

# Insulin Glulisine

Concise evaluated information to support the managed entry of new medicines in the NHS

## Summary

- Insulin glulisine is a new recombinant analogue of human insulin. It has a faster onset and shorter duration of action than regular human insulin.
- It is the third short acting insulin analogue to be launched in the UK (the other two being insulin aspart and insulin lispro) and is licensed for use in both type 1 and type 2 diabetes.
- Studies have compared insulin glulisine with insulin lispro and regular human insulin. Non-inferiority has been shown.
- Insulin glulisine can be given up to 15 minutes before meals or soon after, and should be used in combination with an intermediate or long acting insulin, or oral hypoglycaemic agents.
- When insulin glulisine was given before meals, blood glucose measurements were lower than when it was given after meals.
- Rates of hypoglycaemia associated with the use of insulin glulisine did not differ significantly from those seen with the comparator insulins.
- Insulin glulisine is available in vials, penfills for the OptiPen and as a prefilled OptiSet pen.

## Introduction

Insulin glulisine is a new analogue of human insulin produced by recombinant DNA technology. It differs from human insulin by two amino acid substitutions on the B chain of the protein, which prevent the formation of inactive hexamers when injected and results in a faster onset and shorter duration of action. Insulin glulisine can be given just before or after meals. It is available in vials, penfills for the OptiPen and as a prefilled OptiSet pen.

## Evidence

The data submitted to the EMEA supporting the clinical efficacy of insulin glulisine in patients with type 1 and 2 diabetes were based on three pivotal trials: studies 3001, 3004 (both type 1) and 3002 (type 2). At the time of writing only study 3002 was fully published.

The trials were all randomised, controlled, open-label studies. The open label design was due to the fact that the insulins compared had to be given at different times in relation to meals or by different devices. The dose of short-acting insulins was titrated to achieve a blood glucose goal 2-hours post food of 6.7-8.9 mmol/L.

The primary objective of the trials was to demonstrate non-inferiority of glulisine compared with the comparator insulins in the change in total HbA1c from baseline to endpoint. Non-inferiority was deemed to have been demonstrated if the upper boundary of the confidence interval (CI) for the adjusted mean difference in change in HbA1c was <0.4%. Ideally HbA1c should be between 6.5% and 7.5% or less. The studies also assessed safety.

**Study 3001<sup>1</sup>** was a 26-week study comparing insulin glulisine (n=339) with insulin lispro (n=333) injected 0-15 minutes before meals. Insulin glargine was used as basal therapy by all patients.

Non-inferiority was demonstrated between the two products: HbA1c reductions in the intention-to-treat

**Brand Name, (Manufacturer):** Apidra, (Aventis)

**BNF Therapeutic Class:** 6.1.1.1 Short-acting insulins

**Licensed Indications:** Treatment of adult patients with diabetes mellitus.

**Dosage and Administration:** by subcutaneous injections shortly before or soon after meals. .

**Marketed:** September 2005

**Cost Comparisons:**

Cost for 5x3ml cartridges for insulin pen (eMIMS August 2005)



N.B. Doses shown for general comparison and do not imply therapeutic equivalence.

## Insulin Glulisine

(ITT) population were  $-0.14 \pm 0.04\%$  in both groups. (95% CI for difference  $-0.09, 0.10$ ). No between-treatment differences in severe and/or nocturnal hypoglycaemic episodes per patient per month were seen.

**Study 3004<sup>2,3</sup>** was a 12 week parallel-group study comparing pre- (n=286) and post- (n=296) meal administration of glulisine and pre-meal regular human insulin (n=278). All patients received insulin glargine as the basal therapy. Glulisine was injected either 0-15 minutes pre meal or 20 minutes post meal. Regular human insulin was injected 30-45 minutes pre-meal.

