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The Pharmaceutical Technology Specialists

Exenatide and Its Life Cycle
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www.drugdeliveryexperts.com
Achieving Target Product Profile Requires A Deep Understanding of Active, Formulation, Device

Leveraging a deep understanding of molecular properties, formulation, and device
Integrating delivery system R&D project into your development program
Optimizing target product profile to enhance value proposition

Discovery Support
- Lead molecule profiling
- Clinical candidate evaluation
- Biologic half-life extension

Drug Product Development
- Formulation design
- Drug product development
- Analytical methods

Device Development
- Device identification
- Integration with formulation
- Development and selection
Market Preference for Non-invasive Delivery

- **Injection**
- **Oral**

- **device** --- Transdermal --- patch
  - Nasal
  - Buccal
  - Sublingual

- Once per day >>> BID or TID
Injection Frequency Preferences

Decreasing Injection / Administration Frequency

- Multiple Daily Inj
- Daily Injection
- Weekly Injection
- Monthly Injection
- Quarterly Injection
- 6 to 12 Month Inj

Patient Self-Injection Common: Product Profile More Critical

Potential for Office Administered Product: Good Product Profile Not Critical

Product Profile Parameters

- Complexity of product handling
- Ready-to-use product
- Needle size for injection (viscosity)
- Injection force (viscosity)
- Pain on injection (volume)
- Duration of injection (volume)
- In-Use stability constraints
Commercially Approved Delivery Technologies for Systemic Delivery of Peptides

**Injection Systems**
- **Implantables**
- **XTEN, ELP, PAS conjugates**
- **Fc and Albumin fusion**
- **PEGylation, Acylation**
- **Microspheres**

**Risk**
- Vial and Syringe
- Pen Injectors

**Characteristics:**
- Moderate to High BA
- Acceptable Variability
- Continuous Exposure

**Non-Invasive**
- **Pulmonary**
  - Pulmozyme, Insulin
- **Oral (Systemic)**
  - Microneedle
  - PTH, glucagon phase 3
- **Nasal**
  - DDAVP, sCT, Buserelin, Nafarelin, Oxytocin

**Characteristics:**
- Low Dose
- Low BA
- Variability
- Pulsatile Exposure

**Risk**
- Commercialized Products
- Products in Development
## Importance of Target Product Profile

Most Parameters Affect the User Experience

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Suggested for Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>Subcutaneous, Intravenous, Intramuscular Non-invasive (Nasal, microneedle)</td>
</tr>
<tr>
<td>Dose Frequency and Pharmacokinetics</td>
<td>Daily or multiple daily injection (with native PK profile) Weekly, Monthly, Quarterly (with continuous exposure)</td>
</tr>
<tr>
<td>Projected Dose</td>
<td>Projected human, animal, toxicity doses (drives concentration in dosage form)</td>
</tr>
<tr>
<td>Dose Volume</td>
<td>( \leq 1\text{mL} ) for subcutaneous injection (also drives concentration in dosage form)</td>
</tr>
<tr>
<td>Ease of Use and Handling</td>
<td>Easily injected through a 26G or smaller needle Minimal handling by care giver (simple reconstitution)</td>
</tr>
<tr>
<td>Device and Container Closure System</td>
<td>Vial and syringe, pre-filled syringe, dual-chamber syringe, cartridge Multi-use pen, or auto-injector</td>
</tr>
<tr>
<td>Stability In-use</td>
<td>25°C, 1 week to 1 month</td>
</tr>
<tr>
<td>Stability for Long Term Storage</td>
<td>2-8°C, minimum 24 months</td>
</tr>
</tbody>
</table>
Sustained Release Formulation Approaches

- Daily Injection
- Weekly Injection
- Monthly Injection
- Quarterly Injection

- Increasing Drug Potency

- Suspension
- Liposome
- In Situ Gel-Forming System
- Microsphere
- Non-Aqueous Solution/Suspension
- Implant

