

 **Drug Formulary Commission**

**Bureau of Health Care Safety and Quality**

**Department of Public Health**

**January 7, 2016**

**Opening Remarks**

* Drug Formulary Commission Statutory Mission
* Schedule II and III Opioid Universe
* Component 1: Drugs Of Heightened Public Health Risk
* Component 2: Drug Formulary Therapeutic Substitutes With Abuse Deterrent Properties
* Component 3: “Cross Walk”
* Draft Formulary
* Review of December 17th meeting
	+ Voted to approved Hysingla ER
	+ Voted not to approve Targiniq ER

….or other drugs that are not marketed in the United States for inclusion as a potential substitute

* + Continued discussion OxyContin
	+ Continued discussion Embeda

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 Presentation Agenda

**Therapeutically Equivalent Substitutes FDA Approved ADF Labeling**

**Monograph Review**

**Schedule II Opioids**

**FDA Approved Abuse Deterrent Labeling**

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Therapeutically Equivalent Substitutes
FDA Approved ADF Labeling

|  |
| --- |
| **List of Medications with Abuse-Deterrent Claims in FDA-Approved Labeling** |
| **Product Name** | **Manufacturer****Slide 5** | **Ingredient(s)** | **Dose Form** | **Method of Abuse Deterrence** | **DFC Action** |
| Targiniq ER | Purdue | Oxycodone ER and Naloxone | Tablet | Antagonist | Voted NOT to approve for Crosswalk consideration at December 17, 2015 meeting |
| OxyContin | Purdue | Oxycodone ER | Tablet | Crush-resistant Formulation | Deferred to January 7, 2016 meeting |
| Hysingla ER | Purdue | Hydrocodone ER | Tablet | Crush-resistant Formulation | Voted to approve for Crosswalk consideration at December 17, 2015 meeting |
| Embeda | Pfizer | Morphine ER and Naltrexone | Capsule | Antagonist | Deferred to January 7, 2016 meeting |

**Therapeutically Equivalent Substitutes
FDA Approved ADF Labeling**

**Oxycontin CR ADF Monograph Review**

* Oxycodone HCL
* ADF Property
	+ physical chemical barrier
	+ effective against injection, snorting
* FDA Approval April 2010
* FDA ADF labeling approved April 2013
* Available Strengths
	+ 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg

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**OxyContin® ADF Technology**

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* Reformulated in 2010 with RESISTEC® technology2
* RESISTEC® technology2:
	+ Increases tablet hardness
	+ Forms a viscous gel under attempts to dissolve in aqueous solutions
	+ Resists increased drug delivery rate when mixed with alcoholic beverages
* Abuse-deterrence studies49-51:
	+ OxyContin® with RESISTEC® resisted crushing, breaking, extraction and dissolution using a variety of tools and solvents
	+ Crushed OxyContin® with RESISTEC® was associated with less drug liking and willingness to take drug again when administered intranasally compared to crushed original OxyContin® and oxycodone powder

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* Post-marketing data indicate a reduction in the abuse of OxyContin® after reformulation.54-59
* Post-marketing survey data also indicate that after reformulation some OxyContin abusers (n=88)59:
	+ Switched from non-oral routes of abuse to oral abuse (n=38; 43%)
	+ Successfully defeated the ADF mechanism to continue normal route of abuse (n=30; 34%)
	+ Continued with previous oral abuse independent of formulation (n=20; 23%)
* Anecdotal reports from an internet forum identified methods to bypass the ADF mechanism by using tools such as a Dremel® rotary power tool or Pedi-Paws® pet nail trimmer, and subsequently utilizing a microwave and freezer to prevent complete gel formation. Conversely, some individuals reported difficulty abusing the tablets by methods other than the oral route due to inability to avoid gel formation.60
* Purdue Pharma, LP canceled their scheduled meeting on July 7, 2015 with the FDA intended to review findings of post-marketing OxyContin® abuse data, requesting more time for analysis of the data.61

**OxyContin® Information Requested by DFC**

**Information OxyContin® Requested by DFC**

* The first required postmarketing study results regarding abuse of OxyContin® are due to the FDA in June 2018.61
* OxyContin® is included in the extended-release/long-acting (ER/LA) shared Risk Evaluation and Mitigation Strategy (REMS) program.48
* Initial Dose (opioid naïve adults): 10 mg every 12 hours.1
* Initial Dose (pediatric): Pediatric patients should not start until they have tolerated other opioids equivalent to at least 20 mg oxycodone per day for at least five consecutive days.1
* Two FDA advisory committees voted 14 to 4 with one abstention in favor of approval of the reformulated OxyContin® (ADF).46

