LONG-ACTING INJECTABLES AND IMPLANTABLES WORKSHOP

CONTROLLED RELEASE SOCIETY 2019
VALENCIA SPAIN

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19JUL2019
LONG-ACTING DOSAGE FORM OUTLINE

• Design considerations
• Life Cycle Example

• Overview of Commercial Products
• Formulation considerations for injectables
• Formulation considerations for implantables
### How Do I Choose a Technology?

<table>
<thead>
<tr>
<th>Technology</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Quarterly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension</td>
<td></td>
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<tr>
<td>Liposome</td>
<td></td>
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<tr>
<td>In Situ Gel-Forming System</td>
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<tr>
<td>Microsphere</td>
<td></td>
<td></td>
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<tr>
<td>Non-Aqueous Solution/Suspension</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Implant</td>
<td></td>
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</tr>
</tbody>
</table>

*CRS LAII Workshop 20 July 2019*
LONG-ACTING DOSAGE FORM DESIGN CONSIDERATIONS

• The interplay of conflicting needs affects technology choices
  • Patient convenience (injection or implant frequency)
  • Loading of dosage form (how much drug can be contained) -
  • Patient acceptance (size of dosage form) – impact on administration procedure
  • Physician and market place acceptance - what are competitors doing?

• Key parameters need to be considered prior to moving forward with LAII
  • Drug dose per day (output from dosage form) – potency of drug
    • PKPD modelling may be required
    • Safety issues of concentration excursions (high initial release or too little exposure)
  • Route of administration limits the size of dosage form
  • Stability of drug in dosage form
  • Integrity of drug through manufacturing process
  • Scale-up for commercial manufacturing
  • Time and effort of development – timing to market
A LIFE CYCLE EXAMPLE – NON-OPTIMAL

Exenatide (39 a.a. peptide) first GLP-1 to market for Type 2 Diabetes (Amylin)
- Clear recognition that to compete minimally would require 2X per day with pen
- Clear understanding that continuous exposure would improve outcomes

Byetta
Approved US 2005
Twice daily SC injection
10 to 20 ug per dose

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 BCise
Approved US 2017
Once weekly SC injection
2 mg per week dose

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

Vial and syringe presentation
discontinued Jan 2016 with pen launch

Dual chamber cartridge
In pen device

Autoinjector with cartridge
PLGA oil-based suspension
Formulation composition a significant issue in development
- Initial release a key parameter for GLP-1s
- Particle size distribution affects duration, release profile, patient acceptance
Clinical development focused on formulation selection
• Initial release a key challenge throughout
• Compromise made to administer lower dose weekly as opposed to monthly

Initial release subject of significant formulation process work
And much discussion on clinical development strategy – is monthly achievable?
300 pg/ml continuous exposure desired – initial release too high
Commercial considerations drive technical decisions

- Needle size a key parameter for a weekly injectable chronic drug
- PLGA technology challenges for reconstitution
Each of these programs Required about 10 years Development time and effort
LONG-ACTING DOSAGE FORM OUTLINE

• Design considerations
• Life Cycle Example

• Overview of Commercial Products

• Formulation considerations for injectables
• Formulation considerations for implantables
POLYMER-BASED DRUG DELIVERY PRODUCTS

• Only small molecules or peptides have reached commercialization

• There are about 35 unique types of products
  • 35 products include all molecular entities (small molecules, peptides) and all routes
  • Some products are available in multiple strengths and durations
  • Some compounds appear in different dosage forms
    • Implants, microspheres, or gel

• Therapeutic areas are fairly limited
  • Hormone replacement or suppression
  • Cancer
  • Diabetes
  • CNS disorders
  • Addiction
  • Ocular disease
BIORESORBABLE POLYMER PRODUCTS

- PLGAs are the overwhelming choice among resorbable polymers commercialized
- Three other polymers have been used in approved products for an individual product:
  - polyanhydride implantable disk (GLIADEL)
  - triethylene glycol poly(orthoester) injectable gel (SUSTOL)
  - poly(ε-caprolactone) appeared in an approved product for birth control
    - Product withdrawn in favor of other products
    - Currently used as a material for sutures
- Many other polymers have been used for research
  - Research materials available from polymer suppliers for use by pharma companies
  - A few of the companies can provide GMP grade materials
- Dosage forms include implants, microparticles, and gels
- Only small molecules or peptides have reached commercialization
FDA APPROVED EXTENDED-RELEASE PRODUCTS WITH PLGA

