

FDA Briefing Document

**Joint Meeting of Anesthetic and Analgesic Drug Products Advisory
Committee and Drug Safety and Risk Management Advisory Committee**

April 5, 2017

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought pharmacokinetic data, and results of studies evaluating the abuse of RoxyBond (oxycodone ARIR) oral tablets to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

*Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee
and Drug Safety & Risk Management Advisory Committee*

April 5, 2017

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DIVISION DIRECTOR MEMO



FDA CENTER FOR DRUG EVALUATION AND RESEARCH DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: March 8, 2017

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the Open Session, April 5, 2017 AADPAC/DSaRM Meeting to
Discuss NDA 209777

At this joint meeting of AADPAC and DSaRM, we will be discussing an application from Inspirion Delivery Sciences, LLC for a new immediate-release formulation of oxycodone with the proposed tradename RoxyBond, designed with properties intended to deter abuse. According to the Applicant, RoxyBond tablets have been formulated with physicochemical properties intended to decrease the ability to modify the tablets for abuse by the intravenous and intranasal routes. The proposed indication for RoxyBond is the treatment of moderate-to-severe pain where the use of an opioid analgesic is appropriate.

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. To address this public health epidemic, FDA has announced a comprehensive review of our approach to opioid medications. This multi-year action plan focuses on new and existing policies to help curb abuse, addiction, and overdose of these drugs, while continuing to make them available to patients in need of effective pain relief.

One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. In April 2015, the Agency issued a final guidance to assist industry in the development of opioid drug products with potentially abuse-deterrent properties. The “Guidance for Industry: Abuse-Deterrent Opioids,” explains the Agency’s current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

There are currently no immediate-release opioid analgesics labeled with abuse-deterrent properties as described in the guidance. There are nine approved extended-release/long-acting opioid analgesic products with labeling language describing studies conducted in support of abuse-deterrent properties; OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), Hysingla ER (hydrocodone extended-release tablets), Morphabond (morphine sulfate extended-release tablets), Xtampza ER (oxycodone extended-release capsules), Troxyca ER (oxycodone and naltrexone extended-release capsules), Arymo ER (morphine sulfate extended-release tablets), and Vantrela ER (hydrocodone extended-release tablets).

The results of the Applicant’s in vitro physical and chemical manipulation studies and the in vivo clinical abuse potential study will be presented during this meeting. You will be asked to discuss whether the Applicant has demonstrated abuse-deterrent properties for their product that would support labeling, whether the benefits of RoxyBond outweigh its risks, and whether it should be approved.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

Draft Points to Consider

1. Has the Applicant demonstrated that RoxyBond has properties that can be expected to deter abuse?
 - a. by the IV route of administration
 - b. by the nasal route of administration
2. Are there sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label?
 - a. for the IV route of administration
 - b. for the nasal route of administration
3. Should RoxyBond be approved?



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

M E M O R A N D U M

DATE: March 8, 2017

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Regulatory History of Abuse-Deterrent Opioid Analgesics

Regulatory History of Abuse-Deterrent Opioid Analgesics

The growing epidemic of opioid abuse, misuse, and overdose in the United States is deeply concerning. In light of this, the Agency has encouraged drug companies to develop products that can mitigate abuse, while recognizing the importance of maintaining the availability of opioid analgesics for the millions of patients in this country who suffer from pain. The Agency has supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community.

In April 2015, the Agency issued a final guidance to assist industry in the development of opioid drug products with potentially abuse-deterrent properties. The “Guidance for Industry: Abuse-Deterrent Opioids” explains the Agency’s current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling. It is important to keep in mind that the science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on this, the Agency intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.

An effort has been made to improve the product labels for all opioid analgesics to help ensure safe use of these drugs. In April 2014, the Agency finalized the class-wide safety labeling changes (SLC) for all extended-release and long-acting (ERLA) opioid analgesics in order to better describe their risks and benefits and to better ensure safe use. All ERLA opioid analgesics, those with and without abuse-deterrent properties, used for the management of chronic pain now have a harmonized indication, the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate, which is intended to emphasize the need to balance risk with benefit. The safety labeling changes included the indication stated above, a new warning for Neonatal Opioid Withdrawal Syndrome (NOWS), and updated language in the Warnings and Precautions section of the label regarding addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, and drug interactions. On March 22, 2016, a class-wide SLC for immediate-release opioid analgesics was issued, similar to the 2014 SLC for ERLA opioid analgesics. The labeling changes included a boxed warning with information about the risks of misuse, abuse, addiction, overdose and death, and the potential for neonatal opioid withdrawal syndrome (NOWS) with prolonged maternal use of opioids during pregnancy; an updated indication stating that IR opioids should be reserved to manage pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated; and clearer information regarding patient monitoring and drug administration. New warnings were also included for all opioids regarding serotonin syndrome and endocrine effects.

There are currently no immediate-release opioid analgesics labeled with abuse-deterrent properties, as described in the guidance. There are nine approved ERLA opioid analgesic products with labeling language describing studies that evaluated their abuse-deterrent properties. **Embeda**, approved in 2009, is an extended-release formulation of morphine sulfate with a sequestered opioid antagonist, naltrexone. The naltrexone is intended to be released only if the product is manipulated. In vitro and in vivo data reviewed by the Agency indicate that Embeda has properties that are expected to reduce abuse by the oral (crushing/chewing) and intranasal routes. A human abuse potential study of IV morphine and naltrexone to simulate injection of crushed Embeda demonstrated evidence of abuse deterrence; however, it is unknown whether the results from simulated crushed Embeda can predict a reduction in abuse by the IV route until additional postmarketing data are available.

The first formulation of extended-release oxycodone was **OxyContin** approved in 1995. A reformulation of the original OxyContin, approved in 2010, was designed with physicochemical properties intended to deter abuse by being more difficult to prepare for intravenous abuse by syringe and to resist breaking or crushing for intranasal abuse. The original OxyContin is no longer manufactured or marketed in the US. In 2012, language was added to the label describing OxyContin's abuse-deterrent properties based on the Agency's review of in vitro and in vivo studies.

Targiniq ER, the second extended-release oxycodone product with abuse-deterrent properties, was approved in 2014. It is a fixed-dose combination drug product consisting of oxycodone and naloxone, an opioid antagonist. Naloxone has low oral bioavailability due to high first pass metabolism and is not intended to reach adequate levels to have an effect in patients taking the medication as prescribed. However, if Targiniq ER is manipulated for abuse by injection or nasal insufflation, the naloxone levels are high enough to antagonize the reinforcing opioid effects. Language in the label includes findings of in vitro studies and human abuse potential studies that indicate that Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal and IV routes of administration.

Hysingla ER, approved in 2014, is the first extended-release formulation of hydrocodone with properties intended to deter abuse. In vitro data demonstrate that Hysingla ER's physicochemical properties can be expected to deter intranasal and intravenous abuse. Data from human abuse potential studies also support that these properties can be expected to deter intranasal abuse and oral abuse when chewed.

Morphabond ER, an extended-release formulation of morphine sulfate, approved in 2015, is the second extended-release morphine product with abuse-deterrent labeling. Morphabond ER has physicochemical properties expected to make abuse via injection difficult. Data from human abuse potential studies as well as in vitro data also support that these properties are expected to reduce abuse by the intranasal route of administration.

Xtampza ER, the third extended-release oxycodone product with abuse-deterrent properties, was approved on April 26, 2016. In vitro data demonstrate that Xtampza ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that Xtampza ER has physicochemical properties that are expected to reduce abuse via the intranasal route.

Troxyca ER, an extended-release formulation of oxycodone hydrochloride with a sequestered opioid antagonist, naltrexone, was approved on August 19, 2016. The naltrexone is intended to be released only if the product is manipulated. In vitro and in vivo data reviewed by the Agency indicate that Troxyca ER has properties that are expected to reduce abuse via the oral (crushing/chewing) and intranasal routes. A human abuse potential study of IV oxycodone and naltrexone to simulate injection of crushed Troxyca ER demonstrated evidence of abuse deterrence; however, it is unknown whether the results from simulated crushed Troxyca ER can predict a reduction in abuse by the IV route until additional postmarketing data are available.

Arymo ER, an extended-release formulation of morphine sulfate, approved in January 2017, is the third extended-release morphine product with abuse-deterrent labeling. In vitro data demonstrate that Arymo ER's physicochemical properties can be expected to make abuse by

injection difficult. As discussed at the August 4, 2016 advisory committee meeting, there were data to support that the formulation could be expected to reduce abuse by the intranasal route, but this information was not included in labeling as it was blocked by exclusivity awarded to Morphabond ER. Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that Arymo ER has properties that are expected to reduce abuse via the oral route.

Vantrela ER, approved in January 2017, is the second extended-release formulation of hydrocodone with properties intended to deter abuse. In vitro data demonstrate that the physicochemical properties of Vantrela ER can be expected to deter intravenous abuse. In vitro and in vivo data demonstrate that Vantrela ER has properties that are expected to reduce abuse via the oral and intranasal routes.

All Sponsors of opioid analgesics with approved abuse-deterrent language in labeling are required to conduct postmarketing epidemiologic studies to determine whether the properties of their product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.

It is important to recognize that abuse-deterrent opioid products are not abuse-proof. As stated in the “Guidance for Industry: Abuse-Deterrent Opioids,” “Because opioid products are often manipulated for the purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.”

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

Additional copies are available from:
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**Clinical Medical
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Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

This guidance is intended to assist sponsors who wish to develop opioid drug products with potentially abuse-deterrent properties and is not intended to apply to products that are not opioids or opioid products that do not have the potential for abuse.

This guidance also does not address issues associated with the development or testing of generic formulations of abuse-deterrent opioid products. FDA intends to address that topic in one or more future guidance documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has

¹ This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

For purposes of this guidance, *abuse-deterrent properties* are defined as those properties shown to meaningfully **deter** abuse, even if they do not fully **prevent** abuse. The term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.² Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.³ This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.⁴

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Because FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties, no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.

² Smith S M, Dart R C, Katz N P, et al. 2013. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain*, 154:2287-2296.

³ Ibid.

⁴ FDA's current Good Manufacturing Practice regulations include tamper-evident packaging requirements. See 21 CFR 211.132. There are also requirements for child resistant "special packaging" under the Poison Prevention Packaging Act and regulations adopted by the Consumer Protect Safety Commissioner (CPSC) in 16 CFR 1700.

As with all NDA products, FDA intends to consider opioids with abuse-deterrent properties within the context of available therapy. The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application.⁵

Abuse-deterrent properties can generally be established only through comparison to another product.

FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

FDA believes it is critical to address the problem of opioid abuse while seeking to ensure that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed.

The following section describes the categories of abuse-deterrent products. The premarket and postmarket studies that should be performed to assess the impact of a potentially abuse-deterrent product are discussed in subsequent sections. Finally, information is provided about labeling for abuse-deterrent products.

III. ABUSE-DETERRENT PRODUCTS

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be

⁵ For guidance on the evaluation of abuse potential for purposes of the Controlled Substances Act (CSA), we refer sponsors to FDA's draft guidance for industry *Assessment of Abuse Potential of Drugs*. This guidance is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>. FDA guidances are available at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.
4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs* – The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.
7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls⁶ and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases.

Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product. For example, immediate-release (IR) opioid and acetaminophen combination products are predominantly abused using the oral

⁶ For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.

route. Demonstrating a deterrent effect by the nasal route may not meaningfully reduce overall abuse of the product.

FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-deterrent opioid drug products. This flexibility is intended to permit a sponsor to tailor the development program to suit the abuse-deterrent characteristics of their product and the routes of abuse for that product. The adaptive aspect is intended to permit a sponsor to take into consideration the relevant products on the market at the time they are developing their product, so that appropriate non-abuse-deterrent and abuse-deterrent comparators can be used. For example, for some proposed products the appropriate comparator may be a conventional formulation. However, if there are similar approved products with abuse-deterrent properties described in labeling, the appropriate comparator should be one of those abuse-deterrent products.

The following sections describe three categories of premarket studies. Although, in general, any development program for studying abuse-deterrent technologies should include data from all three categories of studies, there may be exceptions. For example, a formulation with a sequestered antagonist may intentionally be formulated not to resist crushing, so testing the syringeability of the product may not be relevant. In most cases, however, to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarket studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

The results of Category 1 studies may influence the design of Category 2 pharmacokinetic studies and Category 3 clinical abuse potential studies by suggesting the methods of manipulation that would yield the greatest release of opioid. The results of Category 2 studies may influence the need for Category 3 studies of clinical abuse potential and the designs and goals of these studies. For example, if the extended-release characteristics of an abuse-deterrent opioid formulation cannot be defeated and the pharmacokinetic profile remains unchanged following oral or nasal administration of the manipulated product, oral and nasal studies of abuse potential may not be necessary.

Additional studies (i.e., Category 4 studies) analyze postmarket data to assess the impact of an abuse-deterrent formulation on actual abuse. Nonclinical drug discrimination studies are useful in the evaluation of the abuse potential of a drug, but their utility in predicting the impact of abuse-deterrent properties on human behavior has not been established.⁷

⁷ See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs* see <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm198650.pdf>.

A. Laboratory Manipulation and Extraction Studies (Category 1)

The goal of laboratory-based Category 1 studies should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. This information should be used when designing Category 2 and Category 3 studies. These studies are critical to the understanding of product characteristics and performance.⁸

Methodologically, these studies should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing in vitro studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product.

In vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated, such as by (1) defeating or compromising the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration; (2) preparing an IR formulation for alternative routes of administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse-deterrent properties. The goal of these studies is to manipulate the product to the point of defeating its abuse-deterrent properties. Once this goal is achieved, it is no longer necessary to continue experiments using more sophisticated methods. For example, if 90% of the opioid can be extracted under a set of conditions in 10 minutes, there is no need to test the same condition for 30 minutes.

The test product should be compared to appropriate comparator products for ease of mechanical manipulation. The ability to crush, cut, grate, or grind the product formulation using readily available items such as spoons, cutters, and coffee grinders should be assessed. Particular attention should be given to particle size distribution following each mode of physical manipulation because particle size may influence the rate of opioid extraction from manipulated product. The effect of heat and cold on mechanical manipulation should also be studied.

Extractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to

⁸ This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (NDA 022272, *OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf>.

bypass the drug's abuse-deterrent properties. In addition to extraction and solubility studies, an assessment should be made to determine if free-base opioid can be precipitated from solution by pH adjustment. After establishing how a product could be manipulated, chemical extraction of the opioid from the intact and the manipulated product should be assessed and compared to opioid extraction from the selected intact and similarly manipulated comparator products.

The ease of extracting the opioid from the intact and manipulated product should be determined using a variety of solvents that are commonly available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those that have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The effects of time, temperature, pH, and agitation on solvent extraction should also be determined. For products containing more than one drug substance, extractability and solubility studies should be designed to determine whether any of the active ingredients might be differentially solubilized and extracted. Sampling times should start early (e.g., 30 seconds) and continue until at least 80% of the opioid has been released, or 12 hours has been reached. The in vitro drug-release characteristics of the intact and manipulated product should also be compared using a discriminatory and robust dissolution method.

In addition to the general evaluation of the effects of physical and chemical manipulation on the product, there are important route-specific data that should be generated, as follows:

- For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.
- For a product with potential for abuse by smoking, the amount of drug produced by vaporization at temperatures encompassing the range from the melting point of the active ingredient to its degradation point should be determined. Appropriate controls, such as pure active ingredient, both in salt and free-base form should be included in these assessments.
- For a product with potential for abuse by injection, the amount of opioid that can be obtained in a syringe should be based on studies of intact and manipulated test product and comparator(s) using small volumes of water (5-10 mL) at room temperature and at 90° C – 95° C with and without agitation. Extraction times should range from 30 seconds to 30 minutes. The amount of opioid extracted, the volume of solution collected and the viscosity of the samples should be recorded. The ability to get the sample into a syringe and expel the sample using needles of various gauges should also be explored.

The following examples illustrate the kinds of outcomes that in vitro studies should evaluate.

1. Characteristics of the product by crushing, grinding or melting, or by changing the intact formulation using other methods that would limit nasal administration of the manipulated product, and/or that would limit dissolution of the manipulated product and incorporation into a solvent that could then be injected by intravenous or subcutaneous routes.

2. Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe.
3. Quantity of opioid antagonist released from an agonist/antagonist combination when it is manipulated for administration by ingestion, nasal administration, or injection.
4. Quantity of opioid product following in vitro manipulation of the prodrug.

B. Pharmacokinetic Studies (Category 2)

The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. Even though the same routes of administration should be studied for the new product and comparators, if specific circumstances prevent this approach, the study design should be discussed with FDA. The method of manipulation used for the pharmacokinetic studies should be based on the methods explored during in vitro testing that can be expected to result in the greatest drug release. The routes of administration chosen should be relevant to the proposed product, and likely will be based on what is known about the abuse of similar products. Note that, for some development programs, it may be preferable to combine measures of pharmacokinetic parameters for Category 3 studies, in which case separate Category 2 studies may not be necessary.

In general, the pharmacokinetic profile for the oral route of administration should be studied. Appropriate study subjects for Category 2 studies include healthy volunteers as long as naltrexone is used to block the pharmacodynamic effects of the opioids.

Depending on the product, it may be important to evaluate the pharmacokinetic profile for the nasal route of administration as well. For nasal pharmacokinetic studies, it is important to weigh the risk to the subject based on the excipients in the formulation. Only subjects with a history of nasal abuse of opioids should be recruited for these studies. As with the oral route of administration, it may be possible to combine the pharmacokinetic assessment and the pharmacodynamic assessment in one clinical abuse potential study with sampling for the pharmacokinetic analysis.

Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that should be measured in these studies include the following.

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the curve (AUC_{0-t} and $AUC_{0-\infty}$)
- Relevant partial AUC, including early time points such as AUC_{0-30} minutes or AUC_{0-2} hours, the period of time when C_{max} is expected
- Terminal elimination half-life ($T_{1/2}$)

Traditional pharmacokinetic study designs should be employed (e.g., crossover designs), and the results should be analyzed using bioequivalence methods. The rate of rise of drug concentration should be assessed when possible because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.⁹ To support these analyses, it is important to have specimen collection and analysis time points sufficient to cover the onset, peak, and offset of the effects of both IR and ER formulations, in both the intact and manipulated conditions. In addition, these data are necessary to calculate the relevant partial area under the curve, which should capture the time to maximum concentration of the opioid.

If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.¹⁰ If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies of the oral route should be conducted in the fed state to maximize the potential systemic exposure.

In addition to the pharmacokinetic profile of the opioid, for agonist/antagonist combinations , the pharmacokinetic characteristics of the antagonist should be defined for the intact product as well as for the manipulated formulation.

As with all clinical studies, adverse events should be collected, and those that can provide additional insight about the abuse-deterrent effects are especially important. For example, if the manipulated formulation is abused by snorting, it would be important to assess adverse events related to intranasal tolerability.

C. Clinical Abuse Potential Studies (Category 3)

In addition to their use by FDA to formulate its scheduling recommendation under the CSA for drug products containing a controlled substance, clinical studies of abuse potential, Category 3, are important for assessing the impact of potentially abuse-deterrent properties. As discussed in

⁹ References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu M E, Bigelow G E, Fleisher L, and Walsh S L. 2001. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology*, 154:76-84.

de Wit H, Bodker B, and Ambre J. 1992. Rate of increase of plasma drug level influences subjective responses in humans. *Psychopharmacology*, 107:352-358.

de Wit H, Didish S, and Ambre J. 1993. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology*, 112: 324-330.

¹⁰ FDA has issued a draft guidance on this topic (*Assessment of Abuse Potential of Drugs*). Once finalized, it will represent FDA's current thinking on this topic.

FDA's guidance on that topic,¹¹ the preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study. These studies generally are conducted in a drug-experienced, recreational user population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can reproducibly distinguish active drug from placebo is a common enrichment strategy used to improve the power of the study to establish a difference between treatments.

Additional considerations applicable to clinical abuse potential studies used to assess potentially abuse-deterrent properties are discussed below. For products that are not susceptible to manipulation based on Category 1 and 2 testing, study designs for Category 3 testing should be discussed with FDA.

1. Blinding

Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled and positive controlled crossover design. Because study subjects are recreational drug users and familiar with the effects of the drug substances being studied, the double-dummy technique or other techniques should be used to ensure the blinding of all tests when possible. However, alternative designs may be suitable when the blinding of the study drug and the positive control cannot be maintained and treatment by period interactions may lead to sequence effects in a crossover design. For example, a parallel design may be useful when studying the intranasal route of administration, where subjects may be able to see the differences in volume or color between test drug and placebo or positive control, or when it is not possible to create similar results from manipulation, such as particle size from crushing. In these circumstances, early discussion with FDA is recommended.

For clinical abuse potential studies in which the subjects will snort test samples, administration of the samples in a narrow neck, opaque container with a pre-inserted straw may help facilitate blinding. However, even though subjects might not be able to see the sample, un-blinding may still occur due to the physical properties of samples with similar particle size distribution. In some formulations, higher crushed tablet/capsule volume or larger particle size may inhibit complete intranasal administration thereby contributing to the deterrence effects. To be able to evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent formulation and the comparator. To facilitate blinding and maintain the crossover design, placebos matched to each of the differing weights or particle sizes may be useful. The details of the preparation of the samples should be provided in the study protocol.

2. Pre-qualification Phase

The purpose of the pre-qualification phase is to increase the power of a study to detect differences in the abuse potential of the various formulations of drug and placebo.¹² In general,

¹¹ Ibid.

¹² An additional advantage of a pre-qualification phase is that it helps familiarize subjects with and train them in the use of various scales and questionnaires that measure subjective effects.

the pre-qualification phase should ensure that subjects can distinguish between placebo and a conventional IR formulation of the same opioid being developed in an abuse-deterrent formulation, using the same route of administration as planned for the assessment phase. There is little value in having subjects unable to distinguish placebo from active drug continue in the study. The positive control should include a strength that is at least equal to the lowest strength selected for the assessment during the clinical phase. An important aspect of the pre-qualification phase is assessing the ability of subjects to tolerate the study dose. If the dose used in the pre-qualification phase is lower than the lowest strength planned for the assessment phase, some subjects may not be able to tolerate the higher dose that will be administered in the assessment phase. Thus, when tolerability may be an issue, particularly if more than one dose is planned for the assessment phase, a pre-qualification dose that is no lower than the lowest dose planned may be the most efficient choice to establish that the subject can distinguish active drug from placebo and can tolerate the study drug in the range to be tested. For example, a 30 mg or 45 mg dose of opioid could be used in the pre-qualification phase when a 30 mg and 60 mg doses will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, a minimum value for the maximum effect (E_{max}) for the positive control should be defined. The minimum E_{max} for the positive control may vary from measure to measure, and from study to study. However, an acceptable response for the positive control should not overlap with the acceptable range for placebo response.

3. Assessment Phase

The potentially abuse-deterrent product should be compared to a positive control, and the positive control should be compared to placebo to validate the study. For an IR product with potentially abuse-deterrent properties, the positive control should be an IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent properties, the positive control could be an IR formulation of the same opioid or an ER formulation of the same opioid. In general, these studies should include one strength of the positive control which is associated with high levels of drug liking. However, when assessing drug liking through the intranasal route, the use of two strengths of the positive control may be helpful to both identify a strength of the positive control associated with high drug liking scores and to validate the study.

If there are no approved products with the same drug substance, the positive control should be a drug that, based on pharmacological profile or nonclinical data, can be expected to have similar pharmacodynamic effects. Selection of the positive control in this setting should be discussed with FDA.

4. Subjects

Studies should be conducted in opioid-experienced, recreational drug users who have experience with the particular route of abuse being studied. Subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse. Depending on the

formulation being studied, however, clinical abuse potential studies can be conducted in physically dependent subjects. For example, if the deterrent product contains an opioid antagonist, clinical abuse potential studies in a physically dependent population may provide information not only on the drug liking of the product, but on the ability of the antagonist to precipitate withdrawal in this population.

Detailed characteristics of the study population with respect to past and current drug use and abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).

5. Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation

The selection of the route(s) of administration should be based on epidemiological data showing that a selected route is a relevant route of abuse. For NMEs, the sponsor should review the relevant routes of abuse for products similar to the test product and discuss the selected routes with FDA. For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels. The dose of the opioid selected for the study should be known to produce high levels of liking in non-tolerant opioid-experienced recreational users.

For studies using the intranasal route of administration, the preparation of the samples is extremely important. The potentially abuse-deterrent product and comparator study drug should be produced with similar particle size distribution based on a detailed protocol for the preparation of the samples, even if different methods are necessary to do so.¹³ With some formulations, a high volume of the crushed tablet/capsule or larger particle size may inhibit complete intranasal administration and, thereby, contribute to deterrence effects. To evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent product and the comparator.

For studies using the intravenous route of administration, the oral formulations may not be safe for intravenous use depending on the excipients used in the formulation. In place of the manipulated oral formulation, a solution for injection should be prepared using approved, commercially available parenteral products when available, or products suitably formulated for the study. The amount of the opioid and that of the antagonist, when relevant, should be based on extrapolation from in vitro extraction studies of manipulated solid formulations.

6. Outcome Measures and Data Interpretation

In abuse potential studies, the primary method for evaluating the subjective effects of drugs should be through the use of standardized instruments.

¹³ Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies before the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

In typical abuse potential studies, several instruments have been used to measure subjective responses predictive of the likelihood of abuse. These instruments include:

- Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other drug abuse-related effects
- Profile of Mood States

The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Other measures of particular interest include assessment of likelihood to take the drug again and assessment of overall drug liking.¹⁴

These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be provided for the choice for a particular scale. In general, FDA recommends using a bipolar scale for the primary measure of drug liking. Unipolar scales have been used to measure other drug effects, such as good and bad effects. Regardless of whether a unipolar or bipolar scale is selected, FDA recommends that for purposes of training subjects, the same scale be used in the pre-qualification and assessment phases.

7. *Data Interpretation*

For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug products, the primary analysis should be the difference in means of the E_{max} ¹⁵ for the primary measure(s) based on the population of study completers. A statistical analysis plan (SAP) should be included in the study protocol or submitted as a separate document before un-blinding the study. The sponsor should provide data and dropout information for non-completers. To ensure adequate power, the sponsor should take into account that there will be subjects who drop out of the study early and plan the sample size calculation accordingly. Proper planning should avoid any need to replace subjects who discontinue without completing the study.

Additional pharmacodynamic measures, including positive subjective effects other than drug liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are generally considered secondary endpoints. Other subject-rated assessments of interest include: alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

Some sponsors provide descriptive statistics including mean, standard error, median, and interquartile range, calculated for all pharmacodynamic endpoints by time and treatment.¹⁶ What

¹⁴ Overall drug liking measures the user's retrospective assessment of a drug, whereas VAS for drug liking measures the user's immediate assessment.

¹⁵ In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

¹⁶ See Statistical Analysis Section for further guidance.

constitutes a clinically significant difference in drug liking, between the manipulated and intact versions of the potentially abuse-deterrent product and positive control, is an area requiring further research and will be evaluated on a case-by-case basis. Analysis of postmarket data on abuse levels associated with the potentially abuse-deterrent product being studied may help to support the findings from abuse potential studies.

In addition, when interpreting results from clinical abuse potential studies, attention should be given to the profile of subjective effects produced by the manipulated and intact formulation in terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent product should be given appropriate weight in the overall analysis of the abuse-deterrent properties. A more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential. Regarding the duration of effect, it may be difficult to interpret the abuse potential of a formulation that produces a sustained liking effect when taken intact or after manipulation, though lower than that produced by the positive control formulation.

The overall assessment of abuse potential should be based on the pattern of findings across all of the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug liking response and duration of the liking effects associated with manipulated formulations, should be taken into consideration, along with other positive effects and negative effects.

8. *Statistical Analysis*

a. *Background*

The overall goal of a clinical study of abuse potential is to assess a number of abuse potential outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent product (T) relative to a formulation of the drug without abuse-deterrent properties (C), or a newly formulated opioid product (positive control). Substantial decreases in the responses for the potentially abuse-deterrent formulation compared to the positive control are evidence of deterrence.

A clinical study of abuse potential should be validated by comparing the responses to C with those of placebo (P). Thereafter, the assessment of the abuse-deterrence properties of T is of primary interest. This can be achieved by comparing the difference in means between C and T with a *margin* for abuse potential measures and comparing the difference between C and T relative to C in drug liking on a bipolar VAS.

The statistical analysis of the data in a clinical study should begin with descriptive statistics making up tabulations and graphs that include tables of the mean, standard error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses of interest for each treatment and for each paired difference among treatments.

Useful graphs include mean time course profiles, heat-maps,¹⁷ and continuous responder profiles.

The next subsection describes the statistical test that sponsors should use for the primary analysis of E_{max} on the VAS for drug liking. An analysis of the percent reduction in drug liking for T relative to C on the individual level in subsection c is recommended as a secondary analysis.

b. Primary analyses

The primary analysis of abuse-deterrant effects should be based on the comparison of means¹⁸ between crushed, chewed, or otherwise modified T and C with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \leq \delta_1 \text{ versus } H_a : \mu_C - \mu_T > \delta_1$$

where $\delta_1 = \delta^*(\mu_C - 50)$, and $0 < \delta^* < 1$. Because C is an opioid drug, the validation test also needs a margin, say δ_2 . That is,

$$H_0 : \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

where $\delta_2 \geq 15$.

The significant level for both tests is 2.5%.

The actual value of δ_1 is related to μ_C , hence, it may vary according to abuse potential measures and the route of drug administration. The δ^* should be pre-specified in the protocol. We also suggest the use of 95% confidence intervals to assess both the differences $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

c. Secondary analyses

In addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrant product T relative to C from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100. One definition for percent reduction for individual subjects is as follows:

$$\% reduction = \frac{c_i - t_i}{c_i - p_i} \times 100\%, \quad i = 1, 2, \dots, n,$$

where c_i , t_i and p_i are the E_{max} values for C , T , and P from the i th subject, respectively; n is the sample size.

¹⁷ Chen L and Wang Y. 2012. Heat map displays for data from human abuse potential crossover studies. *Drug Information Journal*, 46:701:707.

¹⁸ If a nonparametric method is necessary, analysis of the median difference in E_{max} may be appropriate.

However, this definition is problematic because for two subjects having the same E_{\max} values for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by the neutral score 50 on a bipolar scale; that is,

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n$$

where we assume that $c_i > 50$. In case some subjects have $c_i \leq 50$, define % reduction = 0.

Note that even though most abuse potential studies have a pre-qualification phase, approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 75 in the assessment phase. Consequently, it may be necessary to penalize subjects with large values of p_i in computing percent reduction. For example, the percent reduction could be multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment factor in computing percent reduction and an appropriate formula for defining the penalty to be applied before finalizing the study protocol.

Two approaches for assessing the deterrent effects using percent reduction for crossover design studies are provided below. Note that when a parallel design is used, the percent reduction for individual subjects is not applicable, and the primary analysis may also serve the purpose for assessing the percent reduction based on $\mu_C - \mu_T$ related to $\mu_C - 50$.

- Responder Analysis

A *responder* is defined as a subject who had at least $\delta^* 100\%$ of reduction, in E_{\max} for T relative to C. To ensure that a majority of subjects are responders, a proportion test can be used to test the null hypothesis that 50% or fewer subjects are responders. That is, test

$$H_0 : p^* \leq 50\% \text{ versus } H_a : p^* > 50\%$$

at the 2.5% significance level where p^* denotes the percentage of responders. The 95% confidence interval of p^* can also be calculated.

- Analysis of the Median Percent Reduction

The median of the percent reduction (ptr) is a descriptive measure of central tendency of ptr . At most 50% of subjects have ptr less than the median, and at most 50% of subjects have ptr greater than the median. If the median of ptr is equal to 30%, for example, it means that approximately 50% of subjects have greater than or equal to a 30% reduction.

For assessing deterrent effects, we can test

$$H_0 : \text{median}(ptr) \leq DR\% \text{ versus } H_a : \text{median}(ptr) > DR\%$$

at the 2.5% significance level, where DR denotes deterrent reduction. To be consistent with the responder analysis, we recommend $DR\% = \delta^* 100\%$. If the distribution of ptr is symmetric, the Wilcoxon-signed rank test can be used to test the null hypothesis that $\text{median}(ptr) \leq DR\%$, and a 95% confidence interval for the median based on this test can be readily calculated using standard methods. Otherwise, the sign test should be used or an alternate method of this test can be pre-specified in the SAP.

Sponsors should pre-specify one of the two analysis methods for the percent reduction in their SAP in addition to the primary analysis in their clinical studies and discuss with FDA the definition of a responder in the responder analysis or the value of DR% used in the analysis of the median percent reduction before finalizing the study protocol.

d. Multiplicity

Whether or not an adjustment for multiplicity is needed for claiming significant results on the primary or key secondary endpoints varies from study to study. Sponsors should refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance *E9 Statistical Principles for Clinical Trials*¹⁹ for statistical principles regarding the multiplicity adjustment.

V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket²⁰ studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. As more abuse-deterrent products are approved, it is possible that the amount of reduction observed in an epidemiologic study may also change. Consequently, a reduction that is deemed meaningful at one time may not be meaningful at another. Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.

Currently, data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited, and thus the optimal data sources, study variables, design features, analytical

¹⁹ ICH guidelines are available on FDA's guidance webpage at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²⁰ FDA requires postmarket studies for all opioids with abuse-deterrent labeling claims. For more information on postmarket requirements, see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm>.

techniques, and outcomes of interest of postmarket epidemiologic studies are not fully established.

Postmarket evaluations of abuse deterrence fall into two categories—formal studies and supportive information. Sponsors should submit protocols to FDA for all formal studies of abuse deterrence. Supportive information can also be submitted to FDA, but cannot substitute for formal studies.

A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse; therefore, the effects of an abuse-deterrent formulation can manifest in a variety of ways.

Understanding the actual impact of a particular abuse-deterrent formulation may require using a variety of study designs to examine different abuse-related outcomes in given populations of interest. Generally, multiple formal studies using a variety of data sources should be conducted to provide insights into product-specific abuse and the effect of an abuse-deterrent product on the outcomes of interest for other opioid drug products. The use of multiple study designs will also generally help with assessment of the impact of abuse-deterrent products on the full spectrum of abuse-related outcomes (i.e., addiction, overdose, and death) and to characterize and quantify the relevant clinical events that are associated with these outcomes.

Recognizing that the current thinking in this area may change, the following subsections provide recommendations for designing postmarket epidemiologic studies that are capable of detecting a change in the occurrence of abuse as a result of a drug product's abuse-deterrent properties.

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

1. They are hypothesis-driven, population-based, observational evaluations that follow good epidemiological practices^{21,22} and use outcomes that provide meaningful measures of abuse deterrence.
2. They capture one or more outcomes that can be used to assess meaningful reductions in misuse, abuse, addiction, overdose, and death.
3. They produce estimates of abuse and related clinical outcomes that are nationally representative, or are based on data from multiple large geographic regions that can reasonably be generalized to the national level. In the absence of nationally generalizable

²¹ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf>.

