglycaemic episodes or regarding the incidence of hypoglycaemic episodes over time on therapy.

As was seen with IAsp (NovoRapid), BIAsp 30 was associated with increased titres of cross-reactive anti-insulin antibodies during the 12-week study period. Antibodies could not be correlated with metabolic control or insulin doses. BIAsp 30 was not associated with increased rates of allergic or injection site reactions, compared with BHI 30. Long-term data on the relationship between antibody titres and efficacy and safety of IAsp 30 will be reported post-marketing.

5. 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 pharmacology and toxicology of the active ingredient, insulin aspart, has already been characterised. There are no new issues related to the active component per se or to the components included, except those that can be derived from the change in the pharmacokinetic profile. Relevant aspects of the pharmacological profile have been discussed in the assessment for NovoRapid.

With regard to the clinical documentation, it was concluded that the activity profile of BIAsp 30 has been acceptably documented. Compared with BHI 30, BIAsp 30 has a quicker onset of action, resulting in improved prandial control around those meals when the insulin is given. Dosing immediately before meals appears adequate and may be an advantage. In a twice-daily insulin regimen, extra insulin or a redistribution of calorie intake may in some cases be needed to provide for lunchtime control. The overall balance of benefit and disadvantage resulting from this can be assessed only in the individual patient.

Confirmatory clinical experience is relatively short term. An extension trial is ongoing and 12 months data from this extension should be reported as a post approval commitment.

The studies with BIAsp 30 did not give rise to any unexpected safety findings. The incidence of hypoglycaemic events was similar to that found for BHI 30 As for IAsp, increased titres of cross-reactive antibodies were noted during the early phases of therapy and remained to some extent after 12 months. Although there is reasonable reassurance that this will not be a clinically important problem, long-term data (24-month data) from the ongoing extension trial should be reported post marketing.

6. Post marketing experience

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 NovoMix 30 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.

Combination use with metformin

The combination use of NovoMix 30 and metformin has been studied in multi-centre trials, showing an additional effect of NovoMix 30, given *b.i.d.* or *q.d* on glycaemic control in patients with type 2 diabetes on insufficient or failing metformin monotherapy.

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 NovoMix 30 is favourable in the treatment of patients with diabetes mellitus.