Reductions in HbA1c were similar for post-meal glulisine (from 7.70 to 7.58,  $-0.11\%$ ) and regular human insulin (from 7.64 to 7.52,  $-0.13\%$ ) [98.33% CI for difference  $-0.11, 0.16$ ]. The reduction with pre-meal glulisine was larger (from 7.73 to 7.46,  $-0.26\%$ ,  $p=0.0062$  compared with post-meal glulisine and  $p=0.0234$  compared with regular human insulin) [98.33% CI for difference 0.02, 0.29 and  $-0.26, 0.01$ , respectively]. HbA1c fell within the ideal range with pre-meal insulin glulisine. However with continued treatment it is likely that the HbA1c for all treatment groups would fall below 7.5%.

Throughout the study the pre-meal glulisine blood glucose values were statistically significantly lower than in the other two groups for the 2-hour post-breakfast and post-dinner measurements. Actual figures are not stated and it is not known whether the findings are clinically significant.

Severe symptomatic hypoglycaemia affected 8.4% of patients in both glulisine groups and 10.1% in the regular human insulin group.

**Study 3002<sup>4</sup>** was a 26-week study comparing the effects of glulisine (n=435) with regular human insulin (n=441) in patients who had been using insulin for at least 6 months prior to study entry. Basal insulin therapy was with twice daily normal

protamine human insulin (isophane). Oral hypoglycaemic agents were allowed during the treatment phase.

The change in HbA1c at endpoint was  $-0.46\%$  with glulisine and  $-0.30\%$  with regular human insulin ( $p<0.05$ ). The mean difference of  $0.16\%$  [95% CI  $-0.26, -0.05$ ] indicates that glulisine was non-inferior to regular human insulin treatment. Blood glucose values were lower with glulisine than with regular human insulin at all on-treatment points, with statistical significance reached at 2 hours post-breakfast and post-dinner ( $p<0.05$ ). No statistically significant differences in the incidences or monthly rates of overall, nocturnal or severe symptomatic hypoglycaemia from month 4 [when the authors expected the patients to be acclimated to the study] to end of treatment were seen.

Despite the statistical significance of the differences in HbA1c and self monitored blood glucose, the clinical relevance of the differences is unclear and needs to be established.

### Safety

The rates of hypoglycaemic events, including severe and/or nocturnal events were seen in patients treated with glulisine at rates comparable to the control groups.

Adverse events (including severe events) occurred at similar rates between glulisine and comparator groups in both the type 1 and type 2 diabetes studies. Use of glulisine was not associated with an increase in frequency in injection site reactions.

### Place in Therapy

Insulin glulisine is another short acting insulin analogue to add to the current choices of aspart and lispro. Currently there are limited data to support the use of insulin glulisine and evidence does not suggest that it is associated with

significant improvements in blood glucose control, compared with other short acting insulins.

Patients often inject soluble insulin closer to meals than the recommended 15-30 minutes pre-meals. The use of insulin analogues is more convenient, as these can be injected shortly before meals.

On a pragmatic level the aspect that may influence use is the delivery device: insulin glulisine is available in vials, penfills for use with the Optipen set and a prefilled OptiSet pen (see Risk Management issues below for problems associated with these devices).

### Key Papers

- (1) Dreyer M et al. Abstract 520-P.
- (2) Garg S et al. Abstract 529-P.
- (3) Garg S et al. Abstract 530-P.

(1) – (3) from: American Diabetes Association 64th Scientific Sessions, June 4-8th, Orlando, Florida, 2004

- (4) Dailey G et al. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care* 2004; 27(10):2363-2368.

**The full LNDG publication can found on the [NeLM](#).**

### Risk Management Issues:

Two Medical Device Alerts have been issued for the Aventis Optipen:

- Problem with plunger and dose setting difficulties resulting in administration problems (MDA/2004/002)
- Potential for dosage button to fail to engage at the end of an injection and potential for patient to believe injection was unsuccessful (MDA/2005/003).

Produced for the UK Medicines Information Service

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