**Slide 1**

 **Drug Formulary Commission**

**Bureau of Health Care Safety and Quality**

**Department of Public Health**

**Junne 2, 2016**

* Review of May 5th meeting
* List of non-opioid pain management alternatives.
* ADF Evaluation
	+ Zohydro ER® (reconsideration)
* Crosswalk
	+ Hysingla ER (potential)
	+ Oxaydo
* Next Steps

**Slide 2**

 Presentation Agenda



**The Opioid Epidemic
Burden in Massachusetts**

**MassPAT is a component in the larger opioid effort**

**MassPAT**

**Slide 4**

Recovery

CHIA

Law

Enforcement

Health

Care

Providers

Prof.

Societies

Prof. Boards

VA

PMP

State Linkages in Opioid Epidemic

Law

Makers

Others…

Drug

Treatment

**Non-Opioid Pain Management**

Section 4 of Chapter 52 of the Acts of 2016 amends Section 13 of Chapter 17 of the General Laws to require the Drug Formulary Commission, by September 1, 2016, to publish, distribute, and update annually a list of:

* + FDA approved, non-opioid drug products;
	+ That are effective pain management alternatives; and
	+ Have a lesser potential for abuse than Schedule II and III opioid drug products
	+ By September 1, 2016.

**Slide 5**

* Drug Formulary Commission Statutory Mission

Evaluation - Reconsideration

* 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”

**Slide 6**

Draft Formulary

|  |
| --- |
| **List of Medications with FDA-Approved ADF Labeling**Chemically Equivalent SubstitutesFDA Approved ADF Labeling**Slide 7** |
| **Product Name** | **Manufacturer** | **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 | Voted to approve for Crosswalk consideration at 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 | Voted to approve for Crosswalk consideration at January 7, 2016 meeting |

Chemically Equivalent Substitutes
Abuse-Deterrent Claims

no FDA-Approved Labeling

**Slide 8**

|  |
| --- |
| **List of Medications with Abuse-Deterrent Claims** |
| **Product Name** | **Manufacturer** | **Ingredient(s)** | **Dose Form** | **Method of Abuse Deterrence** | **DFC Action** |
| Opana ER | Endo | Oxymorphone | Tablet | Crush-resistant formulation | Voted NOT to approve for Crosswalk consideration at February 4, 2016 Meeting |
| Oxaydo | Egalet | Oxycodone ER | Tablet | Aversion technology with assumed ADF properties | Voted to approve for Crosswalk consideration atFebruary 4, 2016 Meeting |
| Nucynta ER | Jansen | Tapentadol | Tablet | Crush-resistant formulation | Voted to approve for Crosswalk consideration atFebruary 4, 2016 Meeting |
| Zohydro ER | Pernix Therapeutics | Hydrocodone ER  | Capsule | BeadTek Technology | To be reconsidered atJune 2, 2016 Meeting |

 **Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

**Zohydro ER® Monograph Review**

Chemical name hydrocodone ER

FDA approval October 2013

Reformulation January 2015

Available strengths 10mg, 15 mg, 20mg, 30mg, 40mg, 50 mg

Potential ADP BeadTek®

FDA ADF labeling No

**Slide 9**

\*ADP = abuse-deterrent properties

**Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

* Zohydro ER® was reformulated in 2015 with BeadTek® technology.4
* BeadTek® is a mixture of indistinguishable beads of inactive ingredient, extended-release hydrocodone and immediate-release hydrocodone that reportedly causes gel formation under attempts to crush and dissolve.4
* There is currently a lack of published data regarding clinical abuse potential studies of Zohydro ER® with BeadTek®.
* *In vitro* laboratory manipulation study data for Zohydro ER® with BeadTek® is not available.
* There is no reported mechanism of BeadTek® by which the formulation guards against abuse via insufflation or crushing/chewing and swallowing to release a supratherapeutic immediate-release dose.
* There is a lack of postmarketing data demonstrating a reduction of abuse in the community.

