Insulin glulisine (Apidra) for type 1 diabetes mellitus in adolescents and children

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Insulin glulisine (Apidra) for type 1 diabetes mellitus in adolescents and children

Target group

- Type 1 diabetes mellitus: adolescents and children 6 years or older - where treatment with insulin is required.

Technology description

Insulin glulisine (Apidra, HMR-1964) is a recombinant human insulin analogue that is equipotent to regular human insulin, its primary activity being regulation of glucose metabolism. It has a more rapid onset and a shorter duration of action than regular human insulin. Insulin glulisine is administered subcutaneously shortly before (0-15 minutes) or soon after meals. It should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue, and can be used with oral hypoglycaemic agents. Insulin glulisine is intended to be an alternative to other rapid-acting insulins such as insulin aspart (NovoRapid, Novo Nordisk) and insulin lispro (Humalog, Eli Lilly).

Insulin glulisine was launched in the UK for adults with type 1 diabetes in September 2006.

Innovation and/or advantages

In a clinical trial insulin glulisine enabled a greater proportion of patients to reach American Diabetes Association (ADA) age-specific HbA1c targets than insulin lispro. Its very rapid onset may be a particular advantage in young children where it is difficult to gauge how much they will eat, and in those with learning difficulties. An insulin that can be given immediately before a meal also has advantages for children and adolescents who do not want to wait before they can eat after an injection. Insulin glulisine has a shorter duration of action (1-2.5 hours) compared to insulin lispro and insulin aspart (both 3-5 hours).

Developer

Sanofi-aventis.

Availability, launch or marketing dates, and licensing plans:

In June 2008, the European marketing authorisation for insulin glulisine was extended to include adolescents and children aged 6 years or older.

NHS or Government priority area:

This topic is relevant to:

Relevant guidance

- NICE Technology Appraisals
  - Continuous subcutaneous insulin for the treatment of diabetes mellitus. 2008¹.
  - Inhaled insulin for the treatment of diabetes (types 1 and 2). 2006 (withdrawn from market)².

Other NICE Guidance.
• NICE clinical guideline. Diagnosis and management of type 1 diabetes in children, young people and adults. 2004⁵.
• NICE intervention procedure guidance. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. 2008⁶.

• National Collaborating Centre for Women’s and Children’s Health. Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people. 2004⁷.
• SIGN. Management of diabetes. 2001⁹.
• British National Formulary. Diabetic ketoacidosis. 2008¹⁰.
• Royal College of Nursing. Paediatric diabetes: RCN guidance for newly appointed nurse specialists. Service guidance. 2004¹¹.

Clinical need and burden of disease
Type 1 diabetes is one of the most frequent chronic diseases in childhood⁷. In 2002, there were 16,950 children with diabetes in England (1.62 per 1,000) and 1,121 in Wales (1.8 per 1,000), around 97% of these having type 1 diabetes¹². The incidence rate in 2002 was 14.9 per 100,000 of under 17-year olds, although this figure is believed to be low. Type 1 diabetes is a continuing hormonal deficiency disorder that has significant short-term impacts on health and lifestyle and is associated with major long-term complications and reduced life expectancy. Children with diabetes receive the majority of their care in specialist paediatric units.

Existing comparators and treatments
The main aim of treatment of type 1 diabetes is to obtain normal to near-normal blood glucose control. Children with type 1 diabetes require insulin replacement therapy from diagnosis. The choice of insulin regimen depends on factors such as age, duration of diabetes, lifestyle, targets of metabolic control, and individual patient/family preferences.

NICE guidance states that while the insulin regimen should be individualised for each patient, three basic types of insulin regimen can be considered⁵:
• One, two or three insulin injections per day of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.
• Multiple daily injection regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.
• Continuous subcutaneous insulin infusion (insulin pump therapy).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00115570: insulin glulisine vs insulin lispro; phase III.</th>
<th>Insulin glulisine vs regular human insulin (RHI); phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Sanofi-aventis.</td>
<td>Aventis Pharma.</td>
</tr>
<tr>
<td>Status</td>
<td>Abstract¹³.</td>
<td>Published¹⁴.</td>
</tr>
<tr>
<td>Location</td>
<td>EU, USA, Argentina, Australia and South Africa.</td>
<td>Germany.</td>
</tr>
<tr>
<td>Design</td>
<td>Open-label, stratified, randomised, controlled, non-inferiority.</td>
<td>Randomised, single-dose, double-blind, two-way cross-over.</td>
</tr>
</tbody>
</table>
### Participants and schedule