- Approved products predominately use PLGA polymers
- Small molecule and peptides (9 are peptide products - highlighted)
- Microparticles, implants, and gels made using organic solvent as vehicle

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
<th>Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atridox</td>
<td>doxycycline hyclate</td>
<td>Den-Mat</td>
<td>Atrigel</td>
<td>Periodontitis</td>
<td>Oral - periodontal pocket</td>
</tr>
<tr>
<td>Bydureon</td>
<td>exenatide</td>
<td>AstraZeneca</td>
<td>Microsphere</td>
<td>Diabetes, type II</td>
<td>SC</td>
</tr>
<tr>
<td>Eligard</td>
<td>leuprolide acetate</td>
<td>Tolmar</td>
<td>Atrigel</td>
<td>Prostate cancer</td>
<td>SC</td>
</tr>
<tr>
<td>Lupon Depot</td>
<td>leuprolide acetate</td>
<td>Abbvie</td>
<td>Microsphere</td>
<td>Prostate cancer</td>
<td>IM</td>
</tr>
<tr>
<td>Ozurdex</td>
<td>dexamethasone</td>
<td>Allergan</td>
<td>Implant (rod)</td>
<td>Retinal vein occlusion</td>
<td>Intravitreal</td>
</tr>
<tr>
<td>PROPEL and SINUVA</td>
<td>mometasone furoate</td>
<td>Intersect ENT</td>
<td>Implant</td>
<td>maintain patency of the sinus cavity or sinus ostium</td>
<td>Sinus cavity</td>
</tr>
<tr>
<td>Pervers</td>
<td>risperidone</td>
<td>Indivior</td>
<td>Atrigel</td>
<td>Schizophrenia</td>
<td>SC (abdominal)</td>
</tr>
<tr>
<td>Risperdol Const</td>
<td>risperidone</td>
<td>Janssen</td>
<td>Microsphere</td>
<td>Schizophrenia, Bipolar disorder</td>
<td>IM</td>
</tr>
<tr>
<td>Sandostatin LAR Depot</td>
<td>octreotide acetate</td>
<td>Novartis</td>
<td>Microsphere</td>
<td>Acromegaly</td>
<td>IM</td>
</tr>
<tr>
<td>Signifor LAR</td>
<td>pasireotide pamoate</td>
<td>Novartis</td>
<td>Microsphere</td>
<td>Acromegaly</td>
<td>IM</td>
</tr>
<tr>
<td>Sublocade</td>
<td>buprenorphine</td>
<td>Indivior</td>
<td>Atrigel</td>
<td>Opioid use disorder</td>
<td>SC</td>
</tr>
<tr>
<td>Trelstar</td>
<td>triptorelin pamoate</td>
<td>Allergan</td>
<td>Microgranules</td>
<td>Advanced prostate cancer</td>
<td>IM</td>
</tr>
<tr>
<td>Triptodur</td>
<td>triptorelin pamoate</td>
<td>Arbor</td>
<td>Microgranules</td>
<td>Central precocious puberty</td>
<td>IM</td>
</tr>
<tr>
<td>Vivotrol</td>
<td>naltrexone</td>
<td>Alkermes</td>
<td>Microsphere</td>
<td>Alcohol or opioid dependence</td>
<td>IM</td>
</tr>
<tr>
<td>Zilretta</td>
<td>triamcinolone acetonide</td>
<td>Flexion</td>
<td>Microsphere</td>
<td>Osteoarthritis pain of the knee</td>
<td>Intra-articular</td>
</tr>
<tr>
<td>Zoladex</td>
<td>goserelin acetate</td>
<td>AstraZeneca</td>
<td>Implant (rod)</td>
<td>Prostate cancer, breast cancer, others</td>
<td>SC</td>
</tr>
</tbody>
</table>
### All Polymers Used in Drug Delivery Research

- Many polymers have been used for drug delivery research
- PLGA, a polyanhydride, and a poly(orthoester) are in approved products
- poly(ε-caprolactone) has been in an approved product
- Most resorbable polymers degrade to acidic products except polyketel
- Most resorbable polymers are insoluble in water; PEG has been used as a component to improve aqueous solubility