**Slide 10**

**Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

* Initial dose (opioid naïve adults): 10 mg every 12 hours.1
* Initial dose (converting from other opioids): The manufacturer provides a table of conversion factors to calculate initial doses for patients converting from other opioids (Table 7 in monograph).1
* Time to peak plasma concentration (Tmax) of intact Zohydro ER® capsules is approximately 5 hours.1
* Tmax for crushed or otherwise tampered with Zohydro ER® tablets has not been published.
* The rate of absorption of Zohydro ER® increased on average by 1.2-fold upon co-administration with 40% alcohol.1
* Food effects are not considered significant upon the extent of absorption (no dose dumping); however, peak plasma concentration of hydrocodone increased by 27% when a Zohydro ER® 20 mg capsule was given with a high fat meal.

**Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

* Zohydro ER® is subject to the requirements of the Extended-Release and Long-Acting (ER/LA) Risk Evaluation and Mitigation Strategies (REMS) program.5
* The FDA advisory committee voted 11 to 2 with one abstention against approval of Zohydro ER® in 2013.3
* Information regarding FDA requirements of the manufacturer related to post-marketing epidemiological studies is not available. This is likely due to the lack of ADF labeling.
* Hysingla ER is a hydrocodone product with FDA-approved ADF labelling that this group has already advanced.

**Slide 12**

**Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

* Per request of the Drug Formulary Commission, additional information about the potential abuse-deterrent properties of Zohydro ER® (hydrocodone extended-release) was requested of the manufacturer.
* A representative of Pernix Ireland Pain Limited provided a brief document, identifying polyethylene oxide as the agent used to cause viscous gel formation upon attempts to crush and dissolve the beads within the capsule.
* The document states that the clinical significance of BeadTekTM on abuse or misuse of Zohydro ER® has not been established.
* In addition, the manufacturer was unable to supply any clinical abuse potential studies or *in vitro* laboratory manipulation and extraction studies for Zohydro ER®.
* Review of the Supplemental New Drug Application for reformulated Zohydro ER® with BeadTekTM revealed no information pertinent to the potential abuse-deterrent properties of Zohydro ER®.

**Slide 13**

**Potential Formulary Substitutes
Abuse-Deterrent Claims
Zohydro ER®**

**Zohydro ER® Summary**

* Chemical name hydrocodone ER
* Dosage form Extended-release capsule
* Formulation BeadTek®
* Potential ADP claim Gel formation upon attempts to crush and dissolve/poor syringeability

 A mechanism to protect against crushing the beads for insufflation has not been demonstrated

* ADF studies Not available
* Additional Clinical significance of BeadTekTM on abuse or Information misuse of Zohydro ER® has not been established.

 No clinical abuse potential studies or *in vitro* laboratory manipulation and extraction studies supplied.

**Slide 14**

\*ADP = abuse-deterrent properties

* Drug Formulary Commission Statutory Mission

**Crosswalk**

* 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

**Slide 15**

… In considering whether a drug is a **chemically equivalent substitution** the commission shall consider:

* the **accessibility** of the drug and its proposed substitute;
* whether the drug's substitute is **cost** prohibitive;
* the **effectiveness** of the substitution (FDA approved for pain); and
* whether, based upon the current patterns of abuse and misuse, the drug's substitute incorporates abuse deterrent technology that will be an **effective deterrent** to such abuse and misuse.

**Slide 16**

 Drug Product Criteria

“Chemically Equivalent Substitution”, for the purpose of creating a formulary of drugs with abuse deterrent properties that the commission has determined may be appropriately substituted for opioids that have been determined to have a heightened public health risk due to the drugs’ potential for abuse and misuse, shall mean drug products which contain the same active ingredients, and are equivalent in strength or concentration, dosage form, and route of administration, and produce a comparable biologic effect. Prodrugs or ingredients without analgesic effect that are used solely for abuse deterrent formulations need not be equivalent.

