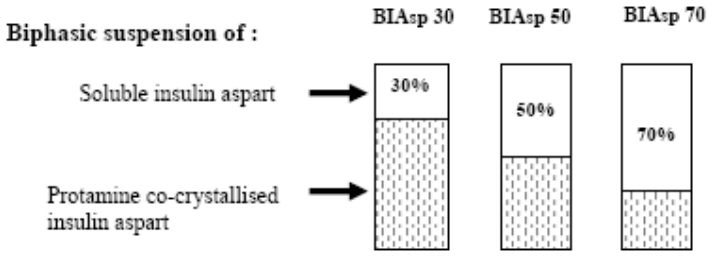
London, 5 October 2005
Product name: NovoMix
Procedure No. EMEA/H/C/308/X/19

SCIENTIFIC DISCUSSION

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1.1 Introduction

Insulin Aspart, (IAsp), is a fast-acting human insulin analogue with the same amino acid sequence as human insulin, with the exception of the substitution of proline with aspartic acid at position 28 of the B-chain. This substitution produces intermolecular repulsion and thereby reduces the tendency of insulin molecules to self associate to dimers and hexamers. Thus, insulin aspart is absorbed more rapidly than regular fast-acting human insulin when given subcutaneously.
Biphasic insulin aspart 30 (BIAsp 30), consists of a mixture of 30% rapid-acting IAsp and 70% intermediate-acting protamine co-crystallised IAsp. BIAsp 30 received marketing approval in the EU in August 2000.
The present line extension application refers to two new premixed dosage forms of rapid-acting IAsp and protamine co-crystallised IAsp, biphasic insulin aspart 50 (BIAsp 50) and biphasic insulin aspart 70 (BIAsp 70) (see figure below). BIAsp 50 and BIAsp 70 have been developed to supplement the already marketed BIAsp 30. This will increase flexibility in treatment options, allowing for treatments tailored to the individual needs of people with type 1 or type 2 diabetes.



1.2 Quality aspects

Drug substance

The drug substance insulin aspart has been described previously and was approved for NovoMix 30 (EMEA/H/C/308/X/11) among other insulin products of the applicant.

Drug Product

Introduction

The drug product NovoMix 70 is biphasic insulin in new mix of 70% soluble insulin, and the remaining 30%, is insulin protamine. This is a line extension to the approved NovoMix 30. The insulin strength of the products is 100 U/ml.

The essential differences compared to the NovoMix 30 are formulation and manufacturing, in other aspects they are similar.

Composition
The finished product is a white suspensions of 70% % soluble insulin aspart and 30% protamine crystallised insulin aspart.

The strength of 100 U of insulin aspart per ml is equimolar to 100 IU human insulin per ml. The finished products contains the following excipients : Protamine sulphate, zinc, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Formulation development
The approved NovoMix 30 has served as basis for the development of the present formulations. During the development phase the formulation underwent changes with respect to: the content of zinc; the content of sodium chloride, the isotonic agent and the manufacturing process.

The choice of excipients is well described and all have been used in other formulations of insulin aspart.

Manufacture of the formulations
The manufacture of NovoMix consists of preparation of 4 bulk solutions, 3 solutions are mixed and sterile filtrated into the filling tank containing sterile filtered solution I. The final bulk solution is allowed to crystallise for about 2 days and is then filled into cartridges.

A process validation at production scale has been performed and an acceptable report has been presented.

Drug product specification
The specifications for NovoMix 70 are identical except for content of insulin aspart in solution and limit for desamido insulin aspart at shelf life. In comparison with the approved NovoMix 30, there are minor differences. The analytical procedures are essentially the same for the three formulations, in some cases supplementary validations was done.

The specifications are suitable and justified.

For Flexpen presentations a dose accuracy test is included.

Container closure system
The container closure systems for NovoMix 70 were used for the approved NovoMix 30 and are well known from the existing insulin human/insulin analogue products.
The primary packing consists of a 3 ml cartridge (Penfill) of type 1 glass with a cap and a stopper. The cap is a laminated rubber disc with two layers: synthetic polyisoprene and bromobutyl rubber. The outer layer of bromobutyl rubber is in contact with the product. The rubber plunger is made of bromobutyl rubber. The cartridge contains a glass bead to facilitate the resuspension.

