Drug Delivery Partnerships 2014

Development of an Active Transdermal System:
Complexity of Parallel Development of Formulation, Device, Patch, and Manufacturing Systems
Outline

- Type II Diabetes Market 2000 to 2020
- Exenatide for Type II Diabetes
- Exenatide Line Extension Options (Amylin-Lilly)
- Altea Passport Patch
  - Formulation Development
  - Device Development
  - Patch Development
  - Manufacturing Systems Development

Transdermal System Development
Diabetes Market 2005-6
Injectable Insulin / Orals

New product options?
• Long-acting
• Non-invasive


○ Transdermal System Development

CHRISTOPHER A RHODES & ASSOCIATES

DDP 01/27/14 ○ 3
Byetta Launched 2005 by Amylin-Lilly Partnership

Exenatide
Drug substance
39 amino acid peptide

Exenatide Injection
1.2 & 2.4mL cartridge for injection
0.25mg/mL strength

Exenatide Disposable Pen-injector
5 mcg or 10 mcg per injection
1.2 mL Demonstration pen

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Diabetes Market
2006 to 2020

HbA1C Change
QD Oral
QW SC Inj
QD Oral

Byetta (exenatide) GLP-1
Januvia (DPP4)
Janumet (DPP4 and metformin)
Victoza (liraglutide) GLP-1
Bydureon (exenatide MS) GLP-1
Invokan (canagliflozin) SGLT2
Farxiga (dapagliflozin) SGLT2
TDD (empagliflozin) SGLT2
albiglutide GLP-1
dulaglutide GLP-1

Q6Mos or Yrly Implant GLP1

BID SC Inj
QD SC Inj
Monthly SC Inj
Oral GLP1
INS-GLP1 combos

HbA1C Change:
-0.9%
-0.7%
-1.2%
-0.7%
-1.5%
GLP-1s Move to Maximize Continuous Exposure

Exenatide (Byetta)
-0.9% HbA1C reduction

Liraglutide (Victoza)
-1.5% HbA1C reduction


Adapted from Elbend et al. Diabetes Care 2002;25:1396-1404. (See for each dose)

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

Transdermal System Development

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Competitive Product Profiles (Insulins, GLP-1s)

- Patient self-administered
  - Simple injection device for impaired patients
- Minimal handling
  - No or easy reconstitution
  - 30 day RT storage for daily pen (warehoused at 5C)
  - 24 hour storage at RT for weekly or monthly injection (warehoused at 5C)
- Subcutaneous injection
- Daily injection
  - 30 day pen containing cartridge and preserved solution (depends on PK)
  - 31 guage needle
- Weekly or monthly
  - Disposable auto-injector with pre-filled syringe (no preservative)
  - No larger than a 27 guage needle (prefer 30 guage)
Is There A Role for Non-Invasive Exenatide?

- Non-invasive systems
  - Multiple Daily Oral, Nasal, Pulmonary
  - Potentially very large market by pushing product into earlier diabetes continuum (larger patient population, general practitioner)

- Transdermal System
  - Potential for extended exposure from a bandaid-like patch
  - ‘Non-invasive’ with continuous exposure efficacy
Non-Invasive Drug Delivery Systems

Nasal spray product
- Aqueous solution formulation
- Simple manufacturing process
- Commercially available device
- Nasal peptide products in market
- BID or TID administration

Pulmonary inhalation product
- Dry powder formulation
- Spray dry manufacturing process
- Alkermes or Nektar device
- Insulin products near market
- BID or TID administration
Nasal Exenatide Exposure in Humans

Plasma exenatide peaked at 15-30 min vs. 2 hours with SC
Exenatide Nasal Conclusions

- Formulations identified and tested in rodents and primates
- Two formulations tested in humans
- Human bioavailability low but not primary issue
- Variability in exposure too high at peak
- Byetta like efficacy was achievable with two to three nasal sprays per day
- Program was halted
Choice of Active Transdermal Program

- Altea had an attractive transdermal system
  - Electroporation system
- Phase 1 completed with insulin
- Opportunity to develop a 24 hour continuous patch
- Amylin and Lilly signed agreement with Altea
- Altea Passport Patch Development
  - Patch formulation needed for exenatide
  - Device design and development needed
  - Patch configuration development needed
  - Commercial manufacturing systems needed
- Lilly also had an active collaboration on PTH with Transpharma
  - No continuous exposure formulation
Development Risks Identified