**Slide 17**

 Chemically Equivalent Substitution

 Single-Dose Pharmacokinetic Data - Hysingla

NDA Data Source:

Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016 [cited 2016 Apr 29]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

CV=coefficient of variation, ER=extended-release Yellow=List A Green=List B

**Single-Dose Pharmacokinetic Data**

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug** | **Dose** | **Peak Concentration (Cmax, mean [CV%])** | **Time to Peak Concentration (tmax, median [range])** | **Elimination Half-Life (t1/2, mean [CV%])** | **Area Under the Curve (AUC0-∞, mean [CV%])** |
| Hysingla ER® (hydrocodone ER tablet) | 40 mg | 33.9 (34.81%) ng/mL |  16.0 (6.0 to 24.0) hours |  7.7 (27.27%) hours | 622 (40.51%) ng • hr/mL |
| Zohydro ER® (hydrocodone ER capsule) | 40 mg | 37.5 (23.52%) ng/mL | 6.0 (4.0 to 10.0) hours | 9.4 (25.53%) hours | 596 (28.97%) ng • hr/mL |

**Hysingla ER**

**Hysingla ER® and Zohydro ER®**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **Active Ingredient** | **Strengths** | **Dosage Form** | **Route of Administration** | **Dosing Schedule** | **Cost/unit\*** | **Units Dispensed 2015** | **Approximate Cost 2015** | **ADP Efficacy** |
| Hysingla ER® | hydrocodone | 20 mg | extended-release tablet | Oral | Q24H | $7.19 | 8,376 | $60,223  | Category II |
| 30 mg | $10.50 | 5,422 | $56,931  |
| 40 mg | $14.15 | 4,612 | $65,260  |
| 60 mg | $19.59 | 2,380 | $46,624  |
| 80 mg | $26.41 | 1,383 | $36,525  |
| 100 mg | $33.61 | 371 | $12,469  |
| Zohydro ER® | hydrocodone | 10 mg | extended-release capsule | Oral | Q12H | $6.75 | 70 | $473  | Category III |
| 15 mg | $7.21 | 352 | $2,538  |
| 20 mg | $7.44 | 230 | $1,711  |
| 30 mg | $7.67 | 0 | $0  |
| 40 mg | $7.90 | 90 | $711  |
| 50 mg | $8.24 | 420 | $3,461  |

Cost of Substitution (100% Conversion): $3,234

Cost of Substitution (75% Conversion): $2,426

Cost of Substitution (50% Conversion): $1,617

Percent Change in Cost: +36.36%

Possible Patient Impact: Approximately 10

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q12H=every 12 hours, Q24H=every 24 hours Green=List B

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**Slide 19**

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q12H=every 12 hours, Q24H=every 24 hours Green=List B

Cost of Substitution (100% Conversion): $3,234

Cost of Substitution (75% Conversion): $2,426

Cost of Substitution (50% Conversion): $1,617

Percent Change in Cost: +36.36%

Possible Patient Impact: Approximately 10

**Slide 20**

**Single-Dose Pharmacokinetic Data**

CV=coefficient of variation, IR=immediate-release Yellow=List A

\*Values represent median (range) Green=List B

†CV not reported

NDA Data Source:

Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016 [cited 2016 Apr 26]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

 Single-Dose Pharmacokinetic Data - Oxaydo

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug** | **Dose** | **Peak Concentration (Cmax, mean [CV%])** | **Time to Peak Concentration (tmax, mean [CV%])** | **Elimination Half-Life (t1/2, mean [CV%])** | **Area Under the Curve (AUC0-∞, mean [CV%])** |
| Oxaydo® (oxycodone IR tablet) | 15 mg (2 x 7.5 mg tablets) | 34.5 (22.70%) ng/mL |  1.18 (48.31%) hours |  3.94 (15.99%) hours | 168.9 (22.20%) ng • hr/mL |
| Oxycodone IR capsule | 15 mg (3 x 5 mg capsules) | 37.1 (36.10%) ng/mL | 1.00 (0.50 to 6.00) hours\* | 3.90 hours† | 192.4 (32.70%) ng • hr/mL |
| Roxicodone® (oxycodone IR tablet) | 15 mg (1 x 15 mg tablet) | 36.5 (24.05%) ng/mL | 0.98 (40.82%) hours | 3.99 (19.80%) hours | 163.4 (25.76%) ng • hr/mL  |

**Oxaydo®**

**Slide 21**

**Oxaydo® and Oxycodone Immediate-Release Capsule**

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q4-6H PRN=every four to six hours as needed Green=List B