The FlexPen is a pre-filled multiple dose disposable insulin delivery device. The device consists of the following: The dose expelling part, the parts for dialling up and dialling down a dose and a 3 ml cartridge.

Stability
Based on the real time stability data a shelf life for the finished product has been accepted.

1.3 Non-clinical aspects

No additional non-clinical data have been generated by the MAH to support this application

1.4 Clinical aspects

Pharmacokinetics
Bioequivalence between the formulations used during development and the formulation to-be-marketed in terms of $AUC_{0\text{-}16h}$ and C_{max} was sufficiently well demonstrated.

The pharmacokinetics and pharmacodynamics of BIAsp 50 and BIAsp 70 were investigated in healthy subjects and in subjects with type 1 or type 2 diabetes.

The single dose pharmacokinetics of BIAsp 50, BIAsp 70 and the marketed dosage forms (IAsp and BIAsp 30) was compared in healthy subjects. Serum IAsp concentrations during the early absorptive phase (0 to 4 hours) increased significantly with the increasing fraction of soluble IAsp (30%, 50%, 70% and 100%). Both maximum serum IAsp concentrations (Cmax) and AUC0-4h increased by more than 20% between the adjacent premixed dosage forms. Time to maximum serum insulin concentration (tmax) was estimated to be about 60 minutes with all four dosage forms.

Single and multiple dose pharmacokinetics were investigated in subjects with type 1 and type 2 diabetes. The single dose pharmacokinetics gave similar results as in healthy volunteers. A slight increase of the serum IAsp levels in terms of Cmax and AUC was noted for the BIAsp preparations when day 8 and day 1 of treatment was compared indicating that it will take a few days to reach steady state. However, the differences were small and are judged to be of minor clinical relevance.

Pharmacodynamics

The glucodynamic response to BIAsp 50 and BIAsp 70 was investigated in two euglycaemic clamp trials, one in healthy subjects and one in subjects with type 1 diabetes. The rapid absorption of soluble IAsp was reflected by a similar early onset of action (within 10 to 20 minutes) for all three premixed dosage forms. The maximum glucodynamic effect (GIR_{max}) was exerted after about 2 hours; or approximately 1 hour later than the corresponding C_{max}. As expected, both the peak effect (GIR_{max}) and the extent of glucodynamic action over the first 4 hours ($AUC_{GIR,\ 0\text{-}4h}$) increased with increasing fraction of soluble IAsp. The duration of action was up to 14 to 24 hours

The glucodynamic action of BIAsp 30 and BIAsp 70 could be differentiated both during the early and late phases of absorption after 8 days of multiple dose treatment (thrice-daily) in subjects with type 1 diabetes. $AUC_{GIR\ 0\text{-}4h}$ (area under the glucose infusion rate-time curve) was greater with BIAsp 70 than with BIAsp 30, reflecting the larger fraction of soluble IAsp. The GIR_{max} with BIAsp 70 tended to be higher than with BIAsp 30, however, this difference did not reach statistical significance. $AUC_{GIR,\ 6\text{-}12h}$ was greater with BIAsp 30 than with BIAsp 70, reflecting the larger fraction of protamine co-crystallised IAsp.

Clinical efficacy

The concept of a thrice-daily meal-related dosing regimen was explored in short-term trials in subjects with type 1 and type 2 diabetes. The test regimens were evaluated over 24 hours in a meal-test procedure. The three trials were of exploratory nature and they were mainly used to define a reasonable BIAsp 50/70 regimen in the confirmative phase III trial (study 1075). The studies provided some limited support for the conclusion that that a thrice-daily regimen may improve day-time glucose control as compared to a twice-daily BIasp 30 regimen.

