National Horizon Scanning Centre

Generex Oral-lyn™ (buccal insulin) for diabetes mellitus

September 2007

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Generex Oral-lyn™ (buccal insulin) for diabetes mellitus

Target group
- Type 1 and 2 diabetes mellitus.

Technology description
Generex Oral-lyn™ (buccal insulin, Oralin) is a liquid formulation of short acting insulin that is administered using Generex's metered dosage aerosol applicator (RapidMist™). Generex Oral-lyn™ is sprayed into the oral cavity, where the insulin is absorbed into the bloodstream through the mucosal lining.

Generex Oral-lyn™ is likely to be used as both an add-on to current long-acting insulin treatment and a substitute for injectable short acting insulin. If licensed, it may replace the need for injectable insulin throughout the day, requiring injections only for overnight insulin maintenance in patients with type 1 disease and for many with type 2 disease. Dosage is equivalent to current short-acting insulin. The formulation can be stored for up to 3 months at room temperature if more than 15 months are left before product expiry.

Generex Oral-lyn™ was launched in Ecuador in December 2005.

Innovation and/or advantages
Generex Oral-lyn™ is the first insulin agonist to be administered and absorbed through the buccal mucosa. Early trials suggest that the formulation is more rapidly absorbed in the mouth with a more rapid onset of action than subcutaneous injected insulin. Generex Oral-lyn™ may reduce the number of required injections, improving compliance, quality of life and reducing needlestick hazards.

Developer
Generex Biotechnology Corporation.

Place of use
- Home care e.g. home dialysis
- Community or residential care e.g. district nurses, physio
- Secondary care e.g. general, non-specialist hospital
- Tertiary care e.g. highly specialist services or hospital
- General public e.g. over the counter
- Emergency care e.g. paramedic services, trauma care
- Primary care e.g. used by GPs or practice nurses
- Other:

Availability, launch or marketing dates, and licensing plans:
Phase III trials.

NHS or Government priority area:
This topic is relevant to the National Service Framework for Diabetes.

Relevant guidance
- NICE clinical guideline in development: type 2 diabetes (update). Expected date of issue March 2008. This is an update of the following guidelines: type 2 diabetes – retinopathy, renal disease, blood glucose, management of blood pressure and blood lipids.
• Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice. December 2005\(^3\).
• NICE have published guidance on the use of inhaled insulin (2006)\(^5\); glitazones (2003)\(^6\); insulin pump therapy (2003)\(^7\); insulin glargine (2002)\(^8\).

Clinical need and burden of disease
In England and Wales there were an estimated 2,018,000 people with diabetes in 2006\(^9\), with type 2 diabetes accounting for more than 85%\(^10\). Type 1 diabetes is classically a disease of the young and is generally of rapid onset, but it can occur at any age. Type 2 diabetes is characteristically a disease of the middle aged or elderly and usually begins subtly. Patients with diabetes have an average reduction in life expectancy of 5-10 years\(^11\). Cardiovascular disease accounts for up to 60% of all deaths from diabetes and is the most common complication in Europeans with type 2 diabetes\(^12\). The risk of myocardial infarction and stroke is two to five times higher for individuals with type 2 diabetes than in the general population\(^11\). For people with type 1 diabetes, there is a two-to threefold increase in risk of developing CHD and stroke in later life\(^3\). Further diabetic complications include nephropathy, retinopathy, foot ulceration and erectile dysfunction.

Existing comparators and treatments
There are three main types of insulin preparation given by subcutaneous injection:

1. short-acting, which have a relatively rapid onset of action and are injected just before meals e.g. soluble insulin, insulin lispro, insulin aspart;
2. intermediate acting, often given at bedtime e.g. isophane insulin, insulin zinc suspension;
3. long-acting, which have a slower onset of action and act for long periods e.g. insulin glargine, insulin detemir.

Short-acting insulin can also be given by continuous subcutaneous infusion using a portable infusion pump and by inhalation. For adults who have special visual needs, a confirmed and severe needle phobia or injection site problems, injection devices or needle-free systems may be used (including inhaled insulin).

Efficacy and safety
A phase III global multi-centre trial is ongoing. The company are unable to provide any information.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type 2 diabetes: placebo-controlled</th>
<th>Type 1: Safety and efficacy</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Generex Biotechnology Corporation</td>
<td>Generex Biotechnology Corporation</td>
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<tr>
<td>Status</td>
<td>Conference abstract(^{11})</td>
<td>Conference abstract(^{14})</td>
</tr>
<tr>
<td>Location</td>
<td>Israel</td>
<td>Ecuador</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Observational</td>
</tr>
</tbody>
</table>

Participants in trial
\(n=26\). Type 2 poorly controlled on once daily insulin glargine and metformin.
• In addition to regular treatment, 10 minutes before meal:
  o Group one: Generex Oral-lyn™ 3 times a day
  o Group two: placebo 3 times a day
• If glucose values above 12mmol/L before meal or before bedtime,
\(n=29\) (24 adolescents, 5 young adult). Type 1 diabetes. Stabilisation period of standard therapy for 28 days. Split doses of Generex Oral-lyn™ replaced lunchtime injection of regular insulin for 6 months.
### Key results

**Interim results at 8 weeks:**
- No change in fasting glucose
- 15.4% reduction in postprandial glucose in Generex Oral-lyn™ group (211.2mg±53.7 to 178.5mg±39.1) vs. 3.5% elevation (202.7mg±60.1 to 210.1mg±5.2) in placebo
- Fructosamine 6.4% reduction in Generex Oral-lyn™ group vs 3.6% in placebo
- HbA1c 6.6% reduction vs 3.4% in placebo

21 subjects had good compliance. 8 subjects had very poor compliance. Good compliance score: 51.9 (standard deviation 14.97) vs. poor compliance score 14 (standard deviation 10.87) (P<0.001).

### Major adverse effects

None stated

### Trial

**Type 1: Controlled**

**Sponsor** Generex Biotechnology Corporation

**Status** Conference abstract

**Location** Ecuador

**Design** Cohort, controlled

**Participants in trial**
- n=25. Type-1 diabetes. Stabilisation period of standard therapy.
  - Control Group (n=11) twice daily isophane insulin + three times daily regular insulin
  - Treated Group (n=14) twice daily isophane insulin and three times daily prandial split doses of Generex Oral-lyn™.

**Follow-up** 99 days

**Outcomes** Fructosamine, HbA1c

**Key results**
- HbA1c: 7.3% to 6.8% in control group vs. 6.8 to 6.1% in Generex Oral-lyn™ group (P≤ 0.035)
- Fructosamine: 355.7 to 354.6 in control group vs. 313.2 to 319.2 in Generex Oral-lyn™ group (not significant)

**Major adverse effects** None stated

### Estimated cost and cost impact

The cost of Generex Oral-lyn™ is currently unconfirmed. Any potential increase in treatment costs may be offset by savings from better health outcomes, potential reduced healthcare service use due to improved compliance and improved glycemic control.

### Potential or intended impact – speculative

**Patients**
- ☑ Reduced morbidity
- ☑ Improved quality of life for patients and/or carers
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☑ Other:
- ☑ Non identified

**Services**
- ☑ Increased use: monitoring of change from subcutaneous insulin
- ☑ Service reorganisation required
- ☑ Staff or training required
- ☑ Decreased use
- ☑ Other:
- ☑ Non identified
Costs

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- Savings: improved compliance and control
- Other:

References