Strategies for Sustaining Exposure of Peptide Therapeutics: Case Studies

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• Delivery Technologies for Sustained Exposure of Peptides
• Diabetes Product Landscape and Relevance to GLP-1
• Commercial GLP-1 Agonist Products
• Development Programs for GLP-1
Peptide Drug Products: Combination Products with Trivalent Complexity

Molecule
- Efficacy / side effects
- Continuous or pulsatile
- Cost per gram
- Physicochemical properties

Formulation
- Process complexity / scale-up
- Bioavailability / efficiency
- Cost for process / fill / finish
- Compatibility with molecule

Device
- Device complexity
- Ease of use / acceptance
- Cost per unit
- Formulation compatibility

Biology & Chemistry
PK & Formulation
Device & Handling
PEPTIDES AND DELIVERY NEEDS

- Typically water soluble > 1 mg/ml
- Stability in solution is often limited (2-8°C storage)
- Half-life typically 1 to 2 hrs (multiple daily injection)
- Immunogenicity a concern and needs study
- First drug product is usually solution for injection
- Life cycle interest in non-injection / sustained release injection
COMMON CHALLENGES FOR NOVEL DELIVERY SYSTEMS

- Compatibility of drug, formulation, device
- Predictability of in vitro and in vivo methods
- Variability in Exposure (Cmax, AUC, Tmax)
- Cost (drug, device, formulation, manufacturing)
- Maturity of the technology (commercial or clinical?)
- Scale up experience, manufacturing systems
- Regulatory experience and acceptance
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**
- **Complex Dispersion Formulations**

Atrigel

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SUSTAINED EXPOSURE CONJUGATE APPROACHES

- Daily Injection
- Weekly Injection
- Monthly Injection

Increasing Drug Potency

Acylation (albumin binder)

Carbohydrate analogues

HESylation, Glycosylation

Poly Amino Acid Fusions

XTN, ELP, Poly Lys

PEGylation

Various including Reversible PEG

Albumin or Fc Fusion (FcRn recycling)

Slowed Clearance via Bulking
PRESENTATION OUTLINE

• Delivery Technologies for Sustained Exposure
• Diabetes Product Landscape and Relevance to GLP-1
  • Commercial GLP-1 Agonist Products
  • Development Programs for GLP-1
INJECTABLE GLP-1S ENTER A CROWDED MARKET

Key Takeaway: The diabetes market will see a steady stream of new product launches over the next six years.

Total Type 2 Diabetes Therapeutics Market: Timeline of Product Launches, Global, 2010–2018

Injectables
TYPE 2 NON-INSULIN MARKET LANDSCAPE
**INSULIN PATENT EXPIRATIONS CHALLENGE NCE PRICES**

**Basaglar 2016 approval**
First insulin biosimilar
INJECTABLE GLP-1 NEW PRODUCTS IN WORLD OF GENERICS
CVO TRIALS A PRIMARY REASON INVESTORS SHY AWAY

Injectables

Cardiovascular Outcomes Trials Timeline

Total Type 2 Diabetes Therapeutics Market: Cardiovascular Outcomes Trials Timeline, Global, 2012

- Sitagliptin TECOS (N = 14,000)
- Albiglutide EXAMINE (N = 5,400)
- Canagliflozin CANVAS (N = 4,300)
- Exenatide EXSCEL (N = 9,500)
- Lixisenatide EUSA (N = 6,000)
- Empagliflozin N = 7,000
- Linagliptin LEADER N = 9,340
- Linagliptin CAROLINA N = 6,000
- Dulaglutide REWIND (N = 9,622)

Year 2010 2015 2020

Source: ClinicalTrials.gov and Frost & Sullivan analysis

FROST & SULLIVAN

NC67-52

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Presentation Outline

- Delivery Technologies for Sustained Exposure
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  - Commercial GLP-1 Agonist Products
- Development Programs for GLP-1
Launched by Amylin and Eli Lilly Partnership (now owned by Astra Zeneca)

Exenatide
Drug substance
39 amino acid peptide

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

Exenatide Disposable Pen-injector
5 mcg or 10 mcg per injection
2 year shelf-life
30 day in-use period at RT

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-10
—Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-—20
—Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2—39

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GLP-1S MOVE TO MAXIMIZE CONTINUOUS EXPOSURE

Exenatide (Byetta)  -0.9%


Liraglutide (Victoza)  -1.2%

Exenatide MS (Bydureon)  -1.5%

US 2005
EU 2006

EU 2009
US 2010

EU 2011
US 2012

Adapted from Elbrand et al. Diabetes Care 2002;25:1390-1404. (n=6 for each dose)

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EXENATIDE AND LIXISENATIDE

- Exenatide is 50% homologous to GLP-1
- Lixisenatide is based on Zealand poly lysine extension system

