Scottish Medicines Consortium

insulin glulisine for subcutaneous injection 100 units/ml (Apidra Ò) No. (298/06)

Sanofi Aventis

4 August 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

Insulin glulisine (Apidra Ò) is accepted for restricted use within NHS Scotland for the treatment of adult patients with diabetes mellitus in whom treatment with a short-acting insulin analogue is appropriate.

Insulin glulisine has similar efficacy to other short-acting insulins in reducing glycated haemoglobin and a similar pharmacokinetic profile to at least one other insulin analogue. It is restricted to use in patients where regular human insulin is inappropriate.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

insulin glulisine 100units/ml injection (Apidra®)

Indication
Treatment of adult patients with diabetes mellitus

Dosing information
The dosage of insulin glulisine should be individually adjusted. It should be given shortly (0-15 minutes) before or soon after meals in regimens that include an intermediate or long-acting insulin or basal insulin analogue, and can be used with oral hypoglycaemic agents.

It should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

UK launch date
September 2005

Comparator medications

Short-acting insulins, including regular human insulin, insulin aspart and insulin lispro

Cost of relevant comparators

Cost comparisons are given below on a unit/unit basis for human sequence insulins and insulin analogues. However the dose of insulin administered to an individual patient is highly variable according to a wide range of factors.

Cost of 1 x 10ml vial 100 insulin units/ml

Insulin glulisine (Apidra®)	**£17.27**
Insulin lispro (Humalog®)	£17.28
Insulin aspart (NovoRapid®)	£17.27
Human sequence soluble insulin (Humulin S®)	£15.00
Human sequence soluble insulin (Actrapid®)	£7.48
Human sequence soluble insulin (Velosulin®)	£7.48

Cost of 5 x 3 ml cartridges 100 insulin units/ml

Insulin glulisine (Apidra®)	**£29.45**
Insulin lispro (Humalog®)	£29.46
Insulin aspart (NovoRapid Penfill®)	£29.43
Human sequence soluble insulin (Humulin S®)	£25.56
Human sequence soluble insulin (Insuman Rapid®)	£23.43

Cost of 5 x 3 ml pre-filled pens 100 insulin units/ml

Insulin glulisine (Apidra Optiset®)	**£29.45**
Insulin aspart (NovoRapid Flexpen®)	£32.00
Insulin lispro (Humalog®)	£29.46

Human sequence soluble insulin (Insuman Rapid Optiset®)	£27.90

Summary of evidence on comparative efficacy

Insulin glulisine is an analogue of human insulin manufactured using recombinant DNA technology and has a similar pharmacokinetic profile to insulin lispro i.e. more rapid onset of action and shorter duration than regular human insulin (RHI).

It has been compared to other short-acting insulins as part of a basal-bolus regimen in two pivotal Phase III trials in type 1 diabetes, one with a 26-week extension phase, and one in type 2 diabetes, also with a 26-week extension. All trials were open-label randomised studies in which the primary efficacy variable was the change in glycated haemoglobin (HbA_{1c}). The primary analysis for this endpoint was for non-inferiority of insulin glulisine to the short-acting comparator in an intention to treat (ITT) population, with the option of a superiority analysis if non-inferiority was shown. Doses of short-acting and basal insulins were titrated to achieve pre-defined blood glucose (BG) targets.

Two trials recruited patients aged ≥18 years with established type 1 diabetes, onset of diabetes at <age 40 and >1 year of continuous insulin therapy. Patients were also required to have body mass index <35 kg/m^2 and HbA_{1c} in the range ≥6.0 to ≤11.0%.

In the first trial 672 patients were randomised and received treatment with evening insulin glargine as the basal insulin and insulin glulisine or lispro administered 0-15 minutes before meals as the short acting component. There was a 26-week treatment period following a 4-week run-in phase.

The second trial in type 1 diabetes (n=860) was similar in design but involved a 12-week treatment period with insulin glargine as the basal component, pre-meal regular human insulin (RHI) as a comparator and insulin glulisine given either within 15 minutes prior to a meal or immediately afterwards. There were three comparisons: pre-meal glulisine compared with RHI, post-meal glulisine compared with RHI and pre-meal vs post-meal glulisine. The analyses were adjusted for multiple comparisons.

The type 2 diabetes trial recruited 876 adults to the ITT population, who had ≥6 months continuous treatment with insulin before recruitment. Pre-meal insulin glulisine was compared to pre-meal RHI with NPH (isophane) insulin as the basal component, and the treatment period was 26 weeks. Randomisation was stratified according to whether patients were taking oral hypoglycaemics at baseline, and those could be continued during the study.