²² International Society for Pharmacoepidemiology and Risk Management, Guidelines for Good Practices and Pharmacoepidemiologic Studies, available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm, accessed January 25, 2015.

data, smaller or regional studies may be informative, but must be accompanied by a clear explanation of their representativeness and generalizability for appropriate interpretation.

4. They assess overall and route-specific (i.e., injected, snorted, smoked) changes in abuse levels that are associated with an abuse-deterrent product.
5. They are sufficiently powered statistically to assess meaningful changes in drug abuse and are of sufficient duration to examine trends in abuse following the marketing of the abuse-deterrent product. The necessary duration of the studies will depend on a variety of factors, including drug utilization and market share, early postmarket abuse deterrence data, and changes in the prescription opioid or illicit drug market.

2. Study Design Features

The epidemiologic methods and data sources that underlie formal postmarket studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. In addition, characterizing the relevant clinical events that are most useful for understanding the actual impact of a product on abuse-related adverse events is also an evolving science. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will enable FDA to evaluate the results of formal studies.

1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of abuse. The sampling methods, study population, or catchment area for the data source should be clearly described.²³
3. The choice of population(s) in each study should be carefully considered. The populations included in the study should be described in the protocol. At least one study should include a high-risk population, such as a population of known drug abusers, but formal studies should not be limited to only high-risk populations.
4. The protocol and study reports should thoroughly define the study outcomes. The choice of the outcome measure(s) should be justified. Formal studies should, as a group, capture all relevant outcomes: misuse, abuse, addiction, overdose, and death, as well as misuse and abuse clinical outcomes. Overall and route-specific misuse and abuse estimates should include prevalence and frequency of abuse. Clinical outcomes should include, when possible, an assessment of severity of abuse outcomes (e.g., addiction or overdose).

²³ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

5. Both population- and drug utilization-based estimates should be included in the study protocol.²⁴ Drug utilization-based estimates should use multiple denominators. The denominators are generally the number of prescriptions and the number of extended units (e.g., tablets or capsules). The catchment area for drug utilization data should be specified, particularly for sub-national or regional populations.
6. Sponsors should list all proposed opioid comparators and describe the rationale behind their inclusion. When branded and generic versions of a comparator are marketed, all should be included in the study when possible because many data sources used in abuse studies can identify only active ingredients and do not distinguish between branded and generic products or among multiple generic products. Information should be provided on the ability of data sources and study participants to accurately discriminate among different opioid products and formulations. The choice of comparator is critical for determining if a reduction in drug abuse is the result of a product's abuse-deterrent properties or the result of other factors (e.g., educational programs, prescription drug monitoring programs, changes in law enforcement policies, and the availability of other drugs) or secular trends. The choice of comparators will depend on the particular abuse-deterrent product studied and the opioid market environment at the time the study is initiated. Multiple comparators should be used to achieve the most complete picture of the impact of a product's abuse-deterrent properties. For the purposes of hypotheses, some comparators should be selected and justified as primary comparators in the study protocol before data collection, with additional comparators providing context. The following are examples of several potential abuse-deterrent study comparator scenarios.

If an abuse-deterrent formulation of a previously marketed product is introduced to the market, the primary comparators should include historical and currently available non-abuse-deterrent formulations of the products (including branded and generic whenever possible). Additional individual opioid products should be included as well and should be agreed upon with FDA and identified before the start of the study.

If a new abuse-deterrent product does not have an historical or currently available non-abuse-deterrent version of the same opioid, an appropriate group of comparators should be identified before the start of the study through mutual agreement with FDA. Examples of appropriate primary comparators include immediate release non-abuse-deterrent products with the same active moiety and/or a non-abuse-deterrent product with a relatively stable market share and abuse estimates captured at baseline during the postmarket period. Larger groupings of products can also serve as comparators and can help determine secular trends.

When available, a product that has the same active moiety, but has a different abuse-deterrent property, can serve as a comparator.

²⁴ Secora A, Dormitzer C, Staffa J, and Dal Pan G. 2014. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiology and Drug Safety*, 23(12):1227-37.

7. Understanding the background rates of drug abuse is important for protocol design and interpretation of study results. A baseline assessment of the prevalence of drug abuse for formulations of the same opioid that lack abuse-deterrent properties should be conducted and the baseline time period should be justified.
8. Submissions should include the SAP. The plan should include parameter definitions, unit of analysis, model specification, power and sample size calculations, and any additional variables or predictors. Assessment of the abuse outcome measures should consider both average levels of abuse comparing pre- and post-periods to currently available product (means analysis) and trend analysis.
9. Statistical models should include variables that may affect how the product is used and also other related confounders (e.g., geographic variability and demographic characteristics).
10. Exposure and outcome measures that include self-reported assessments should be validated before the start of the study.
11. The precision of outcome measures will also influence the observational period. Outcome measures with large uncertainty (due to bias or variability) in the exposure or study variable measures, for example, may warrant longer observational periods.
12. Interim analyses are encouraged, but results should be considered tentative in light of their preliminary nature.

B. Supportive Information

Information is considered supportive if it can be used to provide additional context on societal, behavioral, and clinical aspects of abuse and abuse-deterrance. Supportive information may be qualitative or descriptive, and it may rely on sources that capture drug utilization or prescribing patterns, diversion events, attitudes and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Investigations that provide supportive information may also include investigations that are conducted in smaller populations or subgroups, and that while perhaps not broadly generalizable, may contribute to the totality of the evidence relating to abuse deterrence.

As is the case for formal studies, best practices for collecting and submitting supportive information are still evolving. However, below are some basic recommendations relating to supportive information.

1. Supportive information should be clearly stated, and the rationale for how the supportive information contributes to a sponsor's portfolio of abuse-related studies should be clearly identified.
2. How supportive information is representative of the population from which it is derived or sampled should be clearly described.

3. How the exposure and outcome are measured should be clearly described along with the relationship between the outcomes measured and the primary outcomes of interest: misuse, abuse, addiction, overdose, and death.
4. Collections of supportive information that include populations of particular interest or geographically diverse settings is strongly encouraged. Overlapping geographic areas between formal and supportive information should be considered.

VI. LABELING

Including information about a product's abuse-deterrent properties in labeling is important to inform health care professionals, the patient community, and the public about a product's abuse potential. Accordingly, FDA encourages sponsors to propose labeling that sets forth the results of in vitro, pharmacokinetic, clinical abuse potential and formal postmarket studies and appropriately characterizes the abuse-deterrent properties of a product.

There are several important concepts about the state of the science of pre- and postmarket studies of abuse deterrence that should be considered as these are reflected in labeling. First, as stated earlier in the guidance, abuse-deterrent does not mean abuse-proof. Therefore, labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible. Next, premarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies.

When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling.²⁵ When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling. However, if these postmarket data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater risk (e.g., a shift from oral and nasal abuse to intravenous abuse), FDA may determine that labeling revisions are needed.

Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid can be described as limiting manipulation for the purpose of snorting or injection if

²⁵ Abuse-deterrence information in labeling should be presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 Abuse.

the data support such a statement. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary as described above. For example, a product's labeling should explain that the product's abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other potential forms of abuse.

As noted at the outset of this guidance, FDA will take a flexible, adaptive approach to the evaluation and labeling of abuse-deterrent opioid products. FDA expects sponsors to update their formulations to take advantage of technological improvements and further expects to allow labeling statements related to abuse deterrence commensurate with those advances.

Furthermore, FDA expects sponsors to compare their formulations against approved abuse-deterrent versions of the same opioid. The comparisons should be based on the relevant categories of testing. For instance, if a proposed product is less resistant to manipulation than an approved product, the proposed product may not be eligible for labeling regarding abuse-deterrent properties.

FDA is concerned that, with time, abusers may adapt to abuse-deterrent technologies and discover methods to defeat them. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

As discussed below, the nature of information in labeling on abuse deterrence for a particular product will depend on the types of studies performed and the result of those studies. Because it cannot provide specific guidance on the magnitude of effect that would be sufficient to support each type of claim, FDA will assess the appropriateness of all proposed labeling statements about abuse deterrence based on the data provided.

Information describing the results of the evaluation of abuse-deterrent properties can be used to support labeling statements based on the three premarket categories (i.e., in vitro data, pharmacokinetic data, and clinical abuse potential studies) and the fourth category (postmarket data) once it is available.

The data necessary to support abuse-deterrent labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse. In general, most abuse-deterrent information included in product labeling will be based on data from more than one category.

Key elements of the study design and conduct should be summarized in the product labeling. Category 1 studies can be described in general terms to avoid creating a *road map* for defeating the product's abuse-deterrent properties. However, the design, conduct, and results of Category 2 and 3 studies should be described in sufficient detail, including the primary outcome measure data from Category 3 studies, to support clear labeling regarding a product's abuse-deterrent properties.

The following are examples of information for inclusion in labeling for different types of abuse-deterrent effects based on various types of premarket studies performed.

- Category 1

For this product, in vitro data demonstrated that an abuse-deterrent product cannot be crushed and dissolved or extracted in a small volume of solution suitable for injection. In this case, Category 1 in vitro data may be sufficient to support a statement in labeling about abuse deterrence for the intravenous route of abuse (See Section IV Premarket Studies). Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.

These in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter intravenous abuse. However, abuse of this product is still possible by the oral and nasal routes.

- Category 1 and Category 2

For this product, in vitro and pharmacokinetic data from study of the oral and nasal routes of administration demonstrated that no changes occurred in the extended-release properties of the opioid after crushing or dissolution in a variety of solvents. These data may be sufficient to support statements in labeling about abuse deterrence for the nasal and intravenous routes of abuse. Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation, and pharmacokinetic studies of the oral and intranasal routes were performed to determine the effect of manipulation on drug release. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains its extended-release properties despite manipulation.

The in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter oral, nasal and intravenous abuse. However, abuse of intact product is still possible by the oral route.

- Category 2 and Category 3

For this product, pharmacokinetic and clinical abuse potential studies demonstrated the release of an antagonist from an opioid and antagonist combination product following crushing and that the presence of the antagonist resulted in less drug liking compared to a similar amount of opioid alone when administered by the oral and intranasal routes. In

addition, an additional clinical abuse potential study simulating intravenous abuse using the amounts of opioid and antagonist found to be released from the crushed product also demonstrated reduced drug liking.

The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist.

These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.

All of these statements based on Categories 1, 2, or 3 testing should be followed by a statement that data from laboratory and clinical studies may not fully predict abuse potential in the post-approval setting.

As discussed in Section V, postmarket data from a variety of sources can demonstrate that a product's abuse-deterring properties result in persistent and relevant abuse deterrence. These data can result from appropriately designed, conducted, and analyzed formal postmarket studies and from supportive information on the abuse of the product.

FDA is currently considering formal studies plus a variety of supportive information (e.g., data concerning the street value of prescription drugs) as sources that may be acceptable to provide evidence that a product's formulation has had an actual impact on reducing its abuse. FDA anticipates that data from some or all three of the premarket categories along with data from postmarket studies (including both formal studies and supportive information) would be needed to support a statement in labeling that the product has been shown to reduce abuse. The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

An example of labeling for a product with evidence of a reduction in abuse is:

These data demonstrated a reduction in the abuse of Tradename in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterring properties were available. This reduction in abuse appears to be attributable to the product's formulation, which deters abuse by injection or snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.

VII. ADDITIONAL RESEARCH NEEDS

As discussed above, the science of abuse deterrence is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are

rapidly evolving. For these reasons, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent opioid products. Additionally, there is considerable room for additional scientific work that could advance the development and assessment of abuse-deterrent products. In particular, FDA encourages additional research on the following topics:

- The quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations.
- The best assessment methods to employ when analyzing a clinical study of abuse potential.
- The quantitative link between the outcomes from a clinical study of abuse potential comparing formulations and the effect on those same formulations on abuse in the community.
- Further understanding of the best study methods to employ to assess the effect of a product with abuse-deterrent properties on the rates of abuse in the community.
- Development of a communication tool (e.g., a simple graph or chart) to inform prescribers of the relative impact the product has on the different routes of abuse.

Progress on these topics could facilitate the ability of sponsors to propose and FDA to approve labeling that would give a more complete picture of the anticipated effect of products with abuse-deterrent properties. Ultimately, progress in these areas could facilitate product development by reducing the amount of information that is needed to accurately assess a product with abuse-deterrent properties and predict its impact on abuse in the community.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Utilization Review

Date: March 8, 2017

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Subject: U.S. Utilization Patterns of Oxycodone-Containing Products and Other Opioid Analgesics

Drug Name(s): Oxycodone-Containing Products and Other Opioid Analgesics

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2016-2841

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EXECUTIVE SUMMARY

On April 5, 2017, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held to discuss the overall risk benefit profile of a proposed new drug application for an oxycodone immediate-release (IR) product with properties designed to deter abuse. In preparation for this upcoming joint advisory committee meeting, this review examined the national utilization patterns of oxycodone-containing analgesics, with a focus on the single-ingredient IR formulation, and other opioid analgesic products with formulations designed to deter abuse from 2009 through 2016 in the U.S. outpatient retail setting. The drug utilization analyses in this review will be used to provide context for the meeting's discussion.

In 2016, approximately 19 million patients were dispensed prescriptions for oxycodone-containing IR products, and 839,000 patients were dispensed prescriptions for oxycodone-containing ER products from outpatient retail pharmacies. Among patients dispensed oxycodone-containing IR products, approximately 14 million patients were dispensed prescriptions for combination oxycodone-containing IR products, while 6 million patients were dispensed prescriptions for single-ingredient oxycodone IR products. Among patients dispensed oxycodone-containing ER products, the vast majority of patients were dispensed prescriptions for single-ingredient oxycodone ER products with 837,000 patients (99.8% of patients) in 2016.

Utilization of other opioid analgesic products with formulations designed to deter abuse, Hysingla™ ER (hydrocodone ER) and Embeda® (morphine/naltrexone ER), was also examined. In 2016, approximately 54,000 patients received prescriptions dispensed for Hysingla™ ER, and 29,000 patients received prescriptions dispensed for Embeda®.

Approximately one-quarter of prescriptions dispensed for single-ingredient oxycodone IR products were written by family practice/general practice/doctor of osteopathy specialists in 2016. According to office-based physicians survey data, single-ingredient oxycodone IR products were primarily prescribed for the diseases of the musculoskeletal system and connective tissue such as back pain.

In summary, the majority of oxycodone-containing analgesic use was for the IR products. Utilization of combination oxycodone-containing IR products remained relatively stable during the examined time period, while the utilization of single-ingredient oxycodone IR products more than doubled. In contrast, the utilization of single-ingredient oxycodone ER products, which accounted for the vast majority of use of opioid analgesic products with formulations designed to deter abuse, decreased during the study period.

1 INTRODUCTION

In October 2016, a New Drug Application (NDA) was submitted for the approval of an oxycodone immediate-release (IR) product with properties designed to deter abuse in the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is bringing this application to an Advisory Committee (AC) meeting to discuss the overall risk benefit profile for this oxycodone IR product. The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), and the Drug Safety and Risk Management Advisory Committee (DSaRM) joint meeting will be held on April 5, 2017. In preparation for this upcoming AC meeting, DAAAP requested the Division of Epidemiology II (DEPI II) to provide the utilization data for oxycodone-containing analgesics and other opioid analgesic products with formulations designed to deter abuse to provide context for the AC discussion.

2 METHODS AND MATERIALS

2.1 PRODUCTS INCLUDED

The following oxycodone-containing analgesics, including formulations designed to deter abuse such as OxyContin and Xtampza ER, are included in this review. Other opioid analgesics with formulations designed to deter abuse are also included in this review.

- Oxycodone-containing IR
 - Single-ingredient oxycodone IR
 - Combination oxycodone-containing IR (grouped together in the review)
 - Oxycodone/acetaminophen IR
 - Oxycodone/ibuprofen IR
 - Oxycodone/acetilsalicylic acid IR
- Oxycodone-containing ER
 - Single-ingredient oxycodone ER (OxyContin ER, Xtampza ER, and generic oxycodone ER)
 - Combination oxycodone/acetaminophen ER
- Other opioid analgesics with formulations designed to deter abuse
 - HysinglaTM ER (hydrocodone ER)
 - Embeda[®] (morphine/naltrexone ER) was first approved on August 13, 2009, but was voluntarily withdrawn from the market in March 2011, due to testing that found stability concerns in the manufacturing process. The FDA confirmed that these issues were resolved with its approval of a manufacturing supplement in November 2013.¹
 - TarginiqTM ER, MorphabondTM, or Troxyca[®] ER were not included in the analyses of the review because although FDA approved, they were not marketed in the U.S. during the study time period.

2.2 DATA SOURCES USED

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions).

2.2.1 Prescription Data

The IMS Health, National Prescriptions AuditTM database was searched to provide national estimates of prescriptions dispensed for oxycodone-containing analgesics, and other opioid analgesics with formulations designed to deter abuse [Embeda[®] (morphine/naltrexone ER) and HysinglaTM ER (hydrocodone ER)] from U.S. outpatient retail pharmacies from 2009 through 2016. The data on the top ten prescriber specialties for single-ingredient oxycodone IR products were also obtained from this database for 2016.

¹ U.S. Food and Drug Administration News Release. *FDA approves labeling with abuse-deterrent features for third extended-release opioid analgesic.* Accessed February 2017.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm>

2.2.2 *Patient Data*

The IMS Health, Total Patient Tracker database was searched to provide national estimates of patients who received prescriptions dispensed for oxycodone-containing analgesics and other opioid analgesics with formulations designed to deter abuse (Embeda[®], and HysinglaTM ER) from U.S. outpatient retail pharmacies from 2009 through 2016.