Cost of Substitution (100% Conversion): $1,106,787

Cost of Substitution (75% Conversion): $830,090

Cost of Substitution (50% Conversion): $553,394

Percent Change in Cost: +189.12%

Possible Patient Impact: Approximately 1,290

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **Active Ingredient** | **Strength** | **Dosage Form** | **Route of Administration** | **Dosing Schedule** | **Cost/unit\*** | **Units Dispensed 2015** | **Approximate Cost 2015** | **ADP Efficacy** |
| Oxaydo®  | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $4.25 | 0 | $0 | Category II |
| Oxycodone immediate-release | oxycodone hydrochloride | 5 mg | immediate-release capsule | Oral | Q4-6H PRN | $1.47 | 398,125 | $585,244 | N/A |

**Oxaydo®**

**Slide 22**

**Oxaydo® and Oxycodone Immediate-Release Tablet**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **Active Ingredient** | **Strength** | **Dosage Form** | **Route of Administration** | **Dosing Schedule** | **Cost/unit\*** | **Units Dispensed 2015** | **Approximate Cost 2015** | **ADP Efficacy** |
| Oxaydo®  | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $4.25 | 0 | $0 | Category II |
| Oxycodone immediate-release | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $0.12 | 35,983,163 | $4,317,980 | N/A |

Cost of Substitution (100% Conversion): $604,549,779

Cost of Substitution (75% Conversion): $453,412,334

Cost of Substitution (50% Conversion): $302,274,889

Percent Change in Cost: +3,354.37%

Possible Patient Impact: Approximately 94,999

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q4-6H PRN=every four to six hours as needed Green=List B

**Oxaydo®**

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**Oxaydo® and Roxicodone®**

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q4-6H PRN=every four to six hours as needed Green=List B

Cost of Substitution (100% Conversion): $1,101,350

Cost of Substitution (75% Conversion): $826,012

Cost of Substitution (50% Conversion): $550,675

Percent Change in Cost: +171.58%

Possible Patient Impact: Approximately 81

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **Active Ingredient** | **Strength** | **Dosage Form** | **Route of Administration** | **Dosing Schedule** | **Cost/unit\*** | **Units Dispensed 2015** | **Approximate Cost 2015** | **ADP Efficacy** |
| Oxaydo®  | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $4.25 | 0 | $0 | Category II |
| Roxicodone® | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $1.69 | 0 | $0 | N/A |

**Oxaydo® SummaryAll List A Products**

**Slide 24**

**Oxaydo® and All List A Oxycodone Immediate-Release Products**

**TOTAL** Cost of Substitution for **all Products** (100% Conversion): $606,757,916

**TOTAL** Cost of Substitution for **all Products** (75% Conversion): $455,068,437

**TOTAL** Cost of Substitution for **all Products** (50% Conversion): $303,378,958

**TOTAL** Percent Change in Cost for **all Products**: +3,152.01%

**TOTAL** Possible Patient Impact for **all Products**: Approximately 96,370

\*Wholesale acquisition cost per Online Red Book as of 3/15/2016 Yellow=List A

ADP=abuse-deterrent property, Q4-6H PRN=every four to six hours as needed Green=List B

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **Active Ingredient** | **Strength** | **Dosage Form** | **Route of Administration** | **Dosing Schedule** | **Cost/unit\*** | **Units Dispensed 2015** | **Approximate Cost 2015** | **ADP Efficacy** |
| Oxaydo®  | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $4.25 | 0 | $0 | Category II |
| Oxycodone immediate-release | oxycodone hydrochloride | 5 mg | immediate-release capsule | Oral | Q4-6H PRN | $1.47 | 398,125 | $585,244 | N/A |
| Oxycodone immediate-release | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $0.12 | 35,983,163 | $4,317,980 | N/A |
| Roxicodone® | oxycodone hydrochloride | 5 mg | immediate-release tablet | Oral | Q4-6H PRN | $1.69 | 0 | $0 | N/A |

**Meeting Summary**

* Meeting Recap
* Review of takeaways
* Next Steps
	+ Regulations and Formulary review
	+ Next Meeting – June 30, 2016
	+ @ 250 Washington Street

**Slide 25**