Exenatide
Approved US 2005 / EU 2006
Twice daily SC injection
5 or 10 ug per dose

Lixisenatide
Approved EU 2013
Daily SC injection
20 ug per dose
LIRAGLUTIDE AND SEMAGLUTIDE

- Lipidated GLP-1 analogues based on Novo lipidation system
- Liraglutide is 97% homologous to GLP-1
- Albumin binding by lipid for half-life extension
- Semaglutide has an optimized albumin binding side chain

Liraglutide
Approved EU 2009 / US 2010
Daily SC injection
1.2 to 1.8 mg per dose

Semaglutide
NDA 2016
Weekly SC Injection
2 mg per dose
ALBIGLUTIDE AND DULAGLUTIDE

- Albiglutide is a GLP-1 albumin conjugate
- Dulaglutide is an Fc fusion with GLP-1

**Albiglutide**
- Approved US and EU 2014
- Once weekly SC injection
- 30 or 50 mg per dose

**Dulaglutide**
- Approved EU 2013
- Once weekly SC injection
- 0.75 or 1.5 mg per dose
**GLP-1 Agonist Structural Comparison**

- **Exendin-4**
  - GLP-1 dimer
  - Ex plus poly Lys

- **Lixisenatide**
  - 97% homology to GLP-1
  - Lira plus optimized Albumin binder

- **Liraglutide**
  - IgG Fc fragment

- **Albiglutide**
  - IgG Fc fragment

- **Semaglutide**
  - IgG Fc fragment

- **Dulaglutide**
  - Two GLP-1s on Fc fragment

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**Bydureon Life Cycle**

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

**Bydureon**  
Approved EU 2011 US 2012  
Once weekly SC injection  
2 mg per week dose

**Bydureon Pen**  
Approved US 2014  
Once weekly SC injection  
2 mg per week dose

**Bydureon Suspension**  
Anticipated Approval US 2018  
Once weekly SC injection  
2 mg per week dose

Vial and syringe presentation discontinued Jan 2016 with launch of Pen
GLP-1 COMBINATION PRODUCT PROGRAMS

- Xultophy is a combination formulation of insulin and liraglutide
- GLP-1 combinations of interest– enhanced HbA1c reduction

Xultophy
Approved EU 2014 / US 2016
Once daily SC injection
100 Units/ml insulin
3.6 mg/ml liraglutide

Clear colorless solution
32 gauge needle
2 year shelf-life
21 days in-use at 30C
GLP-1 COMBINATION PRODUCT PROGRAMS

- Soliqua is a combination of insulin glargine and lixisenatide
- Benefit of insulin plus weight loss

Soliqua
Approved US 2016 / EU TBD
Once daily SC injection
100 Units/ml insulin glargine
33 mcg/ml lixisenatide
Dial a dose from 15 to 60 Units

Clear colorless solution
29 to 31 gauge needle
2 year shelf-life pen
14 days in-use at RT
PRESENTATION OUTLINE

• Delivery Technologies for Sustained Exposure
• Diabetes Product Landscape and Relevance to GLP-1
• Commercial GLP-1 Agonist Product Examples

Selected Development Programs for GLP-1
ITCA 650

- ITCA 650 is an exenatide formulation in an implantable device
- Exenatide in non-aqueous formulation

ITCA 650
Submitted US 2016 / Anticipated approval 2017
Initial dose for 3 months followed by
Once every 6 months SC injection
40 or 60 ug per day
**BYDUREON LIFE CYCLE**

- Bydureon MS injectable suspension
- To be submitted by Astra Zeneca 2017-2018?

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

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

Bydureon Suspension
Anticipated Approval US 2018
Once weekly SC injection
2 mg per week dose
GLP-1 CONJUGATES WITH PEG AND Fc

Efpeglenatide
Hanmi exenatide analogue
CA-exendin 4 with Lapscovery delivery system
Very long half-life
Potential for monthly injection

Hanmi licensed to Sanofi in 2015

Also being explored in combo programs with insulin
GLP-1 CONJUGATES WITH AMINO ACID POLYMERS

• Exenatide derivatives with specific technology
• Amunix XTN (amino acid PEG replacement)
• PhaseBio Elpylation (elastin like peptide fusion)

Amunix XTN
Recombinant fusion to exenatide
Exenatide analogue completed phase 1

PhaseBio ELP
Recombinant fusion to exenatide
Exenatide analogue completed phase 1
Gels upon injection
Integration of molecular properties, formulation, and device is key to achieving the desired product profile.

Product use and self-administration drive device configuration, formulation design, molecular properties.
THANK YOU

Dog Beach and Hotel Del Coronado, San Diego, CA