**Abuse Deterrent Opioid Formulations**
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**Introduction**\(^1\,2\)**

- Dilemma: Providing balance between providing appropriate access to opioid products in patients who truly need them AND addressing the problem of opioid abuse / misuse
- Guidance for industry finalized and published in April 2015: *Abuse-Deterrent-Opioids – Evaluation and Labeling*\(^3\)

**Abuse-Deterrent Opioid Products**

- Some long & short acting opioid products possess abuse deterrent properties but do not meet the new FDA abuse-deterrent labeling requirements
- Currently 10 agents meet the FDA labeling claim

**Table 1:** Abuse-Deterrent Opioid Products by General Category: **Physical / Chemical Barriers**

<table>
<thead>
<tr>
<th>Agent Brand (Generic) Manufacturer</th>
<th>FDA Approval Date(s)</th>
<th>Abuse Deterrent Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical / Chemical Barriers (in order of FDA approval date)</strong></td>
<td><strong>These agents fully MEET the FDA labeling claim</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OxyContin(^3,15) (Oxycodone ER) Tabs Q 12h Purdue Pharma</td>
<td>• 1995 (original) • April / August 2010 (reformulated)</td>
<td>• INTAC technology • Crush resistant properties, forming a gel that is not easily manipulated</td>
<td>First FDA approved ER formulation with abuse deterrent properties</td>
</tr>
<tr>
<td>Hysingla ER(^16,18) (Hydrocodone ER) Tabs Q 24h Purdue Pharma</td>
<td>November 20, 2014</td>
<td>RESISTEC(^\text{TM}) – confers tablet hardness &amp; imparts viscosity in aqueous solutions</td>
<td>Fourth FDA approved ER formulation with abuse deterrent properties</td>
</tr>
<tr>
<td>MorphaBond(^9,20) (Morphine sulfate ER) Tabs Q 12h Daiichi Sankyo, Inc. &amp; Inspirion Delivery Technologies LLC</td>
<td>October 2, 2015</td>
<td>SentryBond(^\text{TM}) Technology</td>
<td>• Fifth FDA approved ER formulation with abuse deterrent properties • Commercially not available(^3)</td>
</tr>
<tr>
<td>Xstampza ER(^17,23) (Oxycodone ER) Caps Q 12h Collegium Pharmaceutical, Inc.</td>
<td>April 26, 2016</td>
<td>DETERx technology</td>
<td>• Sixth FDA approved ER formulation with abuse deterrent properties • Capsule can be opened – potential use in patients with dysphagia</td>
</tr>
<tr>
<td>Arymo ER(^17,26) (Morphine ER) Tabs Q 8 or Q 12 Egalet Ltd.</td>
<td>January 9, 2017</td>
<td>Guardian technology</td>
<td>• Eighth FDA approved ER formulation with abuse deterrent properties</td>
</tr>
<tr>
<td>Vantrela ER(^26,27) (Hydrocodone ER) Tabs Q 12h</td>
<td>January 17, 2017</td>
<td>Not specified</td>
<td>• Ninth FDA approved ER formulation with abuse deterrent properties</td>
</tr>
<tr>
<td>Agent</td>
<td>Brand (Generic)</td>
<td>Manufacturer</td>
<td>FDA Approval Date(s)</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td><strong>Agonist / Antagonist Combinations</strong> (in order of FDA approval date) <strong>These agents fully MEET the FDA labeling claim</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Embeda ER<sup>39,41</sup> | (Morphine ER + Naltrexone) | Pfizer Laboratories | • August 2009 (withdrawn in 2011)  
• October 2014 | Naltrexone (opioid antagonist) – if crushed, blocks euphoric effects of morphine & precipitate withdrawal | • Third FDA approved ER formulation with abuse deterrent properties  
• Capsule can be opened – potential use in patients with dysphagia |
| Targiniq ER<sup>42</sup> | (Oxycodone ER + Naloxone) | Purdue Pharma | • July 2014 | Naloxone (opioid antagonist) – if crushed & snorted or injected will block euphoric effects of oxycodone | • Second FDA approved ER formulation with abuse deterrent properties  
• Commercially not available<sup>1</sup> |
**Troxyca ER**43  
(Oxycodone ER + Naltrexone)  
Caps Q 12h  
Pfizer Inc  
• August 19, 2016  
Naltrexone (opioid antagonist) – if crushed, blocks euphoric effects of morphine & precipitate withdrawal  
• Seventh approved ER formulation with abuse deterrent properties.  
• Capsule can be opened – potential use in patients with dysphagia  
• Commercially not available1