2.2.3 *Indications for Use*

The inVentiv Health Research & Insights LLC., TreatmentAnswersTM with Pain Panel database was searched to obtain the most frequently reported diagnoses (ICD-10-CM) associated with the mention of single-ingredient oxycodone IR products as reported by U.S. office-based physician surveys for 2016.

3 RESULTS

3.1 DETERMINING SETTINGS OF CARE

In 2016, approximately 67%, 32%, and <1% of bottles of oxycodone-containing analgesics were distributed to outpatient retail pharmacies, non-retail settings, and mail-order specialty settings, respectively.² Utilization patterns from U.S. outpatient retail pharmacies were examined in this review; data from mail-order specialty and non-retail pharmacy settings were not included in this review.

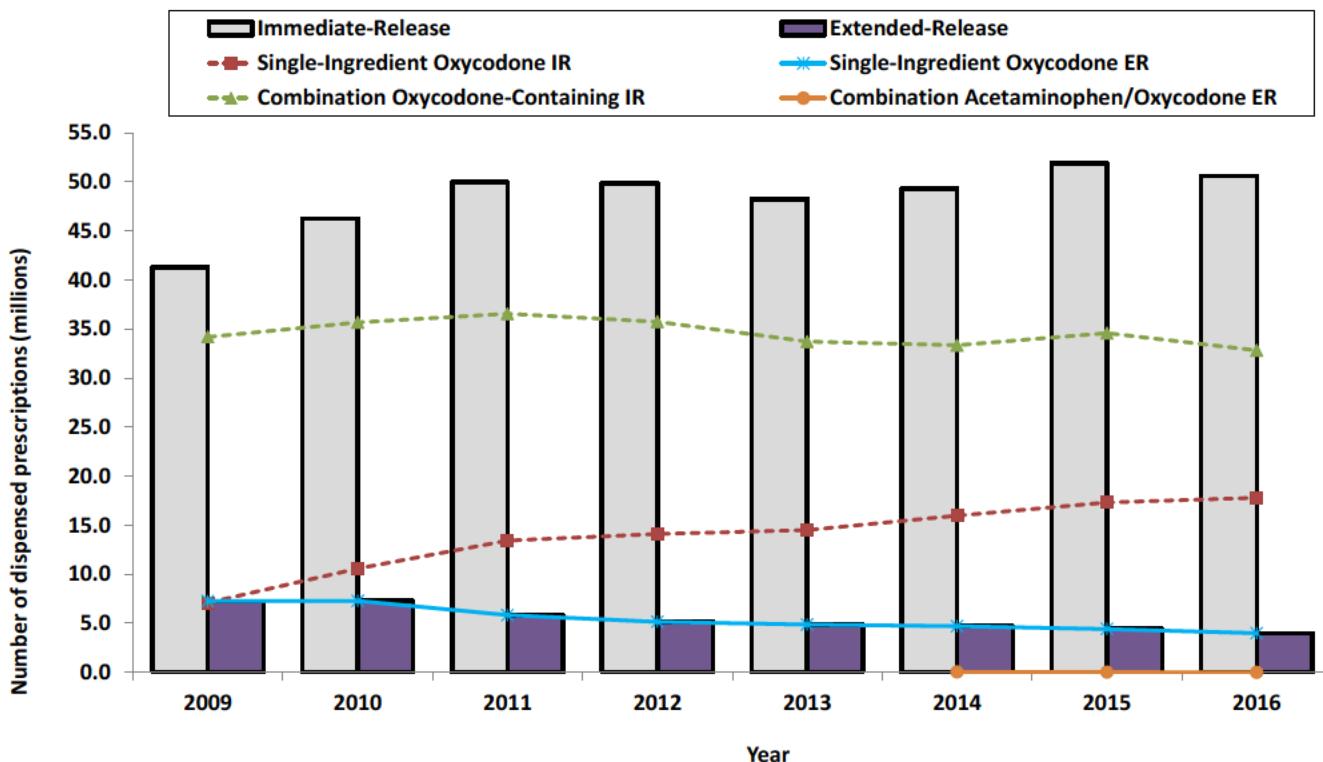
3.2 PRESCRIPTION DATA

3.2.1 *Oxycodone-Containing Analgesics*

Figure 1 below and Table 1 in Appendix B provide national estimates of prescriptions dispensed for oxycodone-containing analgesics from U.S. outpatient retail pharmacies. From 2009 through 2016, oxycodone-containing IR products accounted for the majority of total oxycodone prescriptions dispensed annually. In 2016, approximately 55 million total oxycodone prescriptions were dispensed; of these, IR formulations accounted for 93% (51 million prescriptions), and ER formulations accounted for 7% (4 million prescriptions).

² Source: IMS Health, IMS National Sales PerspectivesTM. Year 2016. Data extracted January 2017. File: NSP 2016-2481 oxycodone ARIR AC channel 1-31-2017.xlsx

Figure 1. National estimates of prescriptions dispensed for oxycodone-containing analgesics from U.S. outpatient retail pharmacies, years 2009-2016



Source: IMS Health, National Prescription Audit™. Years 2009-2016. Data extracted January 2017.

Among prescriptions dispensed for oxycodone-containing IR products, approximately 65% (33 million prescriptions) and 35% (18 million prescriptions) were dispensed for combination oxycodone-containing IR products and single-ingredient oxycodone IR products in 2016, respectively. Among prescriptions dispensed for oxycodone-containing ER products, approximately 99.8% (4 million prescriptions) were dispensed for single-ingredient oxycodone ER products, and 0.2% (7,000 prescriptions) were dispensed for combination oxycodone/acetaminophen ER products in 2016.

From 2009 to 2016, the number of prescriptions dispensed for combination oxycodone-containing IR products remained relatively steady, while the number of prescriptions dispensed for single-ingredient oxycodone IR products more than doubled. In contrast, the number of prescriptions dispensed for single-ingredient oxycodone ER products decreased by 45% over the examined time.

3.2.2 Embeda® and Hysingla™ ER

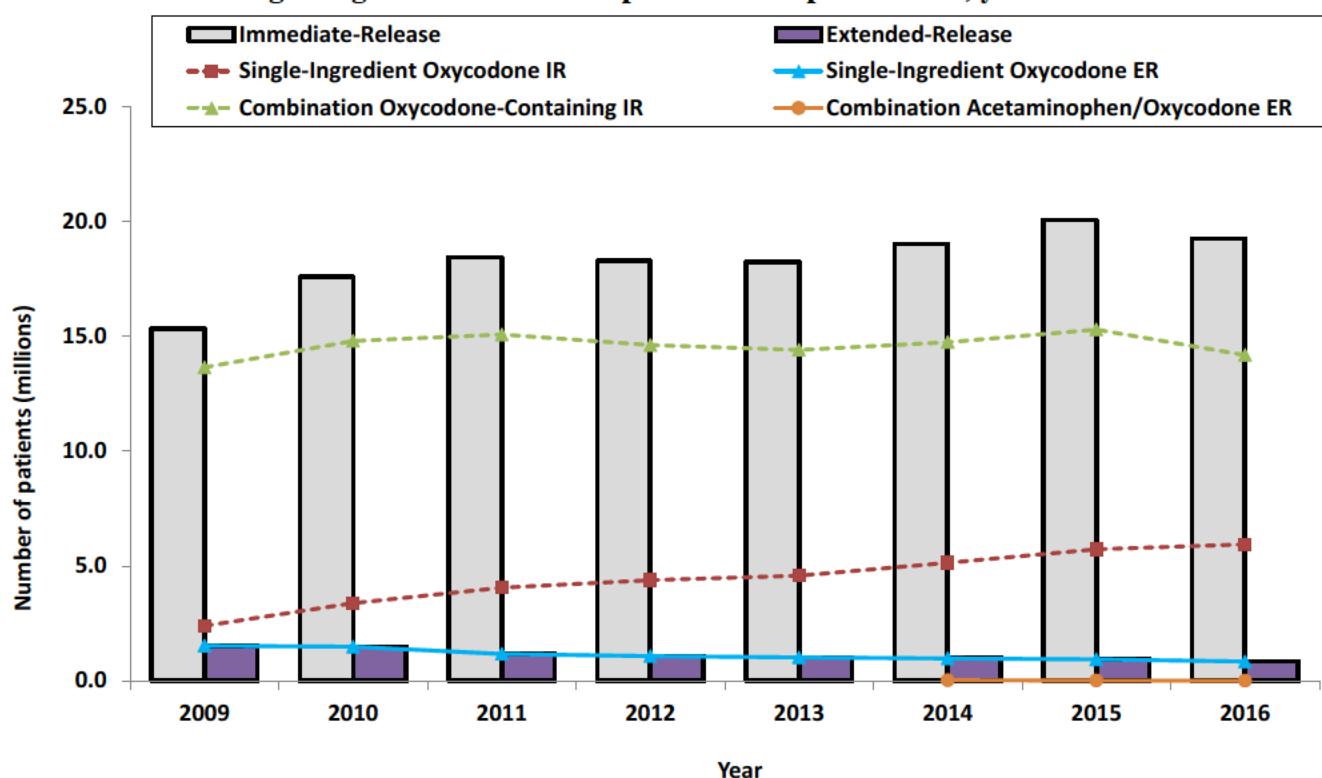
Table 2 in Appendix B provides national estimates of prescriptions dispensed for Embeda® and Hysingla™ ER from U.S. outpatient retail pharmacies. Compared to the 4 million prescriptions dispensed in 2016 for oxycodone-containing ER products with formulations designed to deter abuse, approximately 166,000 prescriptions were dispensed for Hysingla™ ER, and 111,000 prescriptions were dispensed for Embeda®.

3.3 PATIENT DATA

3.3.1 Oxycodone-Containing Analgesics

Figure 2 below and Table 3 in Appendix B provide national estimates of the total number of unique patients who were dispensed prescriptions for oxycodone-containing products from U.S. outpatient retail pharmacies. Similar to dispensed prescription trends, the majority of patients were dispensed prescriptions for oxycodone-containing IR products throughout the examined time period. In 2016, approximately 19.5 million total patients were dispensed prescriptions for oxycodone-containing products; of these, approximately 19 million patients were dispensed prescriptions for IR formulations, and 839,000 patients were dispensed prescriptions for ER formulations. Of note, patients may have received multiple prescriptions and products over the time examined.

Figure 2. National estimates of unique patients who were dispensed prescriptions for oxycodone-containing analgesics from U.S. outpatient retail pharmacies, years 2009-2016



Source: IMS Health, Total Patient Tracker. Years 2009-2016. Data extracted February 2017.

Among patients who were dispensed prescriptions for oxycodone-containing IR products, approximately 14 million patients were dispensed prescriptions for combination oxycodone-containing IR products, and 6 million patients were dispensed prescriptions for single-ingredient oxycodone IR products in 2016. Among patients who were dispensed prescriptions for oxycodone-containing ER products, approximately 837,000 patients (99.8% of patients) were dispensed prescriptions for single-ingredient oxycodone ER products in 2016.

From 2009 to 2016, the number of patients who were dispensed prescriptions for combination oxycodone-containing IR products remained relatively steady, while the number of patients who were dispensed

prescriptions for single-ingredient oxycodone IR products increased by 2.5-fold. In contrast, the number of patients who were dispensed prescriptions for single-ingredient oxycodone ER products decreased by 45% from 2009 to 2016.

3.3.2 *Embeda*[®] and *Hysingla*TM ER

Table 4 in Appendix B provides national estimates of unique patients who were dispensed prescriptions for Embeda[®] and HysinglaTM ER from U.S. outpatient retail pharmacies. In 2016, approximately 54,000 patients were dispensed prescriptions for HysinglaTM ER, and 29,000 patients were dispensed prescriptions for Embeda[®].

3.4 PRESCRIBER SPECIALTIES

Table 5 in Appendix B provides the national estimates of prescriptions dispensed for single-ingredient oxycodone IR products, stratified by the top ten prescriber specialties, from U.S. outpatient retail pharmacies. In 2016, family practice/general practice/doctor of osteopathy specialists were the top prescribers for single-ingredient oxycodone IR products at 24% of total dispensed prescriptions, followed by nurse practitioners at 12.5%, internal medicine at 12%, and physician assistants at 12%.

3.5 INDICATIONS FOR USE

Table 6 in Appendix B provides the diagnoses (ICD-10) in terms of drug use mentions associated with the use of single-ingredient oxycodone IR products as reported by U.S. office-based physician surveys. In 2016, diseases of the musculoskeletal system and connective tissue (M00-M99) such as back pain were the top diagnoses (47% of total drug use mentions) associated with the mention of single-ingredient oxycodone IR products, followed by the diseases of the nervous system (G00-G99) (10% of total drug use mentions).

4 DISCUSSION

Our analyses showed that the outpatient retail utilization of single-ingredient oxycodone IR products more than doubled from 2009 to 2016. In the outpatient retail setting, single-ingredient oxycodone ER products accounted for the vast majority of use of opioid analgesics with formulations designed to deter abuse. The prescription and patient estimates provided in this review are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.

According to survey data in 2016, office-based physicians reported mention of single-ingredient oxycodone IR products primarily in association with the diseases of the musculoskeletal system and connective tissue. The diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month; therefore, diagnosis data are not directly linked to dispensed prescriptions. Due to the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted with caution and may not be representative of national trends.

5 CONCLUSIONS

In 2016, approximately 6 million patients were dispensed prescriptions for single-ingredient oxycodone IR products. The number of patients who were dispensed prescriptions for single-ingredient oxycodone IR products more than doubled from 2009 to 2016. In 2016, approximately 837,000 patients were dispensed prescriptions for single-ingredient oxycodone ER products, which accounted for the vast majority of use of opioid analgesics with formulations designed to deter abuse.

6 APPENDIX A: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eashes, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Data from this review should be interpreted in the context of the known limitations of the databases used. The IMS Health, IMS National Sales Perspectives™ data do not provide a direct estimate of patient use but do provide a national estimate of units sold from the manufacturers to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

IMS Health, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of

diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

7 APPENDIX B: TABLES

Table 1. National estimates of prescriptions dispensed for oxycodone-containing analgesics from U.S. outpatient retail pharmacies, years 2009-2016

	Year																
	2009		2010		2011		2012		2013		2014		2015		2016		
	TRxs	%															
Total oxycodone-containing prescriptions	48,556,454	100.0%	53,532,667	100.0%	55,814,709	100.0%	55,000,827	100.0%	53,101,127	100.0%	54,043,581	100.0%	56,335,360	100.0%	54,619,472	100.0%	
Immediate-Release	41,292,787	85.0%	46,251,658	86.4%	49,983,186	89.6%	49,852,196	90.6%	48,235,638	90.8%	49,313,239	91.3%	51,892,550	92.1%	50,623,996	92.7%	
Combination Oxycodone-Containing IR*	34,195,127	82.8%	35,675,453	77.1%	36,556,132	73.1%	35,744,066	71.7%	33,722,400	69.9%	33,340,684	67.6%	34,575,502	66.6%	32,818,201	64.8%	
Single-Ingredient Oxycodone IR	7,097,660	17.2%	10,576,205	22.9%	13,427,054	26.9%	14,108,130	28.3%	14,513,238	30.1%	15,972,555	32.4%	17,317,048	33.4%	17,805,795	35.2%	
Extended-Release	7,263,667	15.0%	7,281,009	13.6%	5,831,523	10.5%	5,148,631	9.4%	4,865,489	9.2%	4,730,342	8.8%	4,442,810	7.9%	3,995,476	7.3%	
Single-Ingredient Oxycodone ER	7,263,667	100.0%	7,281,009	100.0%	5,831,523	100.0%	5,148,631	100.0%	4,865,489	100.0%	4,699,154	99.3%	4,423,455	99.6%	3,988,481	99.8%	
Combination Acetaminophen/Oxycodone ER	--	--	--	--	--	--	--	--	--	--	--	31,188	0.7%	19,355	0.4%	6,995	0.2%

Source: MS Health, National Prescription Audit™. Years 2009-2016. Data extracted January 2017. File: NPA 2016-2841 oxycodone ARIR AC 1-19-2017.xlsx

*Combination IR products include oxycodone/acetaminophen, oxycodone/acetilsalicylic acid, and oxycodone/ibuprofen. At least 99.5% or more of prescriptions were dispensed for combination oxycodone/acetaminophen IR analgesics annually.