Atrigel
Conjugate Approaches for Half-Life Extension

- **Daily Injection**
  - Acylation (albumin binder)
  - Carbohydrate analogues
  - HESylation, Glycosylation

- **Weekly Injection**
  - Poly Amino Acid Fusions
  - XTEN, ELP, PASylation
  - Various including reversible PEG

- **Monthly Injection**
  - PEGylation
  - Albumin or Fc Fusion (FcRn recycling)
Highly potent drug – 10 to 20 micrograms per day
Highly water soluble peptides – 100s mg/ml
Good stability in aqueous solution
Good metabolic stability
Half-life of 1 to 2 hours in humans
Choices for delivery system are virtually unlimited
Yet, mistakes can be (and were) made
Drug Product Profile Example: Exenatide

Byetta (exenatide injection)
- Launched by Amylin and Eli Lilly Partnership (now owned by Astra Zeneca)
- Discovered by John Eng (VA Hospital) 1996

Exenatide Drug Substance
- 39 amino acid peptide

Container Closure System
- 1.2 & 2.4 mL cartridge for pen
- 0.25 mg/mL strength

Disposable Pen-injector
- 5 mcg or 10 mcg per injection
- Storage: 2 year shelf-life
- In-use: 30 day period at RT
GLP-1s Move to Maximize Continuous Exposure

Byetta (exenatide)
Half-life 1-2 hrs

Liraglutide (Victoza)
Half-life 13 hrs

Bydureon (exenatide MS)

HbA1C Reduction

-0.9%
-1.2%
-1.5%


Kim D et al. Dia Care 2007;30:1487-1493

Adapted from Eibrand et al. Diabetes Care 2002;25:1396–1404. (mmr for each dose)


Kim D et al. Dia Care 2007;30:1487-1493

US 2005
EU 2006

US 2010
EU 2009
EU 2011
EU 2006
Microspheres to Achieve Continuous Exenatide

Exenatide Weekly PLGA Microspheres (SEM)

License PLGA Technology from Alkermes (2000) (Neutropin Depot) was precedent for work
Exenatide Microsphere Manufacture and QC

Exenatide MS Release and Polymer Degradation

Exenatide MS Particle Size Distribution

Particle Size is Controlled by Process and Dictates Device and Needle Gauge

Polymer Type, Formulation and Process Controls Release Profile And Pharmacokinetics
Exenatide Microsphere (Bydureon) Life Cycle

- Bydureon is an exenatide microsphere formulation
- Vial and syringe, pen, suspension in auto-injector

Bydureon (EU 2011 US 2012)
Once weekly SC injection
2 mg per week dose

Bydureon Pen (US 2014)
Once weekly SC injection
2 mg per week dose

Bydureon Bcise (US 2017)
Once weekly SC MS suspension
2 mg per week dose

Vial and syringe presentation discontinued Jan 2016 with pen launch
Importance of Bydureon Bcise Approval
Product Precedent for Microsphere Based Products

• Bcise is a MS suspension in Miglyol (MCT)
• Single-use auto-injector (‘3 step’)
• First microsphere in ready-to-use injectable suspension product
• Needle sheath and no needle handling or observation
• Store in refrigerator laying flat
• May be stored at room temperature for 4 weeks prior to use
• Substantial product improvement for diabetic patients
Dramatically Simplified Instructions-for-Use

3 simple steps

1. MIX
   Shake the autoinjector hard for at least 15 seconds until the medicine is well mixed.

2. UNLOCK
   Medicine must be fully mixed before unlocking. Unlock device and firmly unscrew orange cap.

3. INJECT
   Push the autoinjector against the skin and hold it there for 15 seconds to get full dose.
Bydureon Timeline For Development

