XeriSol™ Glucagon for Congenital Hyperinsulinism

September 2015
GLUCAGON

- increase glucose levels by stimulation of liver glycogenolysis
- 5-10µg/kg/h
- stimulate the beta cell to secrete insulin (Insulinsekretagogue)

side effects:
- Nausea, vomiting,
- reduced pancreatic enzyme secretion,
- reduced myocardial kontraktion,
- Tachyphylaxis
- Erythema necrolyticum migrans
GLUCAGON: WATER CREATES THE PROBLEM

- Poor stability
- Poor solubility

- Complicated formulations
  - Reconstitution/Refrigeration
  - Large volumes, painful

- Poor products
- Poor access
- Poor compliance
SOLUTION – REPLACE THE WATER!

1. **FORMULATE**
   Simplify the formulation

2. **DRY**
   Dry down to a powder

3. **MIX**
   Add non-water, bio-compatible solvent/diluent

4. **PACKAGE**
   Package in auto-injectors, pens & pumps

**Simplifying the formulation**
Can eliminate many ingredients often required in water-based formulations

**Co-formulation**
Process allows two drugs to be combined in the same formulation in a way not before possible

**Intellectual Property**
Xeris has intellectual property at each step of formulation

Xeris Pharmaceuticals, Inc. – Confidential Information
GLUCAGON PRODUCTS IN DEVELOPMENT

XeriSol Glucagon (5 mg/ml)

- G-Pen™
- G-Pen Mini™
- CSI-Glucagon
- G-Pump–HRH™
- G-Pump–AP™
- Diagnostic
GLUCAGON PRODUCTS DEVELOPMENT STATUS

- **G-Pen™**
  - Phase 3 Study Preparation

- **G-Pen Mini™**
  - Phase 2 Study Completed

- **G-Pump APTM**
  - Phase 2 Study Completed

- **G-Pump HRH™**
  - POC Study in Development

- **CSI-Glucagon**
  - Orphan Designation

**Complete**

**In-Process**
EXCELLENT STABILITY IN OMNIPOD® INFUSION PUMPS AT 37°C

Study Highlights

• XeriSol™ Glucagon remained clear and free of particulates over 6 days inside the OmniPod® stored at 37°C
• No significant abnormalities observed in UV spectrum from 350 – 650 nm
• RP-HPLC and SE-HPLC showed high glucagon purity maintained over 6 days inside the OmniPod® stored at 37°C
• Minor and insignificant leachables detected
Mean (± SEM) Plasma Glucose and Glucagon Concentrations after a Single Dose of Xeris or Novo Glucagon (2.0 μg/kg, ~ 150 μg)

Xeris glucagon was stored for 5 months as a liquid, Novo GlucaGen® reconstituted immediately prior to use!!
GLUCAGON INFUSION IS STANDARD OF CARE IN HOSPITAL

Cook Children’s Medical Center - glucagon experience

»10 patients using current

»7 patients treated with glucagon during stabilization pre-surgery – (4 focal, 3 diffuse)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (Kg)</td>
<td>4.3</td>
<td>3.1 - 5.3</td>
</tr>
<tr>
<td>Age at start of glucagon (days)</td>
<td>21</td>
<td>3 - 45</td>
</tr>
<tr>
<td>Dose of glucagon (mcg/kg/hr)</td>
<td>10</td>
<td>7.9 – 13</td>
</tr>
<tr>
<td>Max GIR pre glucagon (mg/kg/min)</td>
<td>23</td>
<td>14 – 41</td>
</tr>
<tr>
<td>Min GIR on glucagon (mg/kg/min)</td>
<td>7.2</td>
<td>1.8 – 8</td>
</tr>
<tr>
<td>Duration of glucagon (days)</td>
<td>9.4</td>
<td>4 - 15</td>
</tr>
</tbody>
</table>

»Complications

- 5 of 8 PICC lines became blocked and needed replacement (1.9F PICC lines)
- Hypoglycemia occurred in each patient with a blocked line

»2 patients arrived on glucagon; weaned off for diagnosis (1 focal, 1 diffuse)