<table>
<thead>
<tr>
<th>Resorbable</th>
<th>Non-Resorbable</th>
<th>Amino Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PLGA, PGA, PLA</td>
<td>• Alginate</td>
<td>poly-L-glutamic acid</td>
</tr>
<tr>
<td>• PEG-PLGA</td>
<td>• Cellulose derivatives (HEC, CMC)</td>
<td>poly-L-lysine</td>
</tr>
<tr>
<td>• PEG-PLGA-PEG</td>
<td>• Hyaluronates</td>
<td>poly-aspartic acid</td>
</tr>
<tr>
<td>• PLGA-PEG-PLGA</td>
<td>• Cross linked HA, CMHA-S Platform (Eyegate)</td>
<td></td>
</tr>
<tr>
<td>• poly(ε-caprolactone)</td>
<td>• Poloxamers (PEO-PPO-PEO tri-block polymers)</td>
<td></td>
</tr>
<tr>
<td>• poly(DL-lactide-co-ε-caprolactone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• polycaprolactone-PEG-polycaprolactone (PLCL-PEG-PLCL)</td>
<td>Note: the following appear in approved products</td>
<td></td>
</tr>
<tr>
<td>• polyanhydrides (approved product – Gliadel® wafers)</td>
<td>• Silicone</td>
<td></td>
</tr>
<tr>
<td>• polyesteramides (PEA)</td>
<td>• EVA</td>
<td></td>
</tr>
<tr>
<td>• poly(ethylene oxide terephthalate)/poly(butylene terephthalate) (PEOT/PBT)</td>
<td>• polyurethane</td>
<td></td>
</tr>
<tr>
<td>• PolyActive</td>
<td>• polyketel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Orthomer™</td>
<td>• Methacrylate-based polymer</td>
</tr>
<tr>
<td></td>
<td>• Biochronomer®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• polyketel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SynBiosys® - proprietary multi-block polymers (lactide, glycolide, ε-caprolactone, polyethylene glycol, butanediisocyanate, and butanediol in various configurations)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• InGell® - proprietary tri-block polymer (PCLA-PEG-PCLA with aliphatic end caps)</td>
<td></td>
</tr>
</tbody>
</table>
NON-RESORBABLE POLYMER PRODUCTS

• Several polymers have been developed in implant form
  • EVA, silicone, polyurethane, polyimide, and a methacrylate-based polymer
  • The DUROS titanium implant is also available as a non-resorbable device

• Dosage forms have been limited to implants to facilitate removal
  • Typical implants are rod-shaped
  • Intravaginal and intrauterine products are also approved

• Only small molecules or peptides have reached commercialization
**FDA Approved Extended-Release Polymer Products (PLGA, Oral, Transdermal Excluded) – 3 Peptide Products Highlighted**