- Exenatide 24 hour patch for once daily administration
  - Uncertain until formulation work complete
- Device and patch under development
  - Configuration sub-optimal and needed work to make it usable
- Manufacturing systems and suppliers under-developed
  - Patch and device supplier would need to be developed
  - Some new materials for pharmaceutical device-drug product
- Approvability uncertain
  - No product precedent approved, but, some in development
  - Safety related to immunogenicity (resolvable with phase 2b)
- Decision was made to proceed despite concerns
- Potential commercial value significant
  - Patch form of GLP-1 delivering Bydureon-like efficacy
Application Process for Altea Passport Patch

Place patch on charged device, expose filament

Apply against skin, Activate current for msec pulse, Remove device leaving patch

Fold formulation over pores leaving ‘bandaid’
Altea Prototype System

Electronic device:
Delivers inductive current to filament

Patch system:
Adhesives / layers house disposable filament and formulation / ‘bandaid’

Challenges
• Size of device / components
  • Patch application confusing
  • Pealing off multiple layers
  • Folding over formulation onto pores
• Multiple MFG partners and unique suppliers
• Regulatory risk of approval
Transdermal Program

- Develop exenatide polymer formulation
  - Optimize for continuous 24 hour exposure (designed for maximum efficacy)
  - Consider minimally acceptable 2X per day application
- Test in hairless rats for PK
  - Identify formulations and poration conditions
  - Optimize bioavailability and onset and duration of exposure
- Develop device
  - Reduce size and improve handling by patients
  - Develop manufacturing process and suppliers
- Develop patch
  - Improve handling and application process
  - Develop manufacturing process and suppliers
- Proof of feasibility
  - Test formulation in human PK study
Exenatide Transdermal Development Program

**Formulation**
- Initial PK Feasibility
  - Altea
- Optimize PK to Extend Exposure at Good BA
- Monitor process integrity
  - Stability prototypes

**Patch**
- Identify Poration Intensity
  - Pore Density, Patch Size
  - Altea
- Optimize Patch Handling
  - Cambridge Consulting
  - Identify Supply Partners
    - 3M, others

**Device**
- Minimize device size and improve patient handling
  - Ideo
- Identify Supply Partners
  - Device manufacturer
Parallel Development

Inter-related Uncertainties

- Formulation identity – Go No Go for proceeding
- Device and patch configuration – commercial implications for patient acceptance
- Manufacturing systems and suppliers – implications for COGs
- Integration challenge – moving parts have an impact on one another
- Importance of market timing – causes parallel development of formulation, device, patch
Exenatide Release and PK

Figure 1. (Top) Exenatide released into PBS from extended-release transdermal film over 24 hours. (Bottom) Exenatide pharmacokinetics in the hairless rat after microporation and 24 h application of extended-release transdermal film.

Figure 2. (Top) Exenatide released into PBS from rapid-release transdermal film over 24 hours. (Bottom) Exenatide plasma in the hairless rat after microporation and 24 h application of rapid-release transdermal film.
New and Improved Altea Device and Patch System

Preclinical proof of concept

Device and patch optimized with IDEO for ease of handling by 55+ year old diabetic

Patch redesigned with Cambridge Consultants for simplified application

Manufacturing partners for supply chain identified (device, formulation / patch)
Exenatide Transdermal
Conclusions

- Formulations identified and tested in rodents
- Acceptable results for proceeding
- Awareness of significant investment required
- Questionable value for a single molecule
- Oral once daily DPPIV had launched
- Program was halted
References for Transdermal Technologies

• Transdermal drug delivery looks for new frontiers
  o Microneedles and 'active' patches extend the reach of transdermal applications
  o Peggy Wright, Pharmaceutical Commerce, February 26, 2013

• Transdermal, Topical & Subcutaneous Drug Delivery:
  o Extending Pipelines & Improving Self-Administration
  o Drug Development and Delivery, July/August 2013

• Transdermal and Intradermal Delivery of Therapeutics:
  o Application of Physical Technologies
  o Ajay Banga, CRC Press 2011

• Transdermal drug delivery

• Painless drug delivery through microneedle-based transdermal patches featuring active infusion
  o Roxhed N, Samel B, Nordquist L, Griss P, Stemme G.
Thank You

- **Altea Therapeutics**
  - Frank Tagliaferi, PhD, VP, R&D, Altea
  - Alan Smith, PhD, VP Clinical and Project Management, Altea
  - Steve Damon, SVP, Business Development and Marketing
  - Michael Hatch, PhD, VP Device Development, Altea