1996
John Eng VA-Amylin NCE License

2000
Exendin-4 R&D

2003
Exen MS R&D

2005
Byetta FDA Approval

2009
MS Dual Chamber Pen

2008
Amylin Product Development

2012
Bydureon FDA Approval

2014
Bydureon FDA Approval

2017
Bydureon Bcise FDA Approval
Bydureon: Single Dose PK Profile (10 to 12 weeks)

SD PK Dose Selection Study 2.5 mg, 6 mg, 7 mg, 10 mg

- Initial release in first day subject of significant formulation and clinical work
- Target product profile was once per month injection – could not be achieved due to initial release
- 300 pg/ml was achievable with low initial release by weekly injection of the same formulation

Dose Selection Study 0.8 mg and 2 mg exenatide

- Initial release in first day subject of significant formulation and clinical work
- Target product profile was once per month injection – could not be achieved due to initial release
- 300 pg/ml was achievable with low initial release by weekly injection of the same formulation
Exenatide Delivery Opportunities Evaluated within Amylin Lilly Alliance (2000 to 2011)

• Nasal formulation taken into clinic
• Transdermal microporation taken into clinic
• Pulmonary dry powder evaluated in preclinical work
• Oral delivery evaluated in preclinical work
• All of these formulations suffered from PK issues
  • Low bioavailability, variability, shorter exposure times than SC injection
Nasal Target Product Profile:
• Aqueous solution formulation
• Simple manufacturing process
• Commercially available devices
• Nasal peptide products in market
• BID or TID administration

Opportunity Abandoned - un-attractive from marketing perspective
• 3 or 4X Nasal Spray required to achieve AUC equivalent to SC Injection (and clinical effect)
Transdermal Microporation Human Data (Altea)

Transdermal Target Product Profile:
- Simple bandaid-like product administered with device
- No pain on administration
- Continuous 24 hour exposure (Bydureon-like)
- Once per day administration (twice as fall back)

Opportunity Abandoned - due to significant investment required (device, patch, manufacturing)
- Once per day 24 hour continuous exposure nearly achieved
Exenatide Lessons

- Byetta was launched in a good pen, but, with a refrigeration pack
  - CMC post-approval supplement required to get RT for 30 days
- Challenges of microsphere sustained release formulation not well understood
  - Initial interest in a once monthly product
  - Weekly product was a compromise due to initial release from particles
- Bydureon was launched in a vial and syringe
  - Importance of device was recognized too late
- Bydureon dual chamber pen was difficult and took too long
  - At launch, inferior to other weekly GLP-1 products on the market
- Bydureon MS suspension could have been completed earlier ($!)
- Decision to build MS plant instead of working with CMOs ($$$)
- Singular focus on MS investment prevented other meaningful approaches
Exenatide Analogues with Clinical Data

- Lixisenatide (Zealand technology)
- Hanmi exendin-4 analogues with Fc conjugate (Sanofi)
- Versartis XTEN exenatide
- PhaseBio ELP exenatide
- Multiple programs in clinical development for analogues based on exenatide
## Numerous Approaches for Long-Acting Formulations and Analogues