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
<th>Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLIADEL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>carmustine</td>
<td>Arbor Pharmaceuticals</td>
<td>polyanhydride implant (disk)</td>
<td>glioma</td>
<td>Intradural</td>
</tr>
<tr>
<td>SUSTOL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>granisetron</td>
<td>Heron Therapeutics</td>
<td>triethylene glycol poly(orthoester) gel</td>
<td>antiemetic for cancer therapies</td>
<td>SC</td>
</tr>
<tr>
<td>TESTOPEL&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>testosterone</td>
<td>Endo (also Slate)</td>
<td>API pellets</td>
<td>androgen replacement therapy</td>
<td>SC</td>
</tr>
<tr>
<td>VIADUR</td>
<td>leuprolide acetate</td>
<td>Bayer</td>
<td>DUROS titanium implant</td>
<td>prostate cancer</td>
<td>SC (upper arm)</td>
</tr>
<tr>
<td>RETISERT</td>
<td>fluocinolone acetonide</td>
<td>Bausch &amp; Lomb</td>
<td>implant, (silicon cup reservoir)</td>
<td>chronic noninfectious uveitis</td>
<td>Intravitreal</td>
</tr>
<tr>
<td>YUTIQ</td>
<td>fluocinolone acetonide</td>
<td>EyePoint Pharmaceuticals US</td>
<td>polyimide implant</td>
<td>chronic noninfectious uveitis</td>
<td>Intravitreal</td>
</tr>
<tr>
<td>ILUVIEN</td>
<td>fluocinolone acetonide</td>
<td>Alimera Sciences</td>
<td>polyimide implant</td>
<td>chronic noninfectious uveitis</td>
<td>Intravitreal</td>
</tr>
<tr>
<td>Various</td>
<td>estradiol</td>
<td>Multiple companies</td>
<td>silicone ring</td>
<td>menopause symptoms</td>
<td>Intravaginal</td>
</tr>
<tr>
<td>Various</td>
<td>levonorgestrel</td>
<td>Multiple companies</td>
<td>silicone device</td>
<td>contraception</td>
<td>Intravaginal</td>
</tr>
<tr>
<td>JADELLE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>levonorgestrel</td>
<td>Bayer</td>
<td>silicone implant</td>
<td>contraception</td>
<td>Intradermal</td>
</tr>
<tr>
<td>TODAY&lt;sup&gt;4&lt;/sup&gt;</td>
<td>nonoxynol-9</td>
<td>Mayer Laboratories</td>
<td>polyurethane sponge</td>
<td>contraceptive</td>
<td>Intravaginal</td>
</tr>
<tr>
<td>CERVIDIL</td>
<td>dinoprostone</td>
<td>Ferring Pharmaceuticals</td>
<td>polyethylene oxide/urethane polymer</td>
<td>cervical ripening/induction of labor</td>
<td>Intravitreal</td>
</tr>
<tr>
<td>SUPRELIN LA</td>
<td>histrelin acetate</td>
<td>Endo Pharmaceuticals</td>
<td>methacrylate-based implant</td>
<td>central precocious puberty</td>
<td>SC</td>
</tr>
<tr>
<td>VANTAS</td>
<td>histrelin acetate</td>
<td>Endo Pharmaceuticals</td>
<td>methacrylate-based implant</td>
<td>prostate cancer</td>
<td>SC</td>
</tr>
<tr>
<td>NEXPLANON</td>
<td>etonogestrel</td>
<td>Organon USA</td>
<td>EVA implant (with Barium Sulfate)</td>
<td>contraceptive</td>
<td>Subdermal (upper arm)</td>
</tr>
<tr>
<td>IMPLANON</td>
<td>etonogestrel</td>
<td>Organon USA</td>
<td>EVA implant</td>
<td>contraceptive</td>
<td>Subdermal (upper arm)</td>
</tr>
<tr>
<td>PROBUPHINE</td>
<td>buprenorphine</td>
<td>Titan Pharmaceuticals</td>
<td>EVA implant</td>
<td>opioid use disorder</td>
<td>Subdermal (upper arm)</td>
</tr>
<tr>
<td>VITRASERT</td>
<td>ganciclovir</td>
<td>DISCONTINUED</td>
<td>tablet coated with EVA</td>
<td>CMV retinitis in AIDS patients</td>
<td>Intravitreal</td>
</tr>
</tbody>
</table>

**Veterinary products for ear implantation in steers and heifers only**

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
<th>Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPUDOSE</td>
<td>estradiol</td>
<td>Elanco</td>
<td>silicone implant</td>
<td>weight gain</td>
<td>SC</td>
</tr>
<tr>
<td>ENCORE</td>
<td>estradiol</td>
<td>Elanco</td>
<td>silicone implant</td>
<td>weight gain</td>
<td>SC</td>
</tr>
</tbody>
</table>

1. Biodegradable
2. Pellet is 75 mg testosterone, 0.97 mg stearic acid, and 2 mg PVP
3. Not available in US; previously NORPLANT
4. 24 hour use period
### FDA Approved Extended-Release Products – Non-Polymer

- 5 FDA approved extended-release non-PLGA polymer products – injectable suspensions
- These modern approvals are all in the schizophrenia indication

<table>
<thead>
<tr>
<th>#</th>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
<th>Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zyprexa Relprevv</td>
<td>Olanzapine</td>
<td>Eli Lilly</td>
<td>Suspension of salt particles</td>
<td>Schizophrenia</td>
<td>IM</td>
</tr>
<tr>
<td>2</td>
<td>Invega Sustenna</td>
<td>Paliperidone prodrug</td>
<td>Janssen</td>
<td>Palmitate ester prodrug particles</td>
<td>Schizophrenia</td>
<td>IM</td>
</tr>
<tr>
<td>3</td>
<td>Invega Trinza</td>
<td>Paliperidone prodrug</td>
<td>Janssen</td>
<td>Palmitate ester prodrug particles</td>
<td>Schizophrenia</td>
<td>IM</td>
</tr>
<tr>
<td>4</td>
<td>Abilify Maintena</td>
<td>Aripiprazole</td>
<td>Otsuka / Lundbeck</td>
<td>Particle suspension injection</td>
<td>Schizophrenia</td>
<td>IM</td>
</tr>
<tr>
<td>5</td>
<td>Aristada</td>
<td>Aripiprazole prodrug</td>
<td>Alkermes</td>
<td>Lauroxil ester prodrug particles</td>
<td>Schizophrenia</td>
<td>IM</td>
</tr>
</tbody>
</table>