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  - Viren Sarin, PhD, Fellow, Eli Lilly
  - Jim Dishong, Senior Director, Program Management, Eli Lilly
  - Andy Eibling and Mark Glick, Project Management, Eli Lilly
  - Robert Jennings, PhD, Senior Director, Drug Delivery Technology, Amylin
  - Steve Prestrelski, PhD, MBA, VP, Pharm R&D, Amylin

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  - Ideo, 3M team, Cambridge Consultants

- **Mentors and Colleagues**
  - Solomon Steiner, William Vincek, Alain Baron
  - Soumitra Ghosh, Christine Smith, Will Clodfelter, Maria Voerhoef, Jonathon Mow

- Transdermal System Development
Backup Slides
## Peptide Products With Polymer MR Technology

<table>
<thead>
<tr>
<th>Brand</th>
<th>Molecule and salt or complex</th>
<th>Depot Form</th>
<th>Injection Frequency</th>
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<tbody>
<tr>
<td>Bydureon</td>
<td>exenatide acetate</td>
<td>PLGA MS</td>
<td>1 wk</td>
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<tr>
<td>Nutropin Depot</td>
<td>hGH zinc complex</td>
<td>PLGA MS</td>
<td>2 wks</td>
</tr>
<tr>
<td>Sandostatin LAR</td>
<td>octreotide acetate</td>
<td>PLGA MS</td>
<td>4 wks</td>
</tr>
<tr>
<td>Trelstar Depot</td>
<td>triptorelin pamoate</td>
<td>PLGA MS</td>
<td>1, 3, 4, 6 mos</td>
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<tr>
<td>Lupron Depot</td>
<td>leuprolide acetate</td>
<td>PLGA MS and Gel forming</td>
<td>1, 3, 4 mos</td>
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<tr>
<td>Zoladex</td>
<td>goserelin acetate</td>
<td>PLGA implant</td>
<td>1, 3 mos</td>
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<tr>
<td>Supprelin LA</td>
<td>histerelin acetate</td>
<td>PMMA implant Nonbiodegrad.</td>
<td>12 mos</td>
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## Peptide Products With Non-Polymer MR Technology

<table>
<thead>
<tr>
<th>Brand</th>
<th>Molecule and salt or complex</th>
<th>Depot Form</th>
<th>Injection Frequency</th>
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<tbody>
<tr>
<td>Insulin Lente, others</td>
<td>insulin zinc complex</td>
<td>Zn salt or complex</td>
<td>Daily</td>
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<tr>
<td>Synacthen Depot</td>
<td>tetracosactide zinc complex</td>
<td>Zn salt or complex</td>
<td>1 wk</td>
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<tr>
<td>Plenaxis</td>
<td>abarelix</td>
<td>CMC Complex</td>
<td>1 wk</td>
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</table>
Commercial Product
Detailed examples
Product Example 1
MR vs IR Injectable Price

- **Byetta versus Bydureon (Amylin - Lilly 2011)**
  - Bydureon is exenatide microsphere suspension for injection
  - Once weekly, patient administered, SC injection, 23 gauge needle
  - Launched in vial and syringe with difficult reconstitution (2 mg in 100 mg PLGA)
  - Dual chamber syringe with improved handling in development + 2-3 yrs
  - Auto-injector with injectable suspension in development + 4-6 yrs
  - Byetta (exenatide) injection (approved 2005), 5-10 microgram BID, 30 day pen

- **Price**
  - Byetta $240 for 30 day pen or $8 per day in market of insulin at $3-4 per day
  - Market flush with several different oral generics at $0.10 per day
  - Bydureon $360 per month, pack of 4 administrations ($12 per day)

- **Market size**
  - Byetta peaked at $750M in 2007
  - Bydureon projected $1.5B 5 years into market (depending on competition)
  - GLP-1 market projected to be $5-10B
Product Example 2
Injection vs Oral Pricing

- **Risperdal Consta versus Risperdal**
  - Respiridone long-acting injection (Janssen approved 2003)
  - Every 2 wks, office administered, IM injection
  - Microsphere vial (12.5, 25, 37.5, 50 mg), prefilled diluent syringe with diluent, preparation aids, needles
  - Risperdal extended release tablet (approved 1993), 4-16 mg per day

- **Price**
  - Risperdal ~$6 per tablet, generic ~$3 per tablet
  - Risperdal consta average wholesale price ~$26 per day

- **Sales**
  - Risperdal Consta 2010 sales $1.5B
  - Risperdal Consta had ~5% of market share in 2008
Product Example 3
Injection vs Oral Pricing