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* Mean time to peak plasma concentration (Tmax)for intact **OxyContin® ADF tablets** (oral administration):
	+ Ranges from 4.15 to 5.11 hours, dependent upon dose1
* Median Tmax for intact **OxyContin® ADF tablets** (oral administration):
	+ 5 hours52
* Median Tmax for crushed **OxyContin® ADF tablets** (oral administration):
	+ 1.75 hours52
* Median Tmax for finely crushed **OxyContin® ADF tablets** (insufflation):
	+ 2.00 to 2.08 hours50,51
* Median Tmax for coarsely crushed **OxyContin® ADF tablets** (insufflation):
	+ 2.62 to 3.00 hours50,51
* Median Tmax for finely crushed **original OxyContin® tablets**: (insufflation):
	+ 1.00 to 1.10 hours50,51

**OxyContin® Information Requested by DFC**

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**Therapeutically Equivalent Substitutes
FDA Approved ADF Labeling**

**Embeda Monograph Review**

* morphine sulfate / naltrexone HCL
* ADF Property
	+ antagonist
	+ effective against crushing, snorting
* FDA Approval August 2013
* FDA ADF Approval October 2014
* Available Strengths 20 /.8, 30/1.2, 50/2, 60/2.4, 80/ 3.2, 100/4mg

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* Embeda® is a µ-opioid receptor agonist (morphine) and µ-opioid receptor antagonist combination ADF.1
* Embeda® capsules contain pellets of extended-release morphine with naltrexone sequestered in the core of the pellets.1
* When Embeda® is taken as directed, the naltrexone is intended to have no clinical effect. If the pellets are crushed or chewed, up to 100% of the naltrexone may be released, which may antagonize opioid effects or precipitate withdrawal symptoms in physically dependent patients.1

**Embeda® ADF Technology**

**Embeda® Information Requested by DFC**

* Embeda® has been evaluated in multiple abuse liability studies:6-9
	+ Crushed pellets and intact Embeda® administered as oral solutions solution.6
	+ There was no significant difference in drug likability between crushed and intact Embeda® administered as oral solutions.6
	+ Crushed Embeda® pellets administered as an oral solution were associated with less “drug liking” and “drug high” compared to crushed morphine sulfate controlled-release (CR) administered as an oral solution.7
	+ Crushed Embeda® pellets administered intranasally were associated with less drug liking and drug high compared to crushed morphine CR administered intranasally.8
	+ Simulated Embeda® solution administered intravenously (IV) was associated with less of a high when compared to morphine solution for IV administration.9

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**Embeda® Information Requested by DFC**

* The FDA expects formal epidemiologic studies to assess whether or not the ADF properties of Embeda® actually result in a meaningful reduction in abuse in the community by October 2020.11
* Anecdotal reports posted on an internet forum identified methods to bypass the abuse deterrent mechanism of Embeda® by the oral and intravenous routes; however, there were reports of precipitated withdrawal after abuse of crushed Embeda® pellets, as well.12
	+ IV abuse report: User combined water and lemon juice, repeatedly used a hot water bath to heat the mixture and waited approximately 12 hours to prepare a solution for injection.
	+ Oral abuse report: User placed Embeda® pellets into a shot glass full of water, and used repeated short microwave sessions to prepare a solution for ingestion, while avoiding ingestion of remainder of the pellets.

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**Embeda® Information requested by DFC**

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* Embeda® is subject to the requirements of the shared system extended-release/long-acting Risk Evaluation and Mitigation Strategies (REMS) program.13
* Initial Embeda® dosing (opioid naïve): 20 mg/0.8 mg every 24 hours.1
* Initial Embeda® dosing (converting from other opioids): 30 mg/1.2 mg every 24 hours.1
* Information regarding FDA advisory committee voting on Embeda® is not readily available. Of note, Embeda® was originally approved in 2009.2
* Median time to peak plasma concentration (Tmax)for intact Embeda.®1
* Morphine Tmax: 7.5 hours.
* Median Tmax for crushed Embeda® pellets administered orally.1
* Morphine and naltrexone: one hour.
* Median Tmax for crushed Embeda® pellets, insufflated.1
* Morphine and naltrexone: 36 minutes.
* The earliest deadline for the manufacturer to submit results of a post-marketing epidemiological study that assesses whether the ADF mechanism results in a meaningful deterrence to abuse or misuse in the community is October 2020.11

**Meeting Summary**

* Meeting Recap
* Review of takeaways
* Next steps
	+ Anticipated materials
* Next Meeting
	+ January 21, 2016 9:00AM-12:00PM

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