The pivotal clinical trial (1075) was designed as a 16-week randomised, parallel group, open-label, multi-centre trial comparing the efficacy and safety of the proposed concept of thrice-daily treatment with BIAsp 50 (BMI >30 kg/ m^2) or BIAsp 70 (BMI ≤30 kg/ m^2), and BIAsp 30 at dinner (where required if the achieved morning blood glucose levels were not lower than 8 mmol/L) with that of biphasic human insulin (BHI) 30 twice daily. The total daily dose of BIAsp was increased by 10% compared with the total daily BHI 30 dose at the end of the run-in period, distributed as 40:30:40% (breakfast: lunch: dinner).The primary objective was to confirm that thrice-daily treatment with BIAsp offers superior glycaemic control compared to twice-daily treatment with BHI 30 in subjects with diabetes who are inadequately controlled on their current twice-daily premixed human insulin regimen.

Results

Approximately 70% of the 664 subjects included had type 2 diabetes and the mean baseline HbA_{1c} was 8.7%. The treatment groups were well balanced regarding baseline demographics and disease characteristics.

Total insulin doses at the end of 16 weeks were slightly higher for subjects in the BIAsp treatment arm compared with the BHI 30 treatment arm.

The thrice-daily BIAsp regimen, provided better overall glycaemic control as judged from the HbA_{1c} values. Results of the 8-point blood glucose profiles recorded at the end of the treatment period revealed that daytime BG values were generally lower with BIAsp than with BHI 30. Significantly lower postprandial glucose levels were recorded after all meals in the BIAsp group as compared to the BHI 30 group. However, the mean fasting BG levels were higher in the BIAsp arm than in the BHI 30 arm.

Clinical safety

In the pivotal study there was a small but significant increase in the relative risk of minor hypoglycaemia during the day.

The higher rate of minor hypoglycaemic events in the BIAsp treatment group most probably reflects the higher doses and the additional lunch dose. There was a tendency for lower night time event rates in the BIAsp as could be expected in relation to the different time action profile of the insulins compared. The number of patients experiencing major hypoglycaemic events was low and did not differ significantly between the treatment groups.

The incidence of other adverse events than hypoglycaemia with the BIAsp dosage forms was similar to that with BHI 30. Less than 5% of subjects discontinued treatment in the confirmatory trial due to adverse events, and there were no pronounced differences between BIAsp three times daily and BHI 30 twice daily. Serious adverse events were uncommon and sporadic, occurring in less than 5% of all subjects. There were no differences in the pattern or in the incidence of serious adverse events between treatments or type of diabetes.

A total of three deaths were reported during the global clinical development programme. A relation to trial products was considered unlikely in all three cases.

1.5 Overall conclusions, benefit/risk assessment and recommendation

Quality

The drug product NovoMix 50 and NovoMix 70 are biphasic insulins in two new mixes of 50% and 70% soluble insulin, the remaining 50% and 30%, respectively, is insulin protamine. These are line extensions to the approved NovoMix 30. The insulin strength of the products is 100 U/ml.
The essential differences compared to the NovoMix 30 are formulation and manufacturing, in other aspects they are similar.

Efficacy

The pivotal 1075 study demonstrated that a BIAsp three times daily regimen is a treatment alternative that can provide acceptable glycaemic control and that postprandial blood glucose elevations can be reduced if such a regimen is compared with a BHI 30 twice-daily regimen. On the other hand the BIAsp thrice-daily regimen more often resulted in elevated fasting morning glucose levels. As well recognised in clinical practice careful individual titration of doses and individual selection of insulins with optimal action-time profiles are necessary components of successful treatment. In such individual titration procedures the two new compositions of BIAsp could serve as alternatives providing advantages for some patients. The efficacy of these new compositions has been sufficiently well demonstrated and the pharmacodynamic action/time profiles are in agreement with what could be expected from the amounts and properties of the two components.

Safety

The safety of BIAsp 50 and BIAsp 70 has been sufficiently well characterised from a clinical point of view taking into account also the experience with pure soluble IAsp and BIAsp 30. The pattern of adverse events in the BIAsp treatment groups was similar to the pattern recorded in the BHI treated group in the pivotal study. The increased incidence of minor hypoglycaemic events among the BIAsp treated patients recorded in the pivotal study is most probably due to the higher total insulin doses and more frequent insulin administration as compared to the BHI treated patients.

Benefit/risk assessment

The benefit/risk balance is considered favourable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of NovoMix 70 in the treatment of patients with diabetes mellitus was favourable.