Table 2. National estimates of prescriptions dispensed for Embeda® and Hysingla™ ER from U.S. outpatient retail pharmacies, years 2009-2016

	Year								
	2009		2010		2011		2012		
	TRxs	TRxs	TRxs	TRxs	TRxs	TRxs	TRxs	TRxs	
Hysingla™ ER	--	--	--	--	--	--	--	85,934	166,243
Embeda®	14,106	145,597	35,081	5	1	--	27,775	110,890	

Source: IMS Health, National Prescription Audit™. 2009-2016. Data extracted January 2017. File: NPA 2016-2841 embeda hysingla 1-19-2017.xlsx

Table 3. National estimates of unique patients* who received dispensed prescriptions for oxycodone-containing analgesics from U.S. outpatient retail pharmacies, years 2009-2016

	Year																
	2009		2010		2011		2012		2013		2014		2015		2016		
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total patients on oxycodone-containing analgesics	15,956,629	100.0%	18,143,346	100.0%	18,776,788	100.0%	18,574,286	100.0%	18,517,035	100.0%	19,265,728	100.0%	20,290,801	100.0%	19,467,209	100.0%	
Immediate-Release	15,357,631	96.2%	17,597,129	97.0%	18,453,131	98.3%	18,292,800	98.5%	18,258,689	98.6%	19,031,537	98.8%	20,081,310	99.0%	19,255,276	98.9%	
Combination Oxycodone-Containing IR**	13,655,653	88.9%	14,807,442	84.1%	15,085,935	81.8%	14,625,053	79.9%	14,415,391	79.0%	14,750,278	77.5%	15,303,765	76.2%	14,192,805	73.7%	
Single-Ingredient Oxycodone IR	2,389,490	15.6%	3,385,810	19.2%	4,052,448	22.0%	4,388,037	24.0%	4,580,887	25.1%	5,143,814	27.0%	5,728,772	28.5%	5,944,398	30.9%	
Extended-Release	1,525,054	9.6%	1,481,740	8.2%	1,172,513	6.2%	1,077,965	5.8%	1,018,434	5.5%	997,409	5.2%	943,295	4.6%	839,161	4.3%	
Single-Ingredient Oxycodone ER	1,525,054	100.0%	1,481,740	100.0%	1,172,513	100.0%	1,077,965	100.0%	1,018,434	100.0%	975,021	97.8%	934,080	99.0%	837,445	99.8%	
Combination Acetaminophen/Oxycodone ER	--	--	--	--	--	--	--	--	--	--	--	--	24,593	2.5%	9,833	1.0%	
															1,855	0.2%	

*Patient subtotals may not sum exactly because patients may be counted more than once in the individual time periods and across products. For this reason, summing patients across time periods or products is not advisable and will result in overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across time periods and products.

** Combination IR products include oxycodone/acetaminophen, oxycodone/acetilsalicylic acid, and oxycodone/ibuprofen. More than 99% of patients received prescriptions dispensed for combination oxycodone/acetaminophen IR.

Source: IMS Health, Total Patient Tracker. Years 2009-2016. Data extracted February 2017. File: TPT 2016-2841 oxycodone total ARIR AC 2-6-2017.xls

Table 4. National estimates of unique patients* who received prescriptions dispensed for Hysingla™ ER and Embeda® from U.S. outpatient retail pharmacies, years 2009-2016

	Year							
	2009	2010	2011	2012	2013	2014	2015	2016
	N	N	N	N	N	N	N	N
Hysingla™ ER	--	--	--	--	--	--	40,073	53,592
Embeda®	9,491	53,227	20,972	--	--	--	12,293	29,289

*Patient subtotals may not sum exactly because patients may be counted more than once in the individual time periods. For this reason, summing patients across time periods is not advisable and will result in overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across time periods.

Source: IMS Health, Total Patient Tracker. Years 2009-2016. Data extracted February 2017. File: TPT 2016-2841 embeda hysingla 2-6-2017.xls

Table 5. National estimates of prescriptions dispensed for single-ingredient oxycodone IR analgesics, stratified by top 10 prescriber specialties, from U.S. outpatient retail pharmacies, year 2016

	Year 2016	
	TRxs	%
Single-Ingredient Oxycodone IR	17,805,795	100.0%
Family Practice/General Practice/Doctor of Osteopathy	4,241,371	23.8%
Nurse Practitioner	2,233,605	12.5%
Internal Medicine	2,095,150	11.8%
Physician Assistant	2,078,226	11.7%
Anesthesiology	1,280,493	7.2%
Physical Medicine & Rehab	990,072	5.6%
Orthopedic Surgery	852,016	4.8%
Pain Medicine	605,144	3.4%
Unspecified	532,374	3.0%
Oncology	488,707	2.7%
All Others	2,408,637	13.5%

Source: IMS Health, National Prescription Audit™. Year 2016. Data extracted January 2017. File: NPA 2016-2841 oxycodone SI IR AC MD 1-19-2017.xlsx

Table 6. Diagnoses (ICD-10) in terms of drug use mentions* associated with the use of single-ingredient oxycodone IR analgesics as reported by office-based physician surveys, year 2016

	Year 2016		
	Uses	95% CI	%
Single-Ingredient Oxycodone IR	4,570,000	4,194,000 - 4,947,000	100.0%
Diseases of the musculoskeletal system and connective tissue (M00-M99)	2,166,000	1,906,000 - 2,425,000	47.4%
Diseases of the nervous system (G00-G99)	453,000	334,000 - 571,000	9.9%
Factors influencing health status and contact with health services (Z00-Z99)	391,000	281,000 - 501,000	8.6%
Injury, poisoning and certain other consequences of external causes (S00-T88)	338,000	236,000 - 440,000	7.4%
Diseases of the genitourinary system (N00-N99)	302,000	205,000 - 398,000	6.6%
Neoplasms (C00-D49)	261,000	171,000 - 352,000	5.7%
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	145,000	78,000 - 212,000	3.2%
Diseases of the digestive system (K00-K95)	124,000	62,000 - 186,000	2.7%
Diseases of the respiratory system (J00-J99)	116,000	56,000 - 176,000	2.5%
Endocrine, nutritional and metabolic diseases (E00-E89)	107,000	49,000 - 164,000	2.3%
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	55,000	14,000 - 96,000	1.2%
Diseases of the skin and subcutaneous tissue (L00-L99)	45,000	8,000 - 82,000	1.0%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	25,000	<500 - 53,000	0.6%
Diseases of the circulatory system (I00-I99)	20,000	<500 - 44,000	0.4%
External causes of morbidity (V00-Y99)	16,000	<500 - 38,000	0.4%
Certain infectious and parasitic diseases (A00-B99)	7,000	<500 - 22,000	0.2%

Source: inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel. 2016. Data extracted February 2017. File: PDDA_2016-2841_oxycodone_SI_IR_AC_ICD10_dx3_2-6-2017.xls

*inVentiv Health Research and Insights LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: March 8, 2017

FROM: Wei Qiu, PhD
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TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Summary of Clinical Data for RoxyBond

Summary of Clinical Data for RoxyBond

The proposed indication for RoxyBond (oxycodone hydrochloride) immediate-release tablets is for the management of moderate-to-severe pain where the use of an opioid analgesic is appropriate. The safety and efficacy of RoxyBond is based on the demonstration of bioequivalence to the listed drug Roxicodone (NDA 021011) for this 505(b)(2) New Drug

Application. The clinical program for RoxyBond consisted of four Phase 1 pharmacokinetic studies and one intranasal human abuse liability (HAL) study. Efficacy studies were not required for this NDA application. The safety information collected in the pharmacokinetic studies was of limited value due to the fact that these were single-dose studies conducted in healthy volunteers who were naltrexone-blocked. The HAL study investigated the effects of intranasal administration of manipulated RoxyBond in opioid-experienced subjects. No new safety signals were identified during the review of the RoxyBond application beyond what is already known for oxycodone.

The clinical pharmacology review focuses on two pivotal comparative bioavailability and dose proportionality studies (O-ARIR-003 and O-ARIR-006) using the to-be-marketed commercial formulation. Both studies were randomized, open-label, crossover studies conducted in healthy volunteers under naltrexone blockade. Study 003 assessed the comparative bioavailability of 30 mg RoxyBond tablets and 30 mg Roxicodone tablets under fasting condition and the food effect for the 30 mg RoxyBond tablet. Study 006 assessed dose proportionality using 5, 15, and 30 mg RoxyBond tablets under fasting conditions. Pharmacokinetic results of comparative bioavailability, food effect and dose proportionality obtained from these two studies are summarized as follows:

Comparative Bioavailability between RoxyBond Tablet and Roxicodone Tablet: RoxyBond tablet (1 x 30 mg) showed equivalent AUC_t and AUC_{inf} values, similar C_{max} values, and slightly longer median T_{max} values (1.8 hour for RoxyBond vs 1.0 hour for Roxicodone) in comparison to Roxicodone tablet (1 x 30 mg) under fasting condition. The oxycodone PK parameters for 30 mg RoxyBond Tablet and 30 mg Roxicodone Tablet under fasting conditions are listed below.

Table 1: Oxycodone Pharmacokinetic Parameters for 30 mg RoxyBond Tablet (also known as O-ARIR) Fasted versus 30 mg Roxicodone Tablet Fasted

Parameter	Unit	O-ARIR (Fasted) ^a (N = 58)	Roxicodone (Fasted) ^a (N = 54)
AUC _{0-t}	ng•hr/mL	287.4 (22.9)	300.3 (22.9)
AUC _{0-inf}	ng•hr/mL	292.7 (23.0)	305.4 (22.9)
C _{max}	ng/mL	57.8 (31.1)	67.7 (35.1)
T _{max}	hr	1.8 (0.8, 5.0) ^b	1.0 (0.5, 5.0) ^b
K _{el}	hr ⁻¹	0.1871 (0.1112, 0.2840) ^c	0.1932 (0.1322, 0.3117) ^c
T _{1/2}	hr	3.8 (2.4, 6.2) ^c	3.7 (2.2, 5.2) ^c

^a Values are arithmetic means (%CV)

^b Median (Range)

^c Range

The total exposures of oxycodone (AUC_t and AUC_{inf}) for 30 mg RoxyBond tablet and 30 mg Roxicodone tablet met bioequivalence (BE) criteria. The point estimate of the geometric mean ratio (RoxyBond tablet /Roxicodone tablet) for oxycodone AUC_t and AUC_{inf} were 95.6% and 95.8%, respectively. The corresponding 90% confidence intervals (CIs) were 92.5 – 98.7% and 92.8 – 98.9%, respectively. All of these 90% CIs fell within the 80 - 125% BE limit.

Oxycodone Cmax values were similar for 30 mg RoxyBond tablet and 30 mg Roxicodone tablet. The point estimate of the geometric mean ratio (RoxyBond tablet /Roxicodone tablet) for oxycodone Cmax was 86.2% and the corresponding 90% CI was 78.8% - 94.3%. The lower limit of the 90% CI for Cmax of 78.8% is very close to the 80% limit BE criterion and RoxyBond will be titrated. Therefore, a 1.2% lower CI for oxycodone Cmax is not anticipated to affect the efficacy of RoxyBond to a substantial degree. Median (min, max) Tmax values were 1.8 (0.8, 5.0) hours for RoxyBond tablet and 1.0 (0.5, 5.0) hour for Roxicodone tablet; RoxyBond had slightly longer median Tmax value than Roxicodone but the range for Tmax was similar between the two products. Considering food caused a delay in Tmax (1.25 to 2.54 hour) for Roxicodone and there is no food restriction for Roxicodone administration, the slightly longer median Tmax value for RoxyBond under fasting condition will not be anticipated to affect the efficacy of RoxyBond to a substantial degree.

Food Effect: The oxycodone PK parameters for RoxyBond Tablet (1x 30 mg) under fasting and fed conditions are listed below.

Table 2: Oxycodone Pharmacokinetic Parameters for 30 mg RoxyBond Tablet (also known as O-ARIR) Fed versus 30 mg RoxyBond Tablet Fasted

Parameter	Unit	O-ARIR (Fed) ^a (N = 58)	O-ARIR (Fasted) ^a (N = 58)
AUC _{0-t}	ng•hr/mL	354.2 (23.3%)	287.4 (22.9%)
AUC _{0-inf}	ng•hr/mL	361.9 (23.9%)	292.7 (23.0%)
C _{max}	ng/mL	68.0 (29.5%)	57.8 (31.1%)
T _{max}	hr	2.0 (1.0, 6.1) ^b	1.8 (0.8, 5.0) ^b
K _{el}	hr ⁻¹	0.1824 (0.1204, 0.2810) ^c	0.1871 (0.1112, 0.2840) ^c
T _{1/2}	hr	3.9 (2.5, 5.8) ^c	3.8 (2.4, 6.2) ^c

^a Values are arithmetic means (%CV)

^b Median (Range)

^c Range

A high-fat meal increased oxycodone Cmax, AUCt, and AUCinf values by 18%, 23%, and 24%, respectively, following the administration of a single dose of 30 mg RoxyBond tablet. Median (min, max) Tmax values were similar under fasting and fed conditions; 1.8 (0.8, 5.0) hours under fasting and 2.0 (1.0, 6.1) hours under fed condition. The food effect on oxycodone AUC for RoxyBond tablet is similar to that for Roxicodone, the identified listed drug for this 505(b)(2) NDA. According to the approved Roxicodone labeling, a high fat meal enhanced the extent of absorption (27% increase in AUC). In addition, food caused a delay in Tmax (1.25 to 2.54 hours). Roxicodone labeling does not recommend a food restriction because of the limited extent of the food effect. Therefore, a food restriction should not be recommended for RoxyBond tablet either.

Dose Proportionality: Following a single dose administration of RoxyBond 5, 15, and 30 mg tablets to healthy volunteers under naltrexone block and fasting conditions, oxycodone Cmax and AUC values were dose proportional based on the analyses on log transformed parameters

using a power model. The slopes of log-transformed Cmax, AUCt, and AUCinf values for oxycodone were 0.9769, 1.0081 and 0.9799, respectively, and they fell within the range of 0.80 to 1.25. In addition, the 90% CIs around the slope were within the predefined boundary (0.8755, 1.1245). Therefore, dose proportionality is demonstrated over the range of 5 mg to 30 mg for RoxyBond. As described in its label, dose proportionality was also demonstrated for Roxicodone tablets.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: March 8, 2017

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Opioids with Abuse-Deterrent Labeling

Opioids with Abuse-Deterrent Labeling: Section 9.2 Drug Abuse

Based on feedback from previous advisory committee meetings where abuse-deterrent opioid analgesics were discussed, included here are excerpts from the labels of approved opioids analgesics with abuse-deterrent labeling, specifically Section 9.2, which describes the in vitro and in vivo studies conducted to support the abuse-deterrent properties. The products are listed in the order in which they were approved.

**EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules
[NDA 022321]**

Approval Date: August 13, 2009

Abuse Deterrence Labeling Update: October 17, 2014

Abuse Deterrence Studies

EMBEDA is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

In Vitro Testing

In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When EMBEDA is crushed and mixed in a variety of solvents, both morphine sulfate and naltrexone hydrochloride are simultaneously extracted.

Clinical Studies

The abuse potential of EMBEDA when crushed was examined in three studies following administration by the oral (Studies 1 and 2) and intranasal (Study 3) routes. A fourth study was conducted with IV administration of simulated crushed EMBEDA (Study 4). These were randomized, double-blind, single-dose, placebo and active-controlled, crossover studies in non-dependent recreational opioid users. Drug Liking in Studies 1- 3 was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Drug Liking in Study 4 and Drug High in all studies was measured on a unipolar 100-point VAS where 0 represents no response and 100 represents maximum response. Response to whether the subject would take the study drug again was also measured in two studies (Study 2, Study 3) on a bipolar 100-point VAS where 0 represents the strongest negative response (e.g., ‘definitely would not’), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., ‘definitely would’). The pharmacokinetics of morphine sulfate and naltrexone hydrochloride were also determined in these abuse potential studies. When EMBEDA was crushed and administered by the oral and intranasal routes, morphine and naltrexone were absorbed with similar median time-to-peak concentration (T_{max}) values of 1 hour following oral administration and approximately 36 minutes following intranasal administration.

Oral Studies

Study 1 compared EMBEDA to IR morphine sulfate. In this study 32 subjects received four treatments: 120 mg/4.8 mg as intact EMBEDA capsules, 120 mg/4.8 mg as crushed EMBEDA in solution, 120 mg IR morphine in solution, and placebo. When EMBEDA was crushed and taken orally, the geometric mean ($\pm SD$) values for naltrexone C_{max} and AUC_{inf} were 1073 ± 721 pg/mL and 3649 ± 1868 pg·hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking and Drug High scores compared with crushed IR morphine (as summarized in Table 3).

Figure 1 (Study 1) demonstrates a comparison of Drug Liking for crushed EMBEDA compared to crushed IR morphine sulfate when given by the oral route in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in Drug Liking with crushed EMBEDA vs. morphine greater than or equal to the value on the X-axis. Of the 32 subjects who completed the study, approximately 81% of subjects had some reduction in Drug Liking and Drug High with crushed EMBEDA compared to administration of IR morphine

sulfate, while approximately 19% had no reduction in Drug Liking or in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to IR morphine was observed in 72% and 56% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 56% and 31% of subjects, respectively.

Study 2 compared EMBEDA to ER morphine sulfate. In this study 36 subjects were randomized to receive three treatments in solution: 120 mg/4.8 mg as crushed EMBEDA capsules, 120 mg crushed ER morphine, and placebo. When EMBEDA was crushed and taken orally, the geometric mean (\pm SD) values for naltrexone C_{max} , AUC_{0-2h} , and AUC_{inf} were 824 ± 469 pg/mL, 1121 ± 561 pg·hr/mL, and 2984 ± 1388 pg·hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 3).

Figure 1 (Study 2) demonstrates a comparison of maximum Drug Liking for crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 33 subjects who completed the study, approximately 85% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 15% had no reduction in Drug Liking. Similarly, 100% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 76% and 52% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 79% and 64% of subjects, respectively.