Note: For completeness, there are two other schizophrenia commercial products based on PLGA:
- Risperdal Consta is a PLGA microsphere of resipridone (Jannsen – developed by Alkermes)
- Perseris is an in situ forming PLGA gel of resipridone (Indivior)
• 31 FDA approved extended-release non-PLGA polymer products – injectable suspensions
• Included here for completeness (and see prior slide for the other 5 products)
LONG-ACTING DOSAGE FORM OUTLINE

- Design considerations
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  - Formulation considerations for injectables
  - Formulation considerations for implantables
• Risperdal Consta is a microsphere formulation
  • First product entrant
• Other LAI products
  • Long-acting injectable drug suspensions
  • Insoluble drug alone as particulate suspension form (no other delivery system used)
  • Drug concentration range from 156 mg/ml to 321 mg/ml
• High dose drugs are the norm
  • Invega Trinza, Abilify Maintenna, Aristada
  • Drug dose 273 to 1,064 mg per dose (depending on duration)
  • Concentration range 200 to 321 mg/ml
  • Delivery system is an injectable suspension of milled drug for all cases
## Characteristics of Approved LAI Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Launch</th>
<th>Dosing Frequency</th>
<th>Active Dose (mg)</th>
<th>Dose Volume (ml)</th>
<th>Drug Concentration (mg/ml)</th>
<th>Delivery Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risperdal Consta</strong></td>
<td>2003</td>
<td>2 weeks</td>
<td>25, 37.5, 50</td>
<td>2, 2</td>
<td>12.5 mg/ml active (32.8 mg/ml solids) 50 mg/ml active (132 mg/ml solids)</td>
<td>PLGA Microsphere suspension 381 mg/g microspheres 38% by weight</td>
</tr>
<tr>
<td><strong>Invega Sustenna</strong></td>
<td>2006</td>
<td>1 month</td>
<td>156, 234</td>
<td>1, 1.5</td>
<td>156</td>
<td>Palmitate ester prodrug of paliperidone Injectable drug suspension</td>
</tr>
<tr>
<td><strong>Invega Trinza</strong></td>
<td>2015</td>
<td>3 month</td>
<td>273, 410, 546, 819</td>
<td>0.9, 1.3, 1.7, 2.6</td>
<td>303, 315, 321, 315</td>
<td>Palmitate ester prodrug of paliperidone Injectable drug suspension</td>
</tr>
<tr>
<td><strong>Abilify Maintena</strong></td>
<td>2013</td>
<td>1 month</td>
<td>300, 400</td>
<td>1.5, 2</td>
<td>200, 200</td>
<td>Aripiprazole Injectable suspension</td>
</tr>
<tr>
<td><strong>Aristada</strong></td>
<td>2015</td>
<td>1 month</td>
<td>441, 662, 882</td>
<td>1.6, 2.4, 3.2, 3.9</td>
<td>275, 275, 275, 275</td>
<td>Aripiprazole lauroxil prodrug of aripiprazole Injectable drug suspension</td>
</tr>
<tr>
<td><strong>Perseris</strong></td>
<td>2019</td>
<td>1 month</td>
<td>90/120</td>
<td>0.6-0.8</td>
<td>150</td>
<td>Resiperidone in PLGA in situ forming gel</td>
</tr>
</tbody>
</table>
Aristada
US 2015 – 6 wks
US 2017 – 2 months
Aristada Initio US 2018
with oral medications as start

- Ready to use pre-filled syringe
- Storage at RT
- Shake vigorously for 15 seconds
- Add needle and inject
- 4 dosage strengths available
- Injected every 4, 6, 8 weeks

Images From Invega Trinza:

- Ready to use pre-filled syringe
- Storage at RT
- Shake vigorously for 15 seconds
- Add needle and inject
- 4 dosage strengths available
- Injected every 3 months
LONG-ACTING DOSAGE FORM OUTLINE

• Design considerations
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• Formulation considerations for injectables
• Formulation considerations for implantables
• Ring works well for intravaginal application with many commercialized