- **Invega Sustenna versus Invega**
  - Paliperidone palmitate, extended release injection (Jannsen approved 2009)
  - Once monthly, office administered, IM injection
  - Prefilled syringe (39, 78, 117, 156, 234 mg) with no reconstitution
  - Invega extended release tablet (approved 2006), 3-12 mg once daily

- **Price**
  - Invega branded $7-16 per day, generic $3-4 per day
  - Invega Sustenna $450-1250 per syringe ($15-40 per day)

- **Market size**
  - Invega Sustenna 2009 sales $183M, projected 2010 sales of $330M
Human PK of Bydureon
Weekly MS Injection

Multiple Dose PK
Weekly inj of microsphere suspension
Steady state reached in 8 weeks

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

Poly-(d,l-lactide-co-glycolide)

PLGA

Single Dose PK

Exenatide Once Weekly 2.5 mg (N = 11)
Exenatide Once Weekly 5 mg (N = 9)
Exenatide Once Weekly 7 mg (N = 11)
Exenatide Once Weekly 10 mg (N = 10)

Mean Plasma Exenatide Concentration (pg/mL)

Time (hours)

2.0 mg Exenatide QW
0.8 mg Exenatide QW

Plasma Exenatide (pg/mL)

Time (wk)

Active Treatment Period  Follow-Up Period

Transdermal System Development

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Human PK of Sandostatin LAR Monthly IM Injection

Single Dose PK of IM Injection Of Sandostatin LAR in Humans

Multiple Dose PK of IM Injection Of Sandostatin LAR in Humans

NDA 21-009 Sandostatin LAR/octreotide acetate for IM Inj – Novartis 1998
Extracted from the Clinical Pharmacology Review by FDA
Human PK of Triptorelin Acetate Following IV Bolus

IV Triptorelin in Humans:
Half-life 2.85 hrs
Cmax 48 ng/ml

Days

Triptorelin (ng/ml)

0.02
0.13
1.0
7.4
54.6

0.0
0.5
1.0
1.5

Days

Romero et al.
JPET 2012 #195560
Human PK of Trelstar Monthly or Quarterly IM Injection

IM Triptorelin Pamoate In Humans:
Half-life 6 to 8 hrs
Cmax 18 ng/ml (1 month)
Cmax 45 ng/ml (3 month)
Tmax 2 hours

NDA 20-715 Trelstar
FDA Biopharm Review
Human PK of Monthly Eligard 7.5 mg SC Injection

PK/PD Response (N = 20) to ELIGARD® 7.5 mg (leuprolide in PLGA gel)
Patients dosed at 0, 1, 2 Months

SC Eligard in Humans: Cmax 25 ng/ml Tmax 5 hours
Eligard Package Insert

IV Leuprolide in Humans: Half-life 3 hours

SC Leuprolide in Humans: Half-life 3.6 hours
Cmax 32 ng/ml Tmax 0.6 hours

Sennello et al. J Pharm Sci 1986 75 (2) 158-160
Human PK of Zoladex Monthly or Quarterly SC Implantation

PK Following SC Implantation in Humans:
3 Monthly 3.6 mg Implants Followed by 1 (Qrtly) 10.8 mg Implant

SC Zoladex 3.6 in Humans:
Tmax 15 days
Cmax (3.6 mg) 3 ng/ml

SC Zoladex 10.8 in Humans:
Tmax 2 hours
Cmax (10.8 mg) 8 ng/ml

Zoladex 10.8 package insert

SC Goserelin in Humans:
Tmax 0.5 to 1 hour
Half-life 2 to 4 hours

Cockshott, Clin Pharmacokinetics 2000 39 (1) 27-48
Human PK of Regular Insulin Daily SC Injection

PK Following SC Injection in Humans:
IRI (immunoreactive insulin)

SC Insulin (50U) in Humans:
Tmax 4 to 6 hours
Cmax 500 to 800 pmol/liter
Half-life 3 to 4 hours

De La Pena, Diabetes Care
2011 (34) 2496-2501
Human PK of Zinc Insulin Daily SC Injection

SC Ultralente Insulin in Humans:
Tmax ~10 hours
Cmax 25 uU/ml
Half-life ~8 hours

SC NPH Insulin in Humans:
Tmax 4 hours
Cmax 23 uU/ml
Half-life ~8 hours

Note:
Ultralente is a Zinc complex
NPH is a protamine Zinc complex
Glargine is an analogue
CSII is continuous subcutaneous insulin infusion

Lepore et al., Diabetes 2000 (49) 2142-2148
Drug Delivery
Partnerships 2014

Developing Combination Device and Drug Products:

*Introduction*