There was no significant difference between insulin glulisine and comparators for the rate of hypoglycaemia in any trial. In type 1 diabetes, there was an increase in total insulin dose from baseline to endpoint with short-acting comparators while glulisine was associated with a reduction or a smaller increase. These differences were significant. For glulisine, the net effects were associated with a reduction in the dose of the short-acting insulin and an increase in dose for the basal component.

In an extension to the first study in type 1 diabetes, levels of HbA_{1c} rose during the second year of the study and returned to near the original baseline values. Control of HbA_{1c} also deteriorated in an extension to the type 2 diabetes study, though values remained above baseline at the end of the extension phase.

Summary of evidence on comparative safety

Adverse events associated with insulin glulisine in trials involving 1617 patients in safety populations were similar in nature and frequency to those associated with the comparators and were as expected in a diabetic population. Hypoglycaemia was seen at a comparable frequency with the control group. Because of the analogue nature of insulin glulisine, immunogenicity studies were performed and the results showed no concern.

Summary of clinical effectiveness issues

For control of HbA_{1c}, insulin glulisine as part of a basal/bolus regimen has been shown to be non-inferior to short-acting comparator insulins in patients with type 1 and type 2 diabetes in the pivotal trials. It was significantly more effective than RHI in one trial in type 2 diabetes however; the European Medicines Agency (EMEA) questioned the clinical relevance of the difference observed. Pre-meal insulin glulisine was superior to RHI and to post-meal insulin glulisine in one study in type 1 diabetes, but the differences were similar to those in the type 2 diabetes trial. Insulin glulisine was not superior to insulin lispro in the only trial where this was a comparator (in type 1 diabetes).

The pharmacokinetic properties of insulin glulisine were similar to those of insulin lispro when they were compared in studies in healthy volunteers, and similar results were seen in type 1 and type 2 diabetes.

Insulin glulisine can be injected into one of three anatomical areas but abdominal injection was the recommended site in all trials. However, pharmacokinetic studies suggest that absorption from other sites will be equivalent. In type 2 diabetes, insulin glulisine can be given concomitantly with oral hypoglycaemic agents (OHA). In the pivotal trial in type 2 diabetes OHA were taken at baseline by 58% of patients and very few patients discontinued or commenced OHA in the course of the trial. Sub-group analysis according to baseline OHA use was reported to be consistent with the overall results for the primary endpoint. Other than this, there are no data on the influence of OHA usage on response.

Summary of comparative health economic evidence

A formal economic analysis was not provided. This decision was based on the clinical trial evidence demonstrating that insulin glulisine was non-inferior to alternative short-acting insulins in the treatment of both type 1 and type 2 diabetes. The clinical evidence from the trials also showed that the safety profiles for the products were similar. Given these findings and the very similar pricing of the comparator products, the manufacturers asserted that a full economic evaluation was not necessary. Given the evidence presented, this was an acceptable stance to take and therefore required that only a budget impact analysis be provided. This is subject to the caveat that the economics case is demonstrated only in the instance where a short-acting recombinant insulin analogue is indicated for treatment. The economics case has not been presented to support the cost-effectiveness of the product versus other types of insulin.

Patient and public involvement

Patient Interest Group Submission: Diabetes UK Scotland

Budget impact

The manufacturer stated that the impact of using insulin glulisine as an alternative when a rapid acting insulin analogue is clinically indicated is expected to be cost-neutral given that it is similarly priced to other human insulin analogues already used in Scotland.

The market projection of the direct costs of rapid-acting insulin analogues was estimated at £4.3m in 2006 rising to £7.7m in 2010. Insulin glulisine's share of this total cost was estimated at 3% in 2006 rising to 24% in 2010.

Guidelines and protocols

Scottish Intercollegiate Guidelines Network. SIGN Guideline Number 55: Management of diabetes was published in November 2001 and is due for review.

National Institute for Clinical Excellence. NICE Clinical Guideline 15. Diagnosis and management of type 1 diabetes in children, young people and adults: published July 2004.

Both guidelines advocate tailoring therapeutic approaches to individual requirements.

Additional information

A Cochrane review of short acting insulin analogues versus regular human insulin in patients with diabetes mellitus was published in April 2006. The authors concluded that their analysis suggested only a minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. It adds, 'Until long term efficacy and safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues. For safety purposes, we need a long-term follow-up of large numbers of patients and well designed studies in pregnant women to determine the safety profile for both the mother and the unborn child.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 10 July 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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