»1 patient with Transient Perinatal Stress HI treated for 74 days due to complex medical problems weaned to 1.4mcg/kg/hr and maintained euglycemia on a 4.1mg/kg/min GIR

Similar experience in other HI centers globally
### GLUCAGON

**Mohnike et al. 2008 Retrospective Study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>No operation</th>
<th>Glucagon after operation</th>
<th>Preoperative glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Histologic type; age at pancreatic surgery</td>
<td>No surgery</td>
<td>No surgery</td>
<td>Diffuse, repeated pancreatic operations at age 33 and 88 days, 2.5 years</td>
</tr>
<tr>
<td>Mutation in ABCG8 (SUR1)</td>
<td>Not tested</td>
<td>R1437Q paternal allele only</td>
<td>Delf1 1388/3992-9 G&gt;A</td>
</tr>
<tr>
<td>Gestation age, weeks</td>
<td>40</td>
<td>Full term</td>
<td>37</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>4,280</td>
<td>Information not available</td>
<td>3,110</td>
</tr>
<tr>
<td>Age of initial hypoglycemia, h</td>
<td>36</td>
<td>Seizures at 2 months of age</td>
<td>24</td>
</tr>
<tr>
<td>Presenting blood glucose, mmol/l</td>
<td>1.1</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Insulin at hypoglycemia, mU/l</td>
<td>26.0</td>
<td>8.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Glucose infusion rate, mg/kg/min</td>
<td>16.0</td>
<td>7.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Maximum dose of octreotide, µg/kg/day</td>
<td>15</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Age at start; maximum dose of s.c. glucagon, mg/kg/day</td>
<td>46 days; 0.026</td>
<td>5.5 months; 0.24</td>
<td>165 days; 0.8</td>
</tr>
<tr>
<td>Discharge from hospital with glucagon</td>
<td>8 weeks</td>
<td>Transferred to local hospital on combination therapy and then home</td>
<td></td>
</tr>
<tr>
<td>Blood glucose &lt;2.6 mmol/l during s.c. glucagon</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Duration of glucagon treatment</td>
<td>4 years</td>
<td>&gt;4 months</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Age at last presentation</td>
<td>5 years</td>
<td>9.5 months</td>
<td>8 months</td>
</tr>
<tr>
<td>Erythema necrolyticum</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Tec = Glucagon-Technosphere™.*
SC glucagon continued for 1-4 years in 3 of 6 children without further symptomatic hypoglycemia, convulsions or unconsciousness.

Central glucose infusions significantly reduced or eliminated in all 9 children.
Glucagon treatment initiated to manage recurrent hypoglycemia after subtotal pancreatectomy in 2 of 9 children;

Pancreatectomy or subsequent resurgeries avoided in 5 of the 9 children

Octreotide was reduced to 8-15 μg/kg/day – considerably lower than if it were given alone, without glucagon (15-60 μg/kg/day)
CURRENT OFF-LABEL USE OF GLUCAGON

Hypoglycemia confirmed

Hyperinsulinism confirmed (n=120-160/year)

IV Glucagon

Trial of diazoxide

Diazoxide responsive (28%)

Diazoxide unresponsive (72%)

IV Glucagon

PET Scan

Focal (50%)

Diffuse (50%)

CSI Glucagon

Hypoglycemia

Xeris Pharmaceuticals, Inc.
Orphan Product Designation received from FDA and EMA

$2M NIH-NIDDK grant received
- Collaboration with Drs. Thornton (Cook Children’s) and DeLeon (CHOP)
- Funds juvenile toxicology study
- Funds short-term clinical trial in US centers

Significant leverage from other glucagon programs
- Non-clinical chronic toxicology program

Pre-IND interaction with FDA
- Filing IND in October 2015

Short-term POC clinical trial to start in 1Q16
PRESENTATION OVERVIEW

» XeriSol Technology Overview
» Xeris Glucagon Programs
» Current Off-Label Use of Glucagon
» Continuous Subcutaneous Infusion (CSI) Glucagon for Treatment of CH
» CSI Clinical Development Plans