

PEHP Report on Abuse Deterrent Opioid Analgesic Drug Products

To the Health and Human Services and Business and Labor Interim Committees

October 2015

I. Background and Summary

The Legislature directed the Public Employees Health Program (PEHP) in SB 265 to prepare this report on new pharmaceutical products designed to deter the abuse of opioid-based (e.g. Percocet[®], Lortab[®], oxycodone) pain medication.

Drug manufacturers use two mechanisms to deter pain medication abuse. The first mechanism adds physical properties that make the tablet difficult to crush or dissolve. For example, some tablets form a gel-like substance in water so that it cannot be drawn into a syringe if dissolved for injection. The second mechanism adds a second drug into the tablet, for example an “antidote,” that when crushed for injection blocks the opioid effect.

We reviewed the medical literature on whether these new products reduce the abuse of pain medication, which included survey results, claims data, event reports, prescribing information, and published FDA guidance. Current data indicates:

- **Clinical trials.** All products with abuse deterrent labeling approved by the FDA have completed controlled studies in opioid-experienced, recreational drug users and demonstrate properties that make the products more difficult to abuse by unintended routes of administration (e.g. injection)
- **U.S. Expanded Data.** Expanded “real world” data is limited to the release of abuse deterrent OxyContin[®]. The release of abuse deterrent OxyContin[®] in 2010 was associated with a reduction in the rate of OxyContin[®] abuse in all available studies. Increased abuse of other opioids coincides with the release of abuse deterrent OxyContin[®] in some studies. Increased abuse of heroin appears to predate the release of reformulated OxyContin[®] and accelerate after release
- **Utah Specific Data.** The prescription volume for oxycodone (OxyContin[®] or other forms) and death rates related to drug poisoning rose between 2010 and 2012
- **FDA Guidance.** No product that has been successful in deterring the most common form of abuse: swallowing intact tablets

We also searched for studies of patients facing barriers in obtaining a medication with abuse deterrent FDA labeling. We found no such studies.

There are potential barriers that can arise from health plan administration, including formulary coverage, prior authorization, and out-of-pocket expense, to ensure that a drug is appropriate and to share the increased costs of a drug with the patient. In the case here, there is a \$9.04 difference between the per tablet average cost of \$3.20 for a non-deterrent opioid and \$12.24 for a deterrent opioid. Specifically we found that:

- Formulary coverage for the three drugs with a current FDA label for abuse deterrence varied. However, six sampled plans cover at least 1 abuse deterrent opioid (OxyContin®).
- Prior authorization for Hysingla ER®, Embeda ER® or OxyContin® is required by five plans.
- Out-of-pocket costs range from \$50 to \$500 depending on plan, drug and dose.

PEHP recognizes the value of abuse-deterrent opioid analgesics and covers 1 with FDA label and 4 with deterrent properties at patient cost-sharing levels that reflect the higher costs associated with these drugs.

II. The FDA requires completion of studies demonstrating a reduced likelihood of abuse before authorizing the use of abuse deterrent labeling

The FDA has published guidance to assist in the evaluation of products with abuse deterrent properties.¹ Inclusion of abuse deterrent labeling requires the completion of laboratory-based manipulation and extraction studies, impact of abuse deterrent properties in recreational drug users, and equivalency studies to determine absorption, metabolism and excretion. Additional studies demonstrating post-marketing effects may be conducted after the product has been on the market. The FDA describes important limitations related to abuse deterrence:

- The presence of abuse deterrent properties does not eliminate the risk of abuse. Abuse deterrent properties may make the product less likely to be altered and abused through an unintended route of administration (e.g. injecting, smoking)
- Abuse deterrent products do not stop the most common form of abuse (swallowing)
- Abuse of opioids will persist regardless of the form (abuse deterrent or other)

The guidance outlines an objective means to measure the effects of abuse deterrent formulations in a controlled environment and recommends studies be conducted in recreational opioid users, who have a history of abuse with the route of administration that will be studied. All available studies use a 0 to 100 scale of drug “liking” where 0 represents the maximum dislike and 100 represents maximum liking.

Medication	Number of Participants	Route of Abuse	Average Drug Liking
OxyContin® ²	30	Intranasal	Mean drug liking was 80.4 for abuse deterrent OxyContin® and 94 for original OxyContin®
Embeda ER® ³	32	Oral	Mean drug liking was reported as 68.1 for crushed Embeda ER® vs. 89.5 for immediate release morphine
Embeda ER® ³	36	Oral	Mean drug liking was reported as 65.2 for crushed Embeda ER® vs. 80.6 for crushed extended release morphine
Embeda ER® ³	33	Intranasal	Mean drug liking was reported as 69 for crushed Embeda ER® vs. 88 for immediate release morphine
Embeda ER® ³	28	Intravenous	Mean drug liking was 34 for IV morphine + IV

		(Embeda ER [®] was not used in this trial)	naltrexone vs. 86 for IV morphine
Hysingla ER [®] 4	25	Intranasal	Mean drug liking was 65.4 for Hysingla ER [®] vs. 90.4 for hydrocodone powder
Hysingla ER [®] 4	35	Oral	Mean drug liking was 69 for chewed Hysingla ER [®] vs. 94 for hydrocodone solution

Currently, three products (Hysingla ER[®], Embeda ER[®], OxyContin[®]) contain FDA approved labeling as abuse deterrent.²⁻⁴ One additional product previously had abuse deterrent labeling but was required by the FDA to suspend use of the label and perform additional testing. At least five other products are in various stages of testing or requesting abuse deterrent labeling.

III. Abuse rates of OxyContin[®] decreased after release of an abuse deterrent formulation

In addition to studies conducted to obtain abuse deterrent labeling, other studies have evaluated the rates of abuse before and after the release of abuse deterrent OxyContin[®] in August of 2010. Similar studies demonstrating the abuse deterrence efficacy of Hysingla ER[®] or Embeda ER[®] are not available.

All available studies demonstrate a decrease in the abuse rates of OxyContin[®] immediately following the release of the abuse deterrent formulation in 2010.⁵⁻¹² Abuse rates declined in the months following release by 19% to 45%.^{10,11} The rate of abuse reaches a plateau after 12-24 months in available studies that is approximately 30% lower than pre-release levels. Deaths related to overdose and abuse from OxyContin[®] and reported to the manufacturer between Q3 2009 and Q3 2013 decreased by 82% (131 to 23).¹² This data is reported by a single study and is limited by capturing only deaths reported to the manufacturer. However, it provides a valuable data point that may indicate that abuse deterrent OxyContin[®] reduced death associated with OxyContin[®] abuse.

Published	Study Author	Study Population	Study Time	Results
April, 2013	Butler et al ⁵	Individuals assessed for substance use problems within the National addictions vigilance intervention and prevention program (NAVIPPRO)	June 2009 through March 2012	Abuse of reformulated OxyContin [®] was 41% lower than the historic abuse of OxyContin [®] . Abuse of Oxymorphone ER increased (significantly), abuse of Morphine ER was unchanged.
October, 2013	Severtson, et al ⁶	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System	October 2008 through March 2012	The two year period following introduction of reformulated OxyContin [®] produced a 38% decrease in the number of poison center abuse exposures.
April, 2014	RADARS ⁷	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System	July 2012 through December, 2013	Median prices for reformulated OxyContin [®] were \$1.00 per milligram versus \$0.63-\$0.75 per milligram for reformulated OxyContin [®] .
January, 2015	Dart, et al ⁸	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System and Survey of Key Informants'	2002 through 2013	Abuse of OxyContin [®] decreased in all studied populations except college students. Heroin use was increasing before release of abuse deterrent OxyContin [®] and accelerated after.

		Patients (SKIP) program		
September, 2013	Coplan, et al ⁹	National Poison Data System	July 2009 through December 2012	Abuse exposures for OxyContin [®] decreased 36% and increased 20% for other long acting oxycodone and 42% for heroin.
March, 2015	Cicero, et al ¹⁰	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System and Survey of Key Informants' Patients (SKIP) program	January 2009 through June 2014	Release of reformulated OxyContin [®] was associated with a 45.1% reduction in recent abuse.
April, 2015	Larochelle, et al ¹¹	US claims data between 2003 and 2012	January 2003 through December 2012	Estimated overdose rates due to long acting opioids decreased by 20% and increased by 23% for heroin. Total opioid dispensing decreased 19% from expected levels. The dose of extended release oxycodone decreased by 11.3mg and increased by 3.26mg for other long acting opioids.
June, 2014	Sessler, et al ¹²	Deaths reported to the manufacturer	July 2009 through July 2013	Deaths reported to the manufacturer decreased by 82% (131 to 23) by the third year after release of abuse deterrent OxyContin [®] .

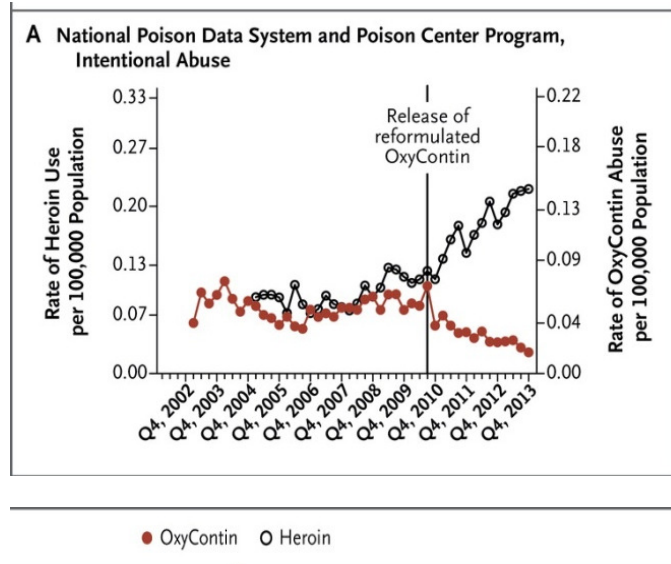
IV. Reported effects on use of other opioids after release of abuse deterrent OxyContin[®]

Available studies indicate that abuse deterrent formulations are less desirable by those who will abuse.^{2-4,7} Four studies provide data detailing subsequent abuse patterns of other opioids after release.^{5,6,9,10} Three of these document an increase in the use of other opioids corresponding with the release of abuse deterrent OxyContin[®].^{5,9,10} The other reports no change in the rate of diversion for potential alternatives. The difference may be driven by population or sampling methodology.

Available data indicate that the abused alternatives did not possess abuse deterrent properties.^{9,10} An increase in the abuse of other prescription opioids not possessing abuse deterrent properties after the release of abuse deterrent OxyContin[®] reported in some trials may indicate that increasing the number of abuse deterrent formulations will further reduce abuse.

V. Reported effects on the use of heroin after release of abuse deterrent OxyContin[®]

Two studies report effects of the change to abuse deterrent OxyContin[®] on the use of heroin.^{8,10} Cicero et al. documents an increase in the rate of heroin abuse corresponding with the release of abuse deterrent OxyContin[®]. Dart et al. provide additional data demonstrating an increase in heroin use. However, increased utilization of heroin is documented before the release of abuse deterrent OxyContin[®] and accelerates after. This data may indicate that economic factors may influence abuse patterns. If cost of prescription opioids is sufficiently high or access sufficiently difficult, persons who abuse may seek less expensive alternatives.



Data for heroin use from the National Poison Data System and American Association of Poison Control Centers and intentional abuse of OxyContin[®] as reported by the RADARS system.⁷

VI. Realized effects in Utah

Utah specific data is not directly comparable to the figures above because it is not similarly reported. However, the volume of oxycodone prescriptions (i.e. all oxycodone related products including OxyContin[®]) in Utah increased 87% from 2004 to 2013.¹³ The most commonly used prescription opioids include methadone, fentanyl, oxycodone and hydrocodone. Reported deaths decreased from 2009 to 2012 for methadone and hydrocodone by 16% and 29% respectively. Deaths related to fentanyl and oxycodone increased during this time period by 21% and 9% respectively.¹³ Published data detailing the drug formulation (e.g. long or short acting, regular or abuse deterrent) or route or abuse (e.g. oral, injected) are not available. Reconciling the increase in prescription volume and death due to drug poisoning against the decreases reported in the studies above will require additional study.

VII. Potential effect of abuse deterrent formulations on opioid abuse

Completed FDA trials demonstrating abuse deterrent properties and subsequent release of abuse deterrent OxyContin[®] resulted in a realized reduction in rates of abuse of OxyContin[®] in the years following in studied populations. The reported street price of abuse deterrent OxyContin[®] and decline in prescription volume in some sources are “real world” indicators that the abuse deterrent mechanism may be functioning as intended. However, Utah prescribing rates and death rates do not match those reported in these studies. This may be due to dissimilarities in the data, population or abuse patterns.

The assessment of efficacy for abuse deterrent opioids may hinge on how broadly abuse is defined. In the case of OxyContin[®], the release of an abuse deterrent formulation reduced abuse rates and in at least one case the death rate associated with abuse of OxyContin[®] in studied populations. However, many abusers altered their choice of drug, route of administration or successfully defeated the abuse deterrent mechanism to continue abusing. Release of additional abuse deterrent mechanisms will impact an abuser’s choice of drug. Based on available data, it appears unlikely that additional mechanisms will

curtail the most common abuse (swallowing intact tablets) or deter some from defeating the abuse deterrence mechanism.

VIII. Potential barriers to use of abuse deterrent opioid analgesics

Medical literature discussing barriers to use of abuse deterrent opioids is not available. “Barrier to use” means barriers, hurdles or difficulties that may prevent a patient from obtaining a medication with abuse deterrent FDA labeling. Because literature demonstrating barriers to use is not available, we report formulary coverage, prior authorization status and out-of-pocket cost as these have been cited as barriers in early discussions of abuse deterrent opioids.

The table below details formulary coverage for six commercial (i.e. not Medicaid or Medicare) Utah health plans according to formulary status published online. All plans cover OxyContin® with varying coverage of Hysingla ER® and Embeda ER®.

	Plan A	Plan B	Plan C	Plan D	Plan E	Plan F
Hysingla ER®	Tier 3, PA	Tier 3	Not Covered	Tier 3	Tier 3, PA	Not Covered
Embeda ER®	Tier 3, PA	Not Covered	Not Covered	Tier 3	Tier 3, PA	Not Covered
OxyContin®	Tier 3, PA	Tier 3, PA	Tier 3, PA	Tier 3	Tier 3, PA	Tier 3, PA
PA: Prior Authorization Sampled plans include: Altius, Arches, EMI Health, PEHP, Regence BCBS, Select Health						

An additional barrier may be prior authorization requirements placed by health plans. Prior authorization refers to a health plan requirement that a service or product is necessary and authorized by the plan before services are obtained. Prior authorization guidelines for the individual plans are not available in the public domain and we are unable to report requirements of the sample. However, PEHP does not prior authorize abuse deterrent opioids differently than non-abuse deterrent opioids. Specifically, the requirements for authorization for all formulations require trial of extended release morphine because it is at least as safe as other opioids, it is at least as effective as other opioids and data indicate it is less abused than other products in Utah.¹³

Out of pocket expense may be an additional barrier. Likely patient out of pocket cost from sampled health plans varies. Copayments in this context refer to fixed dollar amounts charged for a prescription (e.g. the patient pays \$50 for a Tier 3 prescription). Coinsurance refers to a fixed percentage charged for a prescription (e.g. the patient pays 50% of the cost of a Tier 3 prescription). Based on our knowledge of the market, frequently used copayments range from \$40 to \$100 for Tier 3. Coinsurance generally ranges from 50% to 65% for Tier 3. An additional out of pocket cost component is the availability of manufacturer coupons. Available coupons reduce out of pocket spending by various amounts on an ongoing basis. The table below provides a range of potential cost based on dosage strength, potential copay or coinsurance and current coupon value.

Drug Name	Cost for a 30 day supply*	Copay Range [^]	Coinsurance Range [^]	Coupon Value
Hysingla ER [®]	\$236.40 - \$1,224.30	\$50-\$100	50% = \$118.20 - \$612.15	Up to \$100 off per prescription, patient must pay at least \$25
Embeda ER [®]	\$200.10 - \$1,579.80	\$50-\$100	50% = \$100.05 – \$789.9	Up to \$100 off per prescription, patient must pay at least \$25, maximum of \$900 savings per year
OxyContin [®]	\$361.20 - \$1,080.00	\$20-\$100	25% = \$90.30 - \$270 50% = \$180.60 – \$540.00	Up to \$70 off per prescription, patient must pay at least \$45
*Based on average wholesale price (AWP)				
[^] These figures include common benefits for Tier 2 or Tier 3 drugs in the local market				

Health plans tier covered drugs based on safety, efficacy and cost. Studies demonstrating safety and efficacy for opioids to treat pain are limited. We find no studies evaluating the safety or efficacy of long term (e.g. longer than 12 months) use despite the common practice of prescribing over many years. Available studies demonstrating superiority in safety or efficacy in treating pain of one opioid (e.g. morphine vs. fentanyl) or formulation (abuse deterrent vs. non-abuse deterrent) are not available. The lack of available evidence coupled with post-marketing reports of harms associated with the use and abuse of opioids makes cost a factor in tier placement.

The per tablet cost between tier 1 and tier 3 varies in a sample of long acting opioids between 7/1/13 and 6/30/14. During this time, the average cost per tablet in tier 1 was \$1.75 vs. \$7.27 in tier 3. The average cost per tablet for abuse deterrent products in February 2015 is \$12.24. Due to the average cost difference and limited data demonstrating benefits of any opioid, the cost of these new formulations are shared by charging a higher copayment. PEHP recognizes the value of abuse-deterrent opioid analgesics and has included select drugs with an FDA label as abuse deterrent or with abuse deterrent properties on the formulary at patient cost-sharing levels that reflect the higher costs associated with these drugs. In addition, the following interventions are in place to improve the safety risks associated with opioid use:

- Require prior authorization for dose frequency greater than the FDA indication (e.g. the FDA recommended dose is once daily but prescribed three times daily) (does not apply to patients with cancer or at the end of life)
- Require a consult with a pain specialist for dangerous doses (e.g. greater than 200 morphine equivalents per day) (does not apply to patients with cancer or at the end of life)
- Cover select FDA labeled abuse deterrent opioids or opioids with abuse deterrent properties (we currently cover 1 with the FDA label and 4 with abuse deterrent properties)

We anticipate that outcome data demonstrating superiority of one drug (e.g. oxycodone, morphine) or formulation (e.g. abuse deterrent, non-abuse deterrent) over another will alter the current cost sharing of opioids.

References:

1. Center for Drug Evaluation and Research, US Food and Drug Administration, US Department of Health and Human Services. Guidance for Industry: Abuse-Deterrent Opioids-Evaluation and

- Labeling. US Department of Health and Human Services; 2015.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>.
2. Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. *Journal of clinical pharmacology*. Apr 2014;54(4):468-477.
 3. Embeda (R), morphine sulfate and naltrexone hydrochloride extended-release capsules. Pfizer Inc.; 2015. <http://labeling.pfizer.com/showlabeling.aspx?id=694>. Accessed 9/25/15.
 4. Hysingla (TM), hydrocodone bitartrate extended-release tablets. Purdue Pharma L.P.; 2015. <http://app.purduepharma.com/xmlpublishing/pi.aspx?id=h>. Accessed 9/25/15.
 5. Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *The journal of pain : official journal of the American Pain Society*. Apr 2013;14(4):351-358.
 6. Severtson SG, Bartelson BB, Davis JM, et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *The journal of pain : official journal of the American Pain Society*. Oct 2013;14(10):1122-1130.
 7. Dart RC, Martinez E, Severtson SG, Menone C, M, Dasgupta N. Appearance of Canadian Oxycodone extended Release Products in the United States. 2014(RADARS System Technical Report, 2014-Q2).
 8. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. *The New England journal of medicine*. Jan 15 2015;372(3):241-248.
 9. Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology and drug safety*. Dec 2013;22(12):1274-1282.
 10. Cicero TJ, Ellis MS. Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin. *JAMA psychiatry*. May 2015;72(5):424-430.
 11. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. *JAMA internal medicine*. Jun 2015;175(6):978-987.
 12. Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiology and drug safety*. Dec 2014;23(12):1238-1246.
 13. Utah Health Status Update: Prescription Opioid Deaths. Utah Department of Health; 2014. http://health.utah.gov/oph/publications/hsu/1409_RxOpioidDth.pdf.