| n=572; children & adolescents (4-17 yrs); type 1 diabetes; HbA1c 6-11%. Randomised to insulin glulisine (GLU) or insulin lispro (LIS), 0-15 minutes before mealtimes with either glargine or neutral protamine Hagedorn as basal insulin for 26-weeks. Stratified according to type of basal insulin used. |
| n=20; children (5-11 yrs) & adolescents (12-17 yrs); type 1 diabetes. Randomised to subcutaneous injections of 0.15IU/kg GLU or RHI 2 minutes before a standardised meal. Study days were separated by at least 3 and no more than 14 days. |

### Follow-up

| 6 hours. |

### Primary outcomes

| Change in HbA1c from baseline to endpoint. |
| Pharmacokinetics, postprandial glucose excursions and safety. |

### Secondary outcome

| Change in HbA1c at weeks 12 and 26, patients reaching pre-specified HbA1c categories; self-monitored blood glucose parameters (BG); insulin doses; symptomatic hypoglycemia (all, severe, nocturnal and severe nocturnal episodes). |
| |

### Key results

**GLU vs LIS baseline to endpoint HbA1c adjusted mean changes were similar** (GLU–LIS: −0.06, 95% CI: −0.24, 0.12). **Significantly more pts** (p=0.0386) achieved ADA age-specific HbA1c targets with GLU (38.4%) vs LIS (32.0%). This difference was most pronounced in 13-17-yr olds, with 31.1 vs 21.1% of GLU vs LIS pts achieving HbA1c target <7.5% (p=0.0251). Mean BG values were similar for before main meal and 2-hour post-main meal time points. From baseline, both groups showed an increase in daily total insulin dose (+2.53 ± 0.68U/day GLU vs +4.91 ± 0.95U/day LIS; p=0.0074) and daily total insulin dose/kg body weight (+0.01 ± 0.01U/kg GLU vs +0.05 ± 0.01U/kg LIS; p=0.0045).

**Maximum insulin concentrations** (58 vs 33µIU/ml; p<0.05) and initial insulin concentrations (insulin [area under the curve] AUC0-2h 5,232 vs. 2994µIU·min−1·ml−1; p<0.05) were higher after GLU than RHI. Both time to maximum insulin concentration (54 vs 66 min) and mean residence times (88 vs 137 min, p<0.05) were shorter with GLU. Post prandial glucose excursions after GLU were lower than after RHI (p<0.05). The pharmacokinetic profile for GLU was similar for children and adolescents, RHI demonstrated a 64% higher concentration in adolescents.

### Adverse effects

| From month 4 to endpoint, symptomatic hypoglycaemia rates were similar. |
| 19 mild adverse events in 9 patients, of which one (urticaria) was reported to be possibly related to study medication (RHI). |

### Estimated cost and cost impact

The cost for a pack of 5 x 3-mL prefilled insulin glulisine disposable injection devices is either £25 (Apidra® SoloStar®) or £29.45 (Apidra® Optiset®). The cost of 5 x 3-mL cartridges is £29.45 (for OptiPen® Pro 1 and Autopen® 24) and £31.50 (OptiClik® cartridge)15.

The cost of other rapid-acting, recombinant human insulin analogues is15:

<table>
<thead>
<tr>
<th>Recombinant human insulin analogue</th>
<th>Device/cartridge</th>
<th>Amount</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>Autopen® Classic cartridge</td>
<td>5 x 3-mL</td>
<td>£29.46</td>
</tr>
<tr>
<td></td>
<td>HumaPen® cartridge</td>
<td>5 x 3-mL</td>
<td>£29.46</td>
</tr>
</tbody>
</table>
Potential or intended impact – speculative

Patients

☐ Reduced morbidity
☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Reduced mortality or increased length of survival
☐ Other: It is unclear at present whether there are additional long-term benefits from insulin glulisine.
☐ Improved quality of life for patients and/or carers
☐ None identified

Services

☐ Increased use
☐ Decreased use
☐ Service reorganisation required
☐ Other: None identified
☐ Staff or training required
☐ None identified

Costs

☐ Increased unit cost compared to alternative
☐ New costs:
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed
☐ Other: Any possible savings relating to the slightly better glucose control (secondary outcome) will be long-term
☐ Savings:
☐ None identified

References