### Table 1: Summary of long-acting exenatide preparations

<table>
<thead>
<tr>
<th>Preparation method</th>
<th>SR period/Half-life</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsphere</td>
<td></td>
<td>• Technology is mature&lt;br&gt;• Easy to adjust SR period</td>
<td>• Usually requires subcutaneous injection</td>
</tr>
<tr>
<td>PLGA microsphere</td>
<td>5–30 d; mostly 30 d</td>
<td>• PLGA is biocompatible and biodegradable&lt;br&gt;• Approved by FDA</td>
<td></td>
</tr>
<tr>
<td>Polysaccharide microsphere</td>
<td>21 d</td>
<td>• Better encapsulation rate than PLGA microspheres</td>
<td>• Relatively elevated inflammation compared with PLGA microspheres</td>
</tr>
<tr>
<td>Phase-transition gel in situ</td>
<td>Several days to 360 d</td>
<td>• Use of organic solvent avoided&lt;br&gt;• Easy to prepare</td>
<td>• Severe initial burst in the phase-transition process&lt;br&gt;• Usually surgery is required to implant the device</td>
</tr>
<tr>
<td>Implantable device</td>
<td>21 d</td>
<td>• Avoidance of severe initial burst that is found with phase-transition gel</td>
<td></td>
</tr>
<tr>
<td>Structure modification</td>
<td></td>
<td>• Well established and versatile strategy to attain desired properties</td>
<td>• Relatively short SR time&lt;br&gt;• High cost&lt;br&gt;• Safety and efficiency of new molecules need to be evaluated</td>
</tr>
<tr>
<td>PEGylation</td>
<td>43 h</td>
<td>• Reduces the immunogenicity</td>
<td>• Yields complex product mixtures&lt;br&gt;• Harmful to kidneys&lt;br&gt;• Lack of detailed data in vivo</td>
</tr>
<tr>
<td>Introduction of a lysine residue</td>
<td>40 h</td>
<td>• Decreases the degradation by metabolic enzymes&lt;br&gt;• XTEN technology can be universal to peptides and proteins</td>
<td>• Sophisticated&lt;br&gt;• Slight reduction of insulinotropic activity&lt;br&gt;• Slight reduction of cell viability</td>
</tr>
<tr>
<td>Recombinant polypeptide exenatide-XTEN</td>
<td>139 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugation with hyaluronate</td>
<td>96 h</td>
<td>• High bio-conjugation efficiency to hyaluronate of 90%</td>
<td></td>
</tr>
<tr>
<td>Conjugation with acid (lauric, palmitic, stearic)</td>
<td>4–20 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLGA microparticles</td>
<td>7 d</td>
<td>• Pulmonary delivery</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Design, Development and Therapy** 2013:7 963–970
GLP-1 AGONIST MOLECULAR ENGINEERING

Twice Daily Injection

Exendin-4

Lixisenatide

Liraglutide

Once Daily Injection

Once Weekly Injection

Albiglutide

Semaglutide

Dulaglutide

97% homology to GLP-1

Ex-4 plus poly Lys

Two GLP-1s on Fc fragment

97% homology to GLP-1

Ex-4 plus poly Lys

Two GLP-1s on Fc fragment

Once Daily Injection

Liraglutide

GLP-1 dimer

Lira plus optimized Albumin binder

Once Weekly Injection

Albiglutide

Semaglutide

Dulaglutide

Lira plus optimized Albumin binder

Two GLP-1s on Fc fragment

Once Daily Injection

Lixisenatide

Liraglutide

97% homology to GLP-1

Ex-4 plus poly Lys

Two GLP-1s on Fc fragment

Once Weekly Injection

Albiglutide

Semaglutide

Dulaglutide

Lira plus optimized Albumin binder

Two GLP-1s on Fc fragment

Once Daily Injection

Lixisenatide

Liraglutide

97% homology to GLP-1

Ex-4 plus poly Lys

Two GLP-1s on Fc fragment

Once Weekly Injection

Albiglutide

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Lira plus optimized Albumin binder

Two GLP-1s on Fc fragment

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97% homology to GLP-1

Ex-4 plus poly Lys

Two GLP-1s on Fc fragment

Once Weekly Injection

Albiglutide

Semaglutide

Dulaglutide

Lira plus optimized Albumin binder

Two GLP-1s on Fc fragment
Oral GLP-1 - ORMD-0901

Dogs: Oral exenatide delivery amounted to a >50% reduction in mean glucose (similar to SC)

Human (4 healthy volunteers)

150 mg exenatide

ORMD-0901
Integration of molecular properties, formulation, and device is key to achieving the desired product profile.

Product use and self-administration constraints drive device configuration, formulation design, molecular properties.
Have Fun and Ask Questions
The Pharmaceutical Technology Specialists

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