Table 3. Summary of Abuse Potential Maximal Responses (E_{max}) with Oral Administration of Crushed EMBEDA Compared to Crushed IR Morphine Sulfate (Study 1) or Crushed ER Morphine (Study 2)

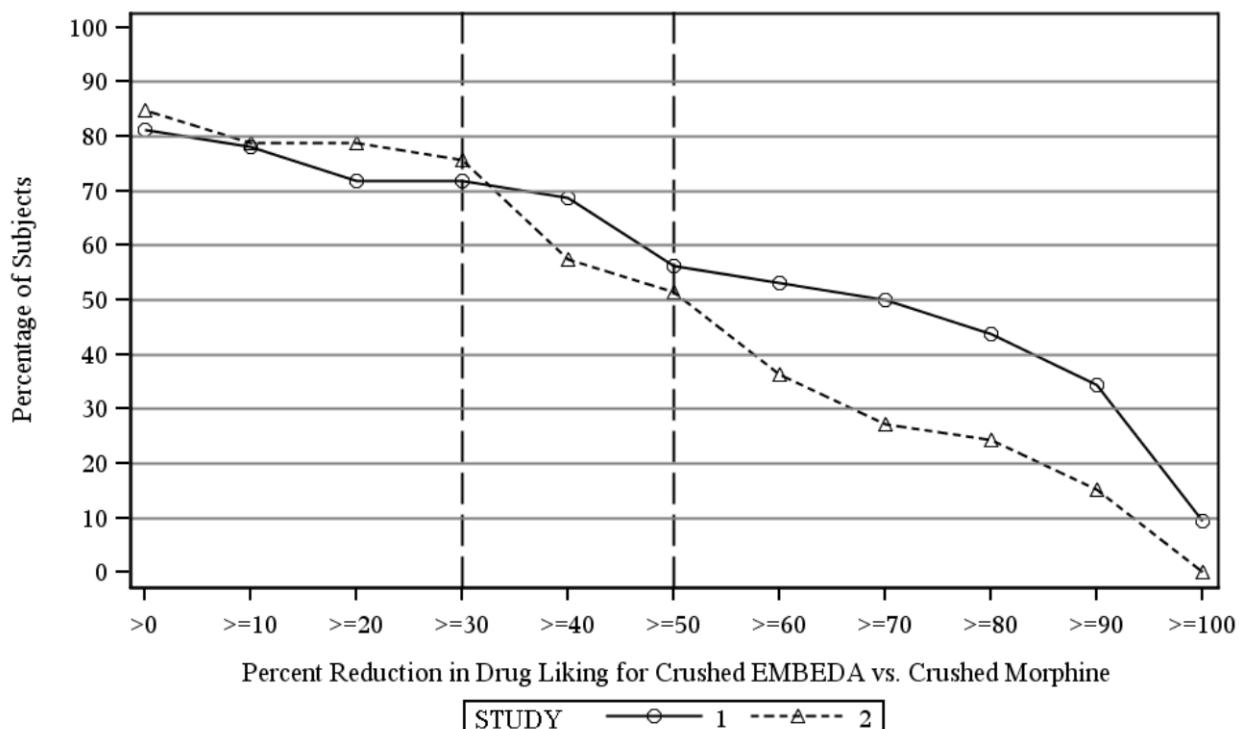
VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (120 mg/4.8 mg)	Crushed Morphine (120 mg)
Study 1		Immediate Release	
Drug Liking*	Mean (SE)	68.1 (3.1)	89.5 (2.2)
	Median (range)	62 (50-100)	93 (57-100)
Drug High**	Mean (SE)	54.7 (6.1)	90.2 (2.1)
	Median (range)	64 (0-100)	97 (61-100)
Study 2		Extended Release	
Drug Liking*	Mean (SE)	65.2 (2.0)	80.6 (2.3)
	Median (range)	65 (51-100)	81 (50-100)
Drug High**	Mean (SE)	29.2 (3.6)	64.1 (3.3)
	Median (range)	27 (0-78)	63 (28-100)
Take Drug Again*	Mean (SE)	58.0 (3.8)	70.6 (4.3)
	Median (range)	58 (9-100)	75 (12-100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

**Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).

E_{max} = maximal response; ER = extended release; IR = immediate release; SE = standard error.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for EMBEDA vs. Morphine Following Oral Administration in Studies 1 and 2.



Intranasal Study

Study 3 compared intranasal administration of crushed EMBEDA to crushed ER morphine sulfate. In this study, 33 subjects were randomized to receive three treatments: 30 mg/1.2 mg as crushed EMBEDA, 30 mg crushed ER morphine, and crushed placebo. When EMBEDA was crushed and taken intranasally, the geometric mean (\pm SD) values for naltrexone C_{max} , AUC_{0-2h} , and AUC_{inf} were 1441 ± 411 pg/mL, 1722 ± 441 pg·hr/mL and 3228 ± 846 pg·hr/mL, respectively. Intranasal administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 4).

Figure 2 demonstrates a comparison of maximum Drug Liking for intranasal administration of crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 27 subjects who completed the study, approximately 78% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 22% had no reduction in Drug Liking. Similarly, approximately 70% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine and approximately 30% of subjects had no reduction in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 63% and 59% of subjects, respectively (summarized in Figure 2). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 59% and 37% of subjects, respectively.

Table 4. Summary of Abuse Potential Maximal Responses (E_{max}) with Intranasal Administration of Crushed EMBEDA Compared to Crushed ER Morphine Sulfate (Study 3)

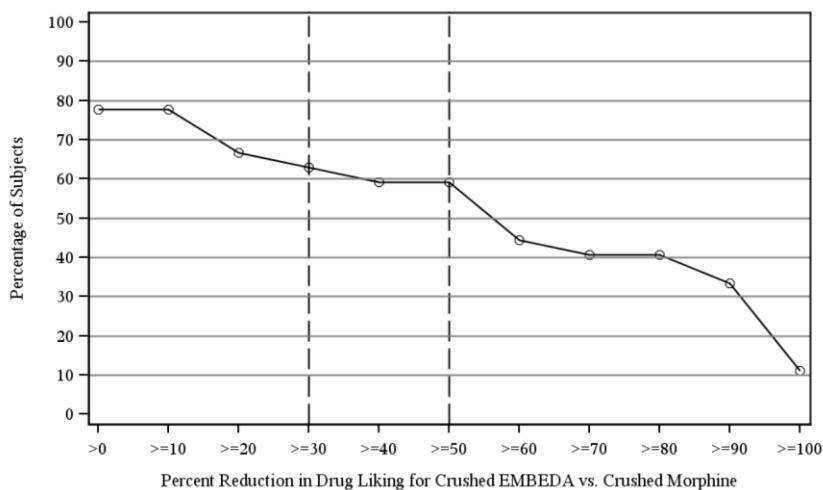
VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (30 mg/1.2 mg)	Crushed ER Morphine (30 mg)
Drug Liking*	Mean (SE)	69.0 (3.5)	88.4 (3.2)
	Median (range)	66 (50-100)	100 (51-100)
Drug High**	Mean (SE)	48.6 (7.8)	84.4 (3.8)
	Median (range)	51 (-39-100)	100 (42-100)
Take Drug Again*	Mean (SE)	59.1 (5.4)	87.0 (4.0)
	Median (range)	56 (0-100)	100 (12-100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

**Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).

E_{max} = maximal response; ER = extended release; SE = standard error.

Figure 2: Percent Reduction Profiles for E_{max} of Drug Liking VAS for EMBEDA vs. Morphine Following Intranasal Administration in Study 3.



Simulated IV Study

Study 4, a randomized double-blind, placebo-controlled, three-way cross-over trial in 28 non-dependent recreational opioid users, was performed using 30 mg of intravenous (IV) morphine sulfate alone and 30 mg of IV morphine sulfate in combination with 1.2 mg of

IV naltrexone to simulate parenteral use of crushed EMBEDA. These doses were based on the assumption of the complete release of both morphine sulfate and naltrexone hydrochloride upon crushing EMBEDA. Intravenous administration of the combination of morphine sulfate and naltrexone hydrochloride was associated with statistically significantly lower mean and median Drug Liking and Drug High scores (median scores 34 and 23, respectively) compared with morphine alone (median scores 86 and 89, respectively). Three of the 26 subjects who completed the study had no reduction in Drug Liking and all the subjects showed some reduction in Drug High. Intravenous injection of crushed EMBEDA may result in serious injury and death due to a morphine overdose and may precipitate a severe withdrawal syndrome in opioid-dependent patients.

Summary

The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride. These data along with results from the oral and intranasal human abuse potential studies indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route. However, abuse of EMBEDA by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of EMBEDA on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

A human abuse potential study of intravenous morphine and naltrexone to simulate crushed EMBEDA demonstrated lower Drug Liking and Drug High compared with morphine alone. However, it is unknown whether these results with simulated crushed EMBEDA predict a reduction in abuse by the IV route until additional postmarketing data are available.

EMBEDA contains morphine sulfate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. EMBEDA can be abused and is subject to misuse, addiction, and criminal diversion

OXYCONTIN (oxycodone hydrochloride) extended-release tablets [NDA 022272]

Approval Date: April 5, 2010

Abuse Deterrence Labelling Update: April 16, 2013

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCONTIN".

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely

crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 4.

Table 4: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

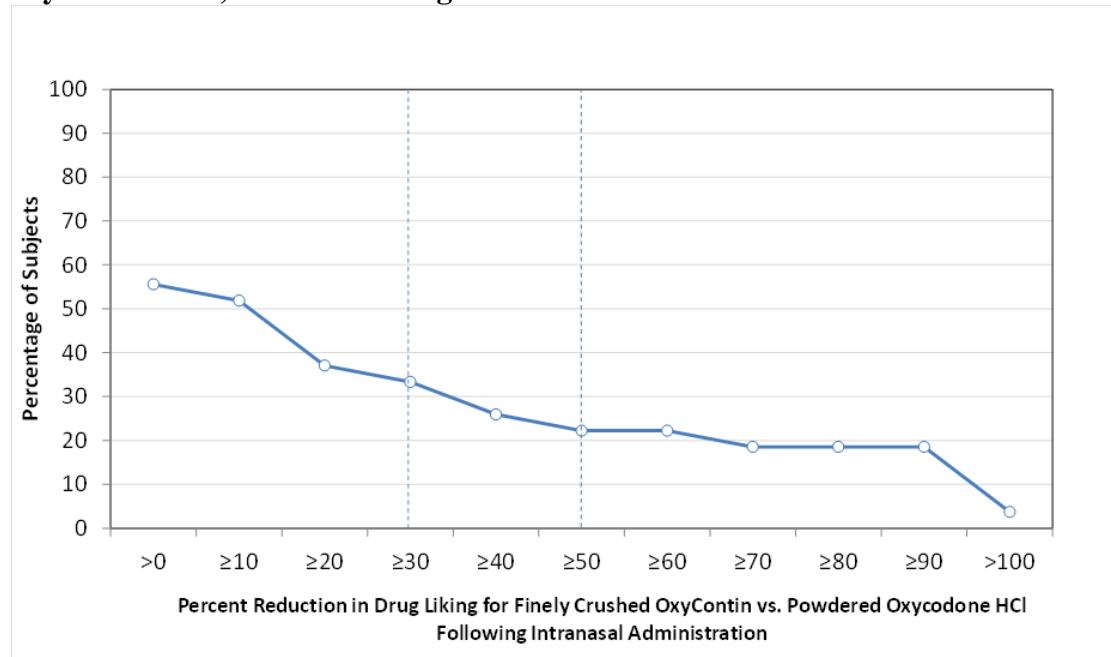
VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of

subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl,

hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride) extended-release tablets [NDA 205777]

Approval Date: July 23, 2014

Abuse Deterrence Studies

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the controlled-release formulation of TARGINIQ ER and separating the oxycodone component from naloxone, a potent opioid antagonist. Laboratory test data demonstrate that TARGINIQ ER can be crushed and dissolved in solution. However, complete separation or complete inactivation of naloxone from oxycodone was not achieved despite using various techniques and conditions.

Clinical Abuse Potential Studies

In the clinical abuse potential studies described below, drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”). Response to subjective feeling of getting “high” was measured on a unipolar scale of 0 to 100, where 0 represents “definitely not” and 100 represents “definitely so”.

Study in Non-Dependent, Opioid Abusers (Intranasal (IN) Administration)

In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 23 non-dependent, opioid abusers with moderate experience with opioids received IN administered TARGINIQ ER 40 mg/20 mg (finely crushed tablets), oxycodone HCl 40 mg powder (active control), and placebo treatments.

IN administration of finely crushed TARGINIQ ER was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to powdered oxycodone HCl, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 5.

Table 5. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal (IN) Administration of TARGINIQ ER, Oxycodone, and Placebo in Non-Dependent, Opioid Abusers (N=23)

VAS		TARGINIQ ER 40 mg/20 mg (finely crushed)	Oxycodone HCl 40 mg (powdered)	Placebo (lactose powder)
Drug Liking*	Mean (SE)	59.1 (2.8)	94.8 (2.2)	53.2 (2.1)
	Median (Range)	51 (50-100)	100 (61-100)	51 (50-100)
Take Drug Again**	Mean (SE)	42.6 (6.4)	93.6 (2.3)	30.7 (6.1)
	Median (Range)	50.0 (0-100)	100 (62-100)	50 (0-100)

VAS: visual analog scale

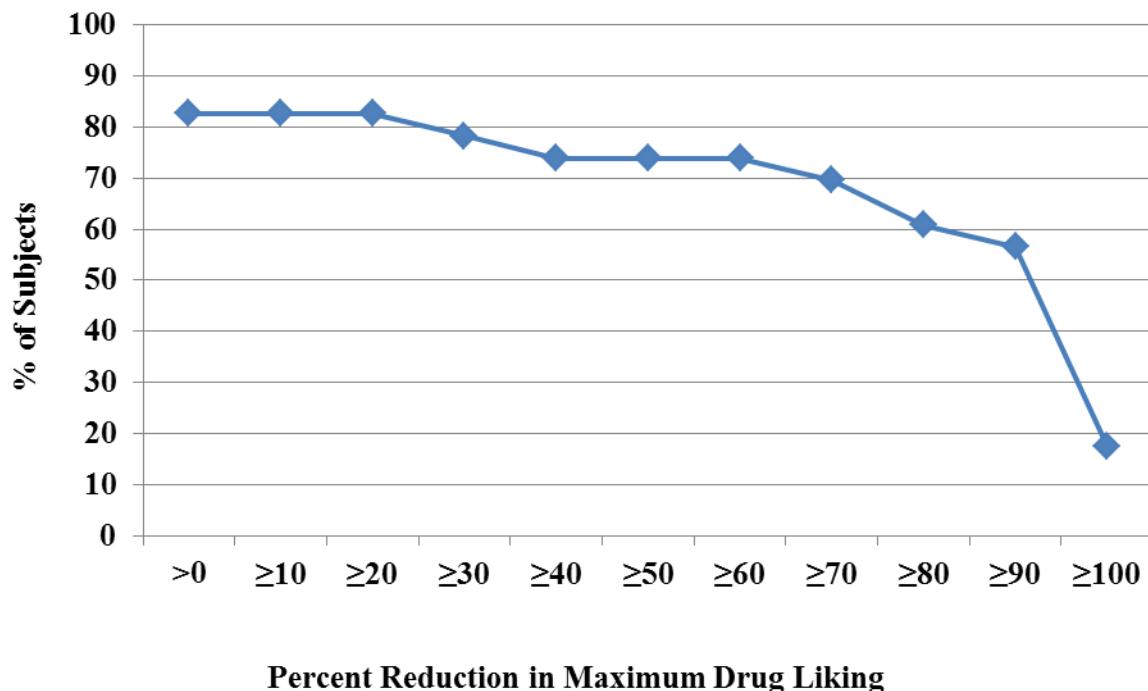
SE: standard error

* Drug Liking Question text: “At this moment, my liking for this drug is”; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.

**Take Drug Again Question text: “I would take this drug again”; scale: 0 = definitely not, 100 = definitely so.

Figure 1 demonstrates a comparison of maximum drug liking for finely crushed TARGINIQ ER compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in maximum drug liking for TARGINIQ ER vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Among non-dependent, opioid drug abusers, 78% (n = 18) of subjects had a reduction of at least 30% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl, and approximately 74% (n = 17) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl.

Figure 1. Percent Reduction in Maximum Drug Liking for Finely Crushed TARGINIQ ER 40 mg/20 mg vs. Powdered Oxycodone HCl 40 mg Following Intranasal Administration in Non-Dependent Opioid Abusers



Study in Non-Dependent, Opioid Abusers (Intravenous (IV) Administration)
 In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 22 non-dependent, opioid abusers with moderate experience with opioids received intravenously administered 0.07 mg/kg oxycodone HCl and 0.035 mg/kg naloxone HCl solution (simulated version of TARGINIQ ER), oxycodone HCl (0.07 mg/kg solution; active control) and placebo (saline) treatments.

The intravenous administration of simulated TARGINIQ ER solution was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 6.

Table 6. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again Following IV Administration of Oxycodone HCl + Naloxone HCl (Simulated TARGINIQ ER Solution), Oxycodone HCl, and Placebo in Non-Dependent, Opioid Abusers (N=22)

VAS		Oxycodone HCl/ Naloxone HCl 0.07/0.35 mg/kg	Oxycodone HCl 0.07 mg/kg	Placebo saline (0.9% NaCl)
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Drug Liking*	Mean (SE)	56.5 (2.8)	96.4 (2.3)	48.7 (2.3)
	Median (Range)	51 (50-100)	100 (50-100)	51.0 (0-53)
Take Drug Again**	Mean (SE)	37.0 (6.2)	82.0 (6.0)	34.5 (5.1))
	Median (Range)	50.0 (0-100)	99.0 (0-100)	50.0 (0-55)

VAS: visual analog scale

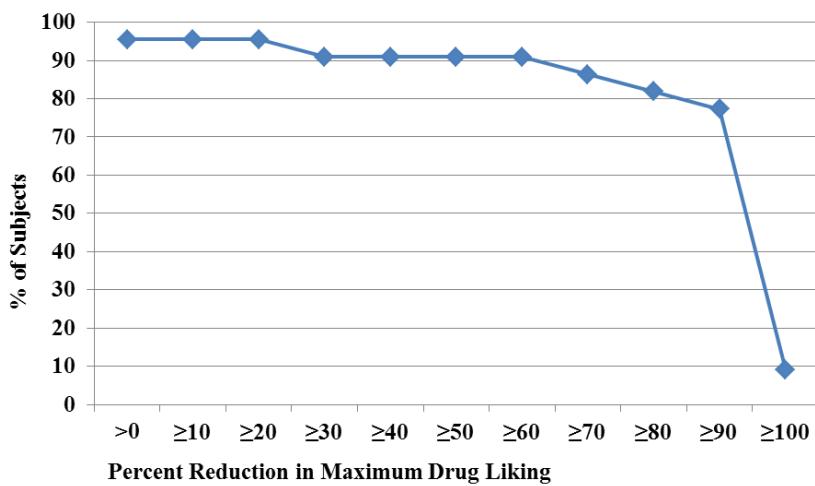
SE: standard error

* Drug Liking Question text: “At this moment, my liking for this drug is”; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.