• Matrix and reservoir systems in rod form are suitable for administration in the arm and abdomen

• Local administration in the back of the eye has been achieved for small molecules
Hot melt extrusion has been used with success to develop small molecule commercial products as well as small peptides.
HOT MELT EXTRUSION FUNCTION

Simple Extrusion Process

API properties to consider:
- Solubility and lipophilicity
- Physical state (solids) – crystallinity
- Melting temperature, thermal stability

Polymer properties to consider:
- Thermoplastic behavior
- Glass transition temperature (Tg)
  - 50 °C to 150 °C optimal
- High thermal stability

Has not yet been demonstrated for heat labile actives
- Small peptides success
- Proteins have not yet been successful

Critical Parts of Extruder
EXTRUDED IMPLANTABLES

OZURDEX®
dexamethasone intravitreal Implant

Implanon NXT
Etonogestrel Subcutaneous Implant

NuvaRing etonogestrel and ethinyl estradiol vaginal ring
You don’t have to do this!
Incredibly inefficient use of resources.
Should have launched one solution and one injectable suspension.
There is enough knowledge in the space to avoid the pitfalls in development.
THANKS AND GREETINGS FROM SAN DIEGO

DEL MAR CALIFORNIA – DOG BEACH
WE THRIVE ON
SOLVING YOUR MOST
CHALLENGING PROBLEMS
3rd LONG-ACTING INJECTABLES AND IMPLANTABLES CONFERENCE

6 - 7 FEB 2020
LA JOLLA
THE ALEXANDRIA OF TORREY PINES

FOR MORE INFO VISIT DDELABS.COM/LAII OR EMAIL LAII@DDELABS.COM
BACKUP SLIDES
Table 1: ARISTADA Dosing Frequency and Site of Injection

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosing Frequency</th>
<th>Site of Intramuscular Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>441 mg</td>
<td>Monthly</td>
<td>Deltoid or Gluteal</td>
</tr>
<tr>
<td>662 mg</td>
<td>Monthly</td>
<td>Gluteal</td>
</tr>
<tr>
<td>882 mg</td>
<td>Monthly or every 6 weeks</td>
<td>Gluteal</td>
</tr>
<tr>
<td>1064 mg</td>
<td>Every 2 months</td>
<td>Gluteal</td>
</tr>
</tbody>
</table>

Use the following ARISTADA doses for patients who are stabilized on oral aripiprazole, as shown in Table 2.

Table 2: ARISTADA Doses Based on Oral Aripiprazole Total Daily Dose

<table>
<thead>
<tr>
<th>Oral Aripiprazole Dose</th>
<th>Intramuscular ARISTADA Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg per day</td>
<td>441 mg every month</td>
</tr>
<tr>
<td>15 mg per day</td>
<td>662 mg every month</td>
</tr>
<tr>
<td></td>
<td>882 mg every 6 weeks</td>
</tr>
<tr>
<td>20 mg or higher per day</td>
<td>1064 mg every 2 months</td>
</tr>
<tr>
<td></td>
<td>882 mg every month</td>
</tr>
</tbody>
</table>

In conjunction with the first ARISTADA injection, administer a single injection of ARISTADA INITIO and one dose of oral aripiprazole 30 mg, or continue treatment with oral aripiprazole for 21 consecutive days [see Recommended Dosage (2.1)].

Adjust the ARISTADA dose as needed. When making dose and dosing interval adjustments, consider the pharmacokinetics and prolonged-release characteristics of ARISTADA.
Mean plasma concentration from first gluteal injection to 24 weeks

*Patients received oral aripiprazole 10 mg/day for 14 days prior to the first ABILIFY MAINTENA injection and concomitant oral aripiprazole 10 mg/day for 14 days after the first injection of ABILIFY MAINTENA.\(^1\)

\(C_{\text{min,ss}}\) = minimum steady-state plasma drug concentration during a dosage interval.\(^1\)
SIMULATED ARIPIPRAZOLE PLASMA CONCENTRATIONS FOR ARISTADA INITIATION REGIMENS ACROSS SELECTED ARISTADA DOSING OPTIONS

21 days of 15 mg oral aripiprazole
882 mg monthly

1 ARISTADA INITIO 675 mg and a single 30 mg dose of oral aripiprazole
Day 1 | 1064 mg every 2 months

Add Dose
Add Dose

Simulator for illustrative purposes only.

Please read the Prescribing Information for ARISTADA INITIO and ARISTADA, including Boxed Warning.
ILUVIEN DESCRIPTION
(LABEL SECTION 11)

- ILUVIEN is a sterile non-bioerodible intravitreal implant containing 0.19 mg (190 mcg) fluocinolone acetonide in a 36-month sustained-release drug delivery system. ILUVIEN is designed to release fluocinolone acetonide at an initial rate of 0.25 µg/day. ILUVIEN is preloaded into a single-use applicator to facilitate injection of the implant directly into the vitreous. The drug substance is a synthetic corticosteroid, fluocinolone acetonide.

- The chemical name for fluocinolone acetonide is \((6\alpha,11\beta, 16\alpha)-6,9\text{-difluoro-11,21\text{-dihydroxy-16,17-}[\text{1-methylethylidene}]bis-(oxy)]\text{-pregna-1,4-diene-3,20-dione}\). Its chemical structure is:

\[
\text{MW 452.50; molecular formula C}_{24}\text{H}_{30}\text{F}_{26}\]

- Fluocinolone acetonide is a white or almost white, microcrystalline powder, practically insoluble in water, soluble in methanol, ethanol, chloroform and acetone, and sparingly soluble in ether.

- Each ILUVIEN consists of a light brown 3.5mm x 0.37mm implant containing 0.19 mg of the active ingredient fluocinolone acetonide and the following inactive ingredients: polyimide tube, polyvinyl alcohol, silicone adhesive and water for injection.
ILUVIEN® IMPLANT

• ILUVIEN is a non-bioerodable intravitreal implant
• Removal is not addressed in the Drug Label
• Telephoned Alimera Sciences
  • Removal is not in the label because it is not required
    • Removal can be performed, but instructions are not in the label
  • Implants can remain in the eye for a lifetime
  • Additional dosing is allowed
    • Approximately 25% of patients in clinical studies received more than one implant
Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH).

Preparation for Dosing

Syringe A: pre-filled with polymer system
Syringe B: pre-filled with leuprolide acetate powder

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>7.5 mg</th>
<th>22.5 mg</th>
<th>30 mg</th>
<th>45 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA:PGA</td>
<td>50:50</td>
<td>75:25</td>
<td>75:25</td>
<td>85:15</td>
</tr>
<tr>
<td>Dose Volume</td>
<td>0.25 mL</td>
<td>0.375 mL</td>
<td>0.5 mL</td>
<td>0.375 mL</td>
</tr>
<tr>
<td>Needle Size</td>
<td>20G, ½”</td>
<td>20G, ½”</td>
<td>20G, 5/8”</td>
<td>18G, 5/8”</td>
</tr>
<tr>
<td>Frequency</td>
<td>Every month</td>
<td>Every 3 months</td>
<td>Every 4 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

Dose Level 7.5 mg contains leuprolide acetate 7.5 mg, PLGA 82.5 mg, NMP 160.0 mg

Dose level 7.5 mg @ initial, 1M, 2M
SOMATULINE DEPOT

- Injectable sustained release formulation containing lanreotide
  - Somatostatin analog that inhibits release of growth hormone and GI hormones, lowering GH & IGF-1
  - Releases active substance over 28 – 56 days
- Provided in prefilled, single-use syringes of 60-mg, 90-mg, or 120-mg strength
- Ready to use — no reconstitution or mixing required
- Needle length: 0.79 in (20 mm)
- Needle gauge: 19 gauge for all doses
- Injection depth/tissue: Deep subcutaneous injection
- Injection volume: 0.2 mL to 0.5 mL
- Storage condition: 2 to 8°C

<table>
<thead>
<tr>
<th>Each syringe contains:</th>
<th>SOMATULINE DEPOT 60 mg/0.2 mL</th>
<th>SOMATULINE DEPOT 90 mg/0.3 mL</th>
<th>SOMATULINE DEPOT 120 mg/0.5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide acetate</td>
<td>77.9 mg</td>
<td>113.6 mg</td>
<td>149.4 mg</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
</tr>
<tr>
<td>Water for injection</td>
<td>156.6 mg</td>
<td>272.3 mg</td>
<td>357.8 mg</td>
</tr>
<tr>
<td>Total Weight</td>
<td>266 mg</td>
<td>388 mg</td>
<td>510 mg</td>
</tr>
</tbody>
</table>