**These agents DO NOT meet FDA labeling claim as abuse deterrent products**

<table>
<thead>
<tr>
<th>Agent Brand (Generic)</th>
<th>FDA Approval Date(s)</th>
<th>Abuse Deterrent Mechanism</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aversion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaydo IR4, 5, 54</td>
<td>Various dates</td>
<td>Naloxone (opioid antagonist) – if injected will precipitate opioid withdrawal</td>
<td></td>
</tr>
<tr>
<td>(Oxycodone IR)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tabs Q 4-6h PRN</td>
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<td></td>
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<tr>
<td>Egalet Ltd.</td>
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</table>
| • Formerly FDA approved in 2011 under brand name Oxecta  
• January 2015 collaboration with Egalet | Combined with sodium lauryl sulfate to irritate the nasal passage if manipulated & components form a gel if exposed to water | FDA has not approved an abuse-deterrent labeling claim |

**Table 3: Abuse-Deterrent Opioid Products by General Category: Aversion**

<table>
<thead>
<tr>
<th>Agent Brand (Generic)</th>
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<tr>
<td><strong>Delivery System</strong></td>
<td></td>
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</table>
| Exalgo5, 35, 36        | March 2010           | OROS push pull osmotic delivery system  
• Delivers over 24 h | FDA has not approved an abuse-deterrent labeling claim |
| (Hydromorphone ER)    |                      |                           |               |
| Tabs Q 24h             |                      |                           |               |
| Mallinckrodt LLC      |                      |                           |               |

**Table 4: Abuse-Deterrent Opioid Products by General Category: Delivery System**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Combination of Technologies</strong></td>
<td></td>
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</tbody>
</table>
| Avridi57-58           | NOT FDA APPROVED     | Physical/chemical barrier  
• Aversion – sodium lauryl sulfate | September 10, 2015 FDA ruled against approving this agent due to safety concerns (must be taken on empty stomach) |
| (Oxycodone IR)        |                      |                           |               |
| Purdue Pharma        |                      |                           |               |

1As of July 28, 2017  
ER = extended release; IR = immediate release
Other Categories of Abuse Deterrent Products

Per FDA guidance categories; No products available to date

- New molecular entities & prodrugs
- Novel approaches

Challenges

- Need to ensure appropriate access to opioids for patients with legitimate use
- Prescribers need to perform a risk / benefit analyses for all patients prior to prescribing an opioid – need to assess who is at high risk, who is at a lower risk of opioid abuse; who should receive an abuse deterrent formulation?
- Current products are brand name only – higher cost, higher co-pay; formulary challenges
- Continued impact on heroin abuse?
- Post marketing surveillance – more pharmacoepidemiology studies are needed
- Manipulation can (& DOES) still occur!

Unique Counseling Points Specific for Abuse Deterrent Products

- Become familiar with the specific agent and technology used
- Substitutions are not be allowed
- Risks of opioid therapy – new language in patient medication guide
- Formulation may appear intact in the stool – re-assure the patient that the drug has been released
- No crushing, breaking or dissolving the tablet or capsule
- Some formulations (Embeda ER, Troxyca ER, Xtampza ER) may be opened / sprinkled onto food – unique counseling
References


17. Purdue. Purdue Pharma L.P. receives FDA approval for Hysingla ER (hydrocodone bitartrate) extended-release tablets CII, a once daily opioid analgesic formulated with abuse deterrent properties. Available at: http://www.purduepharma.com/news-media/2014/11/purdue-pharma-l-p-receives-fda-approval-for-


37. Pernix Therapeutics. Pernix launches Zohydro ER with BeadTek. Available at:


53. CenterWatch. Exalgo (hydromorphone hydrochloride) extended release. Available at: http://www.centerwatch.com/drug-information/fda-approved-drugs/drug/1087/exalgo-hydromorphone-