**Take Drug Again Question text: “I would take this drug again”; scale: 0 = definitely not, 100 = definitely so; Values obtained at 8 hours post dose.

Figure 2 demonstrates a comparison of maximum drug liking for simulated TARGINIQ ER solution compared to oxycodone HCl solution in subjects who received both treatments. Among non-dependent, opioid drug abusers, approximately 91% (n = 20) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone solution.

Figure 2. Percent Reduction in Maximum Drug Liking for Oxycodone 0.07 mg/kg + Naloxone 0.035 mg/kg (Simulated TARGINIQ ER) vs. Oxycodone HCl 0.07 mg/kg Following Intravenous Administration in Non-Dependent, Opioid Abusers



Study in Opioid-Dependent Subjects

In a randomized, double-blind, placebo- and positive-controlled, 4-period crossover pharmacodynamic study, 29 opioid-dependent, methadone-maintained subjects received orally administered TARGINIQ ER 60 mg/30 mg chewed and intact tablets, oxycodone HCl solution 60 mg (active control) and placebo (chewed and intact tablets and solution) treatments.

The oral administration of TARGINIQ ER, either chewed or intact, was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower scores for take drug again ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 7.

Table 7. Summary of High, Maximum Drug Liking (E_{max}), and Take Drug Again Following Oral Administration of TARGINIQ ER (Intact and Chewed), Oxycodone HCl solution, and Placebo in Opioid-Dependent Subjects (N=29)

VAS		TARGINIQ ER 60 mg/30 mg intact	TARGINIQ ER 60 mg/30 mg chewed	Oxycodone HCl solution 60 mg	Placebo chewed and intact tablet, solution
Drug Liking*	Mean (SE)	54.7 (2.0)	54.6 (3.2)	77.9 (3.8)	54.4 (2.1)
	Median (Range)	51.0 (50-99)	51.0 (0-100)	78.0 (50-100)	51.0 (50-100)
Take Drug Again**	Mean (SE)	38.5 (5.7)	32.6 (5.9)	61.4 (5.9)	41.5 (5.0)
	Median (Range)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)
Getting High***	Mean (SE)	20.6 (5.1)	27.7 (6.5)	77.9 (5.0)	20.6 (5.0)
	Median (Range)	1.0 (0-73)	1.0 (0-100)	86.0 (0-100)	1.0 (0-82)

VAS: visual analog scale

SE: standard error

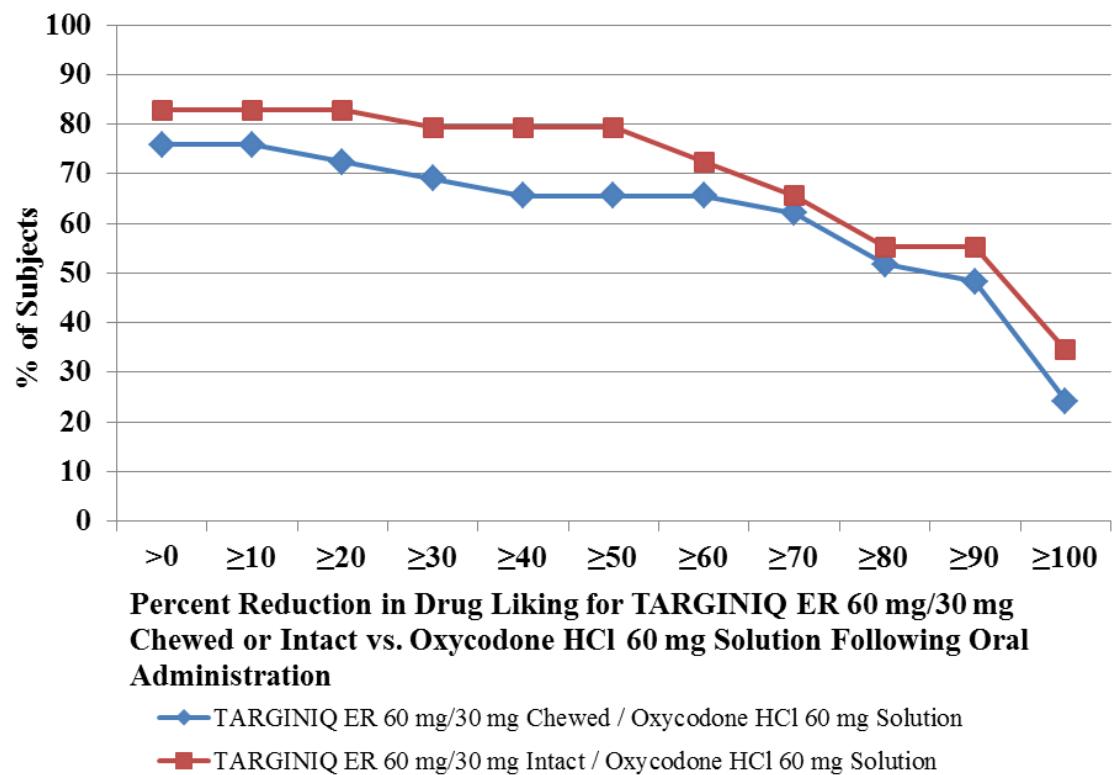
* Drug Liking Question text: “At this moment, my liking for this drug is”; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.

**Take Drug Again Question text: “I would take this drug again”; scale: 0 = definitely not, 100 = definitely so; Values obtained at 12 hours post dose.

***Getting High Question Text: “I am feeling high”; scale: 0 = definitely not, 100 = definitely so.

Figure 3 demonstrates a comparison of maximum drug liking (E_{max}) for TARGINIQ ER either chewed or intact compared to oxycodone solution in subjects who received both treatments. Among opioid-dependent subjects, 69.0% ($n = 20$) had a reduction of at least 30%, and 65.5% ($n = 19$) of subjects had a reduction of at least 50% in maximum drug liking with chewed TARGINIQ ER tablets compared to oxycodone solution; 79.3% ($n = 23$) of subjects had a reduction at least 50% in maximum drug liking with intact TARGINIQ ER tablets compared to oxycodone solution.

Figure 3. Percent Reduction in Maximum Drug Liking for TARGINIQ ER 60 mg/30 mg Chewed or Intact vs. Oxycodone HCl 60 mg Solution Following Oral Administration in Opioid-Dependent Subjects



Summary

Based on the *in vitro* study results, it is expected that abuse of oxycodone from physically and chemically manipulated TARGINIQ ER tablets will be deterred by the inability to separate the two active components.

The data from the clinical abuse potential studies indicate that TARGINIQ ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration. However, abuse of TARGINIQ ER by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of TARGINIQ ER on the abuse liability of the drug in the community. Accordingly, this section may be updated in the future as appropriate.

TARGINIQ ER contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. TARGINIQ ER can be abused and is subject to misuse, addiction, and criminal diversion

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets [NDA 206627]

Approval Date: November 20, 2014

Abuse Deterrence Studies

HYSINGLA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised. To evaluate the ability of these physicochemical properties to reduce the potential for abuse of HYSINGLA ER, a series of in vitro laboratory studies, pharmacokinetic studies and clinical abuse potential studies was conducted. A summary is provided at the end of this section.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that HYSINGLA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When subjected to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies

Studies in Non-dependent Opioid Abusers

Two randomized, double-blind, placebo and active-comparator studies in non-dependent opioid abusers were conducted to characterize the abuse potential of HYSINGLA ER following physical manipulation and administration via the intranasal and oral routes. For both studies, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Intranasal Abuse Potential Study

In the intranasal abuse potential study, 31 subjects were dosed and 25 subjects completed the study. Treatments studied included intranasally administered tampered HYSINGLA ER 60 mg tablets, powdered hydrocodone bitartrate 60 mg, and placebo. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 82% (n = 23) of subjects receiving tampered HYSINGLA ER compared to no subjects with powdered hydrocodone or placebo.

The intranasal administration of tampered HYSINGLA ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 3.

Table 3. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following intranasal Administration of HYSINGLA ER and Hydrocodone Powder in Non-dependent Opioid Abusers

VAS Scale (100 point)	HYSINGLA ER Manipulated	Hydrocodone Powder
<i>Intranasal (n=25)</i>		
Drug Liking*		
Mean (SE)	65.4 (3.7)	90.4 (2.6)
Median (Range)	56 (50–100)	100 (51–100)
Take Drug Again**		
Mean (SE)	36.4 (8.2)	85.2 (5.0)
Median (Range)	14 (0–100)	100 (1–100)

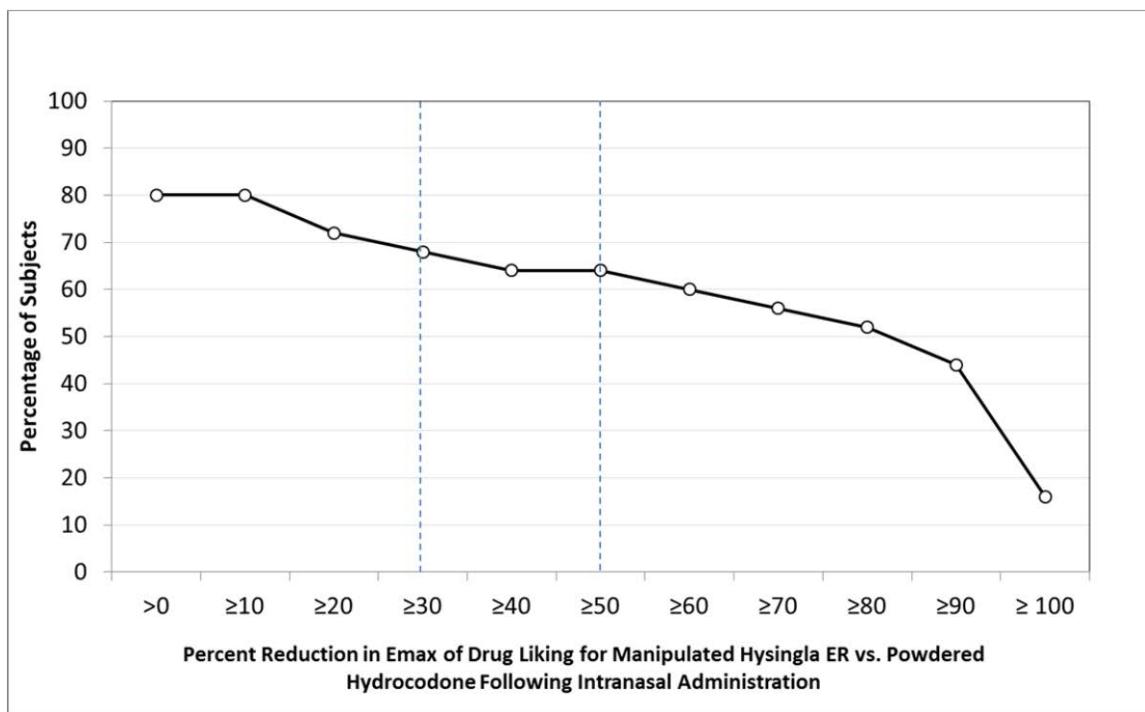
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 1 demonstrates a comparison of peak drug liking scores for tampered HYSINGLA ER compared with powdered hydrocodone in subjects ($n = 25$) who received both treatments intranasally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for tampered HYSINGLA ER vs. hydrocodone powder greater than or equal to the value on the X-axis.

Approximately 80% ($n = 20$) of subjects had some reduction in drug liking with tampered HYSINGLA ER relative to hydrocodone powder. Sixty-eight percent ($n = 17$) of subjects had a reduction of at least 30% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder, and approximately 64% ($n = 16$) of subjects had a reduction of at least 50% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder. Approximately 20% ($n = 5$) of subjects had no reduction in liking with tampered HYSINGLA ER relative to hydrocodone powder.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Manipulated HYSINGLA ER vs. Hydrocodone Powder, N = 25 Following Intranasal Administration



Oral Abuse Potential Study

In the oral abuse potential study, 40 subjects were dosed and 35 subjects completed the study. Treatments studied included oral administrations of chewed HYSINGLA ER 60 mg tablets, intact HYSINGLA ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo.

The oral administration of chewed and intact HYSINGLA ER was associated with statistically lower mean and median scores on scales that measure drug liking and desire to take drug again ($P<0.001$), compared to hydrocodone solution as summarized in Table 4.

Table 4. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following Oral Administration of HYSINGLA ER and Hydrocodone Solution in Non-dependent Recreational Opioid Users

VAS Scale (100 point) Oral (n=35)	HYSINGLA ER Intact	Chewed	Hydrocodone Solution
Drug Liking*			
Mean (SE)	63.3 (2.7)	69.0 (3.0)	94.0 (1.7)
Median (Range)	58 (50–100)	66 (50–100)	100 (51–100)
Take Drug Again**			
Mean (SE)	34.3 (6.1)	44.3 (6.9)	89.7 (3.6)
Median (Range)	24 (0–100)	55 (0–100)	100 (1–100)

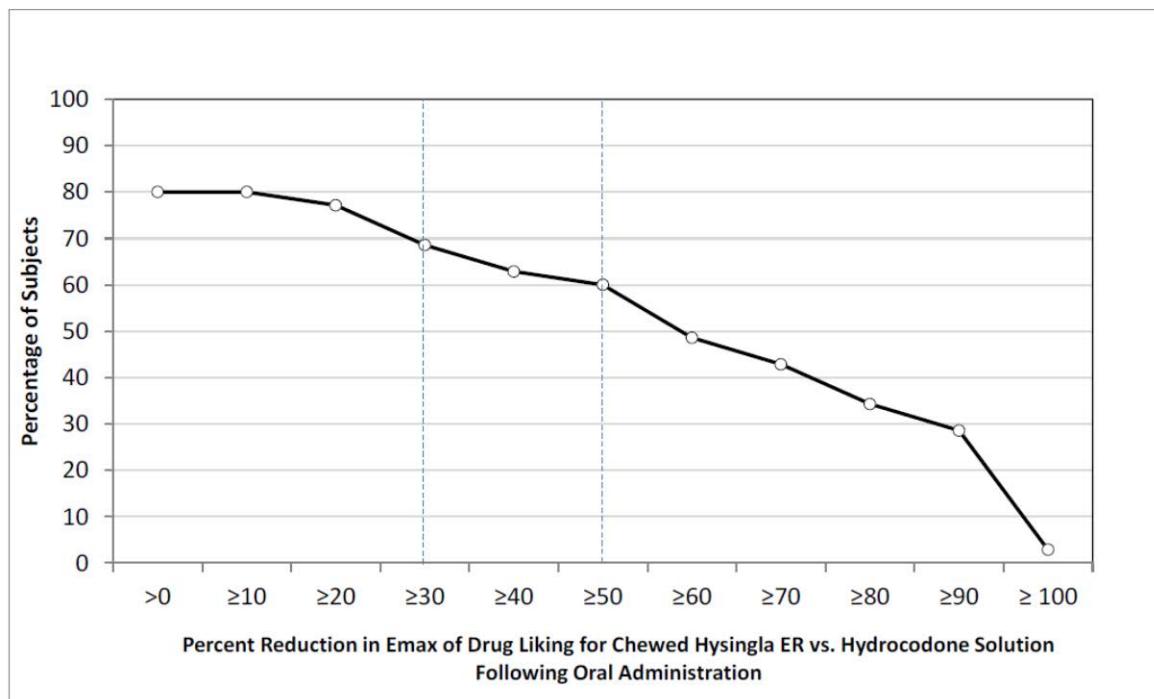
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 2 demonstrates a comparison of peak drug liking scores for chewed HYSINGLA ER compared with hydrocodone solution in subjects who received both treatments orally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for chewed HYSINGLA ER vs. hydrocodone solution greater than or equal to the value on the X-axis.

Approximately 80% (n = 28) of subjects had some reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution. Approximately 69% (n = 24) of subjects had a reduction of at least 30% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution, and approximately 60% (n = 21) of subjects had a reduction of at least 50% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution. Approximately 20% (n = 7) of subjects had no reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution.

Figure 2. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed HYSINGLA ER vs. Hydrocodone Solution, N = 35 Following Oral Administration



The results of a similar analysis of drug liking for intact HYSINGLA ER relative to hydrocodone solution were comparable to the results of chewed HYSINGLA ER relative to hydrocodone solution. Approximately 83% (n = 29) of subjects had some reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution. Eighty-three percent (n = 29) of subjects had a reduction of at least 30% in peak drug liking scores with intact HYSINGLA ER compared to hydrocodone solution, and approximately 74% (n = 26) of subjects had a reduction of at least 50% in peak drug liking scores with intact HYSINGLA ER compared with hydrocodone solution. Approximately 17% (n = 6) had no reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution.

Summary

The in vitro data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion

MORPHABOND (morphine sulfate) extended-release tablets [NDA 206544]

Approval Date: October 2, 2015

Abuse Deterrence Studies

MORPHABOND is formulated with inactive ingredients that make the tablet more difficult to adulterate for misuse and abuse while maintaining extended-release characteristics even if the tablet is subjected to physical manipulation, and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of MORPHABOND, a series of in vitro laboratory manipulation, extraction, and syringeability, studies was conducted. An in vivo clinical abuse potential study was also conducted. The results of these studies are summarized below. Overall, the results indicate that MORPHABOND has properties that are expected to reduce abuse or misuse via injection or insufflation; however, abuse by these routes is still possible.

In Vitro Testing

MORPHABOND has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of extended-release opioids for administration by various routes, including oral consumption, intranasal insufflation, injection, and smoking.

Abusers may manipulate extended-release opioids in order to prepare the tablets for oral, intranasal, or intravenous administration. The laboratory test data demonstrated that, relative to morphine sulfate extended-release tablet, MORPHABOND has increased resistance to cutting, crushing, or breaking using a variety of tools. When subjected to a liquid environment the manipulated MORPHABOND formulation forms a viscous material that resists passage through a needle.

Clinical Studies

A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in 25 non-dependent recreational opioid users with a history of intranasal drug abuse was

performed to determine the relative bioavailability and abuse potential of crushed intranasal MORPHABOND 60 mg tablets compared with crushed intranasal morphine sulfate extended-release tablet 60 mg tablets, and intact orally administered MORPHABOND 60 mg tablets. The intact oral tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route.

Drug liking was measured on a 100 mm bipolar visual analog scale (VAS) where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ('definitely would not take drug again') and 100 represents the strongest positive response ('definitely would take drug again').

Intranasal administration of crushed MORPHABOND was associated with statistically significantly lower drug liking (E_{max}) scores ($P < 0.0001$), and significantly lower willingness to take the drug again (E_{max}) scores ($P = 0.034$), compared to crushed extended-release morphine (Table 2). Drug liking and take drug again scores for crushed intranasal MORPHABOND were not significantly different from those of MORPHABOND taken orally intact. These data are consistent with the similar relative bioavailability after crushed intranasal and intact oral administration of MORPHABOND that support retention of its extended release properties when manipulated compared to morphine sulfate extended-release tablets

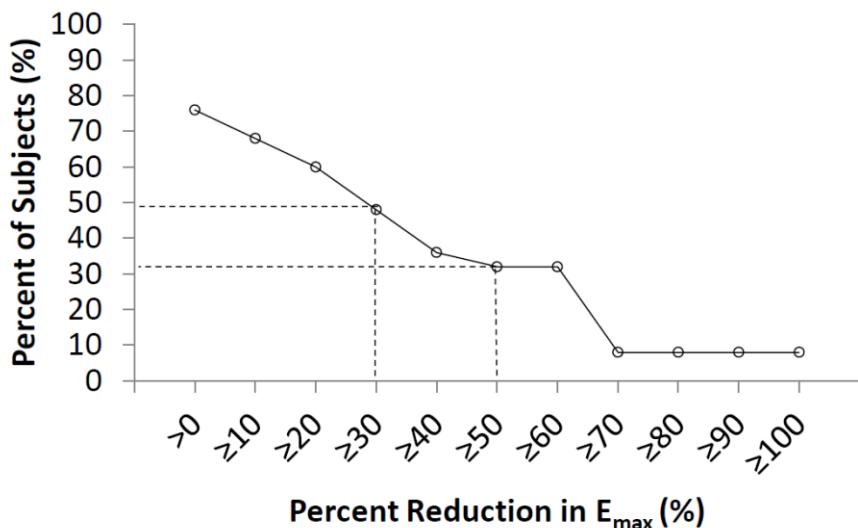
Table 2. **Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Administration of MORPHABOND, morphine sulfate extended-release tablet, and Placebo in Recreational Opioid Users (n=25)**

		Crushed Intranasal MORPHABOND 60 mg	Crushed Intranasal morphine sulfate extended-release tablet 60 mg	Placebo	Crushed Intranasal morphine sulfate extended-release tablet vs. Crushed Intranasal MORPHABOND Difference of LS Means (95% CI)
Drug Liking (E_{max})	Mean (SEM)	71.7 (2.87)	85.3 (2.42)	54.3 (1.63)	13.65 (7.80, 19.51)
	Median (Range)	72 (50-100)	85 (56-100)	51 (50-80)	
Take Drug Again (E_{max})	Mean (SEM)	66.4 (3.76)	76.4 (4.17)	49.1 (2.21)	9.96 (0.77, 19.14)
	Median (Range)	64.0 (38-100)	75.0 (17-100)	50.0 (0-64)	

Figure 1 demonstrates a comparison of peak drug liking scores for crushed MORPHABOND compared to crushed extended-release morphine in subjects who received both treatments intranasally. Seventy-six percent of subjects (n = 19) experienced some reduction in E_{max} of Drug Liking VAS with crushed MORPHABOND compared with crushed extended-release

morphine, 48%; (n = 12) experienced at least a 30% reduction in E_{max} and 32% (n = 8) experienced at least a 50% reduction in E_{max} of drug liking.

Figure 1. Percent Reduction Profiles for E_{max} of Drug Liking for MORPHABOND vs. Morphine Sulfate ER Tablets (n=25), Following Intranasal Administration



Summary

The in vitro data demonstrate that MORPHABOND has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by intranasal, intravenous, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of MORPHABOND on the abuse liability of the drug.

XTAMPZA ER (oxycodone) extended-release capsules [NDA 208090]

Approval Date: April 26, 2016

Abuse Deterrence Studies

XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the success of different methods of defeating the extended-release formulation.

Results support that, relative to immediate-release oxycodone tablets, XTAMPZA ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents.

XTAMPZA ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.

Pharmacokinetic Studies

The pharmacokinetic profile of manipulated XTAMPZA ER capsule contents (36 mg; [equivalent to 40 mg oxycodone HCl]) was characterized following oral (two studies) and intranasal (two studies) administration. The studies were conducted in a randomized, cross-over design. In studies assessing manipulation by crushing, the most effective crushing method identified in previous *in vitro* studies was applied to the product(s).

Oral Pharmacokinetic Studies, Manipulated and Intact XTAMPZA ER

The effect of two types of product manipulation (crushing and chewing) on XTAMPZA ER pharmacokinetics was measured in two studies.

In Oral Pharmacokinetic Study 1, XTAMPZA ER capsule contents were crushed or chewed prior to oral administration in healthy, naltrexone blocked volunteers. The two comparators in this study were intact XTAMPZA ER capsules and an immediate-release solution of oxycodone.

In Oral Pharmacokinetic Study 2, XTAMPZA ER capsule contents were crushed prior to oral administration in healthy, naltrexone-blocked volunteers. The comparators in this study included intact XTAMPZA ER capsules and crushed immediate-release oxycodone tablets.

The pharmacokinetic data displayed in Table 3 illustrate the findings from these two studies. Collectively, the data from the two studies demonstrated that crushing or chewing XTAMPZA ER prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure (AUC_{0-INF}) relative to dosing the intact product under fed conditions. Relative to immediate-release oxycodone, the C_{max} for all XTAMPZA ER treatments was significantly lower and the T_{max} significantly longer, consistent with an extended-release profile.

Table 3: Oxycodone Pharmacokinetic Parameters, Administration of Manipulated Capsule Contents and Intact Capsules (36 mg)

	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-INF} (hr·ng/mL)	
Treatment		Oral Pharmacokinetic Study 1		
Intact XTAMPZA ER Capsules (fed)	62.3 (13.0)	4.0 (1.5-6)	561 (124)	
Crushed XTAMPZA ER Capsule Contents (fed)	57.6 (12.6)	4.5 (2.5-6)	553 (134)	
Chewed XTAMPZA ER Capsule Contents (fed)	55.6 (10.9)	4.5 (2.5-8)	559 (113)	
Immediate-Release Oxycodone Solution (fasted)	115 (27.3)	0.75 (0.5-2)	489 (80.2)	
		Oral Pharmacokinetic Study 2		
Intact XTAMPZA ER Capsules (fed)	67.5 (17.6)	3.5 (1.25 – 6.0)	581 (138)	
Crushed XTAMPZA ER Capsule Contents (fed)	62.9 (12.6)	4.0 (2.0 – 7.0)	597 (149)	
Crushed Immediate-Release Oxycodone Tablets (fed)	79.4 (17.1)	1.75 (0.5-4.0)	561 (146)	

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Studies

The pharmacokinetic profile following intranasal administration of crushed XTAMPZA ER capsule contents was characterized in two clinical studies.

In Nasal Pharmacokinetic Study 1, XTAMPZA ER capsule contents were crushed and intranasally administered by non-dependent, naltrexone-blocked subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and oxycodone HCl powder (intranasal) at an equivalent dose.

In Nasal Pharmacokinetic Study 2, XTAMPZA ER capsule contents were crushed and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and crushed oxycodone immediate-release tablets (intranasal) at an equivalent dose.

The results of Nasal Pharmacokinetic Studies 1 and 2 are comparable and both studies demonstrated that intranasal administration of crushed XTAMPZA ER capsule contents did not result in higher peak plasma concentration (C_{max}) or shorter time to peak concentration (T_{max}) than taking XTAMPZA ER orally. The data from Nasal Pharmacokinetic Study 2 are displayed in Table 4 to represent these findings.

Table 4: Pharmacokinetic Parameters, Nasal Pharmacokinetic Study 2:

Treatment	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-INF} (hr·ng/mL)
Intact XTAMPZA ER Capsules (oral)	41.0 (10.0)	5.1 (1.6-8.1)	477 (89.6)
Crushed XTAMPZA ER Capsule Contents (nasal)	29.8 (6.6)	5.1 (1.6-12.1)	459 (106)
Crushed Immediate-Release Tablets (nasal)	60.9 (11.9)	2.6 (0.3-6.1)	577 (124)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Studies

Oral Abuse Potential Study:

In the Oral Abuse Potential Study, a randomized, double-blind, active- and placebo-controlled, single-dose, six-way crossover pharmacodynamic study, 61 recreational opioid users with a history of oral drug abuse received orally administered active and placebo treatment. The six treatment arms were intact XTAMPZA ER (36 mg, fed and fasted); chewed XTAMPZA ER (36 mg, fed and fasted); crushed immediate-release oxycodone HCl in water (40 mg, fasted, equivalent to 36 mg of XTAMPZA ER), and placebo. Data for chewed XTAMPZA ER and crushed IR oxycodone in the fasted state are described below.

Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 50 represents a neutral response, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar 100-point VAS where 50 represents a neutral response, 0 represents the strongest negative response (e.g., ‘definitely would not take drug again’), and 100 represents the strongest positive response (e.g., ‘definitely would take drug again’).

Thirty-eight subjects completed the study. The results are summarized in Table 5. The oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with statistically lower mean Drug Liking scores compared with crushed immediate-release oxycodone. However, the differences for XTAMPZA ER chewed and intact compared with crushed immediate-release oxycodone for the Take Drug Again scores were small and not statistically significant.

Table 5: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Oral Administration

		XTAMPZA ER Intact (Fasted)	XTAMPZA ER Chewed (Fasted)	Crushed IR Oxycodone (Fasted)	Placebo
Drug Liking* (E_{max})	Mean (SEM)	68.8 (2.11)	73.4 (2.26)	81.8 (1.86)	54.9 (1.37)
	Median (Range)	72 (50-89)	76 (50-95)	83 (50-99)	51 (50-84)
Take Drug Again (E_{max})*	Mean (SEM)	70.2 (2.59)	73.7 (2.42)	75.4 (2.72)	52.7 (2.17)
	Median (Range)	69 (50-98)	74 (50-98)	76 (37-100)	50 (3-95)

* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

Emax = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SEM= standard error of the mean.

Nasal Abuse Potential Study:

In a randomized, double-blind, active- and placebo-controlled, single-dose, four-way crossover pharmacodynamic study, 39 recreational opioid users with a history of intranasal drug abuse received nasally administered active and placebo drug treatment. The four treatment arms were crushed XTAMPZA ER 36 mg dosed intranasally; intact XTAMPZA ER 36 mg dosed orally; crushed immediate-release oxycodone HCl 40 mg (equivalent to 36 mg of XTAMPZA ER) dosed intranasally; and placebo. Data for intranasal XTAMPZA ER and crushed immediate-release oxycodone are described below.

Thirty-six subjects completed the study. Intranasal administration of crushed XTAMPZA ER was associated with statistically lower mean Drug Liking and Take Drug Again scores compared with crushed immediate-release oxycodone (summarized in Table 6).

Table 6: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Intranasal Administration

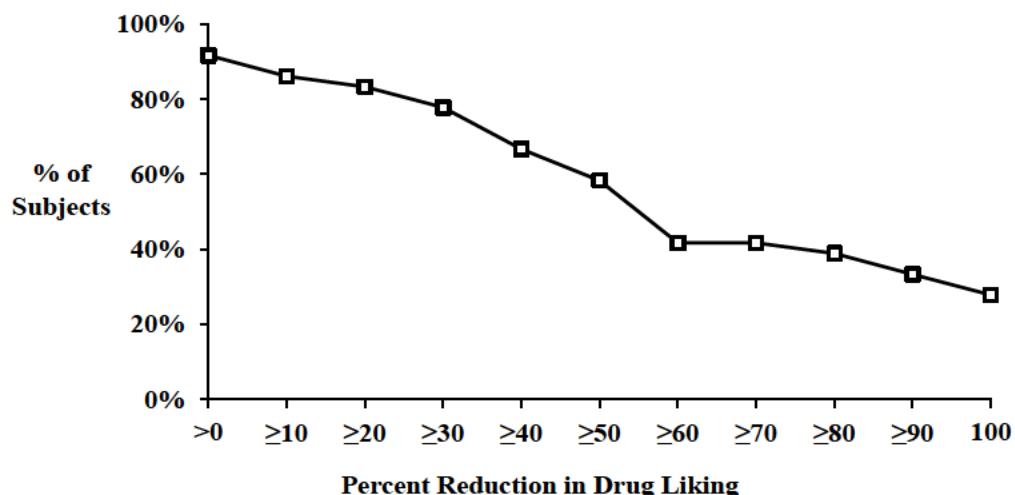
		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SEM)	61.8 (2.6)	82.7 (1.8)	54.5 (2.0)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SEM)	47.7 (4.6)	71.4 (3.9)	45.9 (2.9)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SEM = Standard error of the mean.

Figure 1 demonstrates a comparison of Drug Liking for intranasal administration of crushed XTAMPZA ER compared to crushed immediate-release oxycodone in subjects who received both treatments (N=36). The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for XTAMPZA ER vs. immediate-release oxycodone greater than or equal to the value on the X-axis. Approximately 92% (n = 33) of subjects had some reduction in drug liking with XTAMPZA ER relative to crushed immediate-release oxycodone HCl. 78% (n = 28) of subjects had a reduction of at least 30% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl, and approximately 58% (n = 21) of subjects had a reduction of at least 50% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Crushed XTAMPZA ER vs. Crushed Immediate-release Oxycodone, N=36 Following Intranasal Administration



Summary

The in vitro data demonstrate that XTAMPZA ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the intranasal route. The data from the oral pharmacokinetic studies of manipulated XTAMPZA ER demonstrated a lack of dose dumping with no increase in oxycodone levels compared to intact XTAMPZA ER. Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the oral route.

However, abuse of XTAMPZA ER by injection and by the nasal route of administration, as well as by the oral route is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of XTAMPZA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

XTAMPZA ER contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. XTAMPZA ER can be abused and is subject to misuse, addiction, and criminal diversion

TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules [NDA 207621]

Approval Date: August 19, 2016

Abuse Deterrence Studies

TROXYCA ER is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

In Vitro Testing

In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When TROXYCA ER is crushed and mixed in a variety of solvents, both oxycodone HCl and naltrexone HCl are simultaneously extracted.

Clinical Abuse Potential Studies

Two randomized, double-blind active- and placebo-controlled studies were conducted in non-dependent opioid abusers to characterize the abuse potential of oral or intranasal administration of TROXYCA ER following physical manipulation. A third randomized, double-blind, single-dose, placebo and active-controlled study was conducted with IV administration of simulated crushed TROXYCA ER. For these studies, Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Response to whether the subject would Take Drug Again was measured on a bipolar 100-point VAS where 0 represents strongest negative response (e.g., ‘definitely would not take drug again’), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., ‘definitely would take drug again’).

The pharmacokinetic profiles of oxycodone HCl and naltrexone HCl were also determined in these abuse potential studies. When TROXYCA ER was crushed and administered orally (40 mg/4.8 mg and 60 mg/7.2 mg doses) or intranasally (30 mg/3.6 mg doses), oxycodone HCl and naltrexone HCl were both absorbed rapidly with median time-to-peak concentration (T_{max}) values of approximately 0.6-1 hour and 0.6 hours, respectively, following oral administration and 1.6 hours and 0.3 hours, respectively, following intranasal administration.

Oral Abuse Potential Study

In this study, 31 non-dependent, recreational opioid abusers received all six treatments by the oral route: crushed 40 mg/4.8 mg TROXYCA ER in solution, crushed 40 mg immediate-release (IR) oxycodone HCl in solution, intact 60 mg/7.2 mg TROXYCA ER, crushed 60 mg/7.2 mg TROXYCA ER in solution, crushed 60 mg IR oxycodone HCl in solution, and placebo. When 40 mg/4.8 mg TROXYCA ER and 60 mg/7.2 mg TROXYCA ER were crushed and taken orally, the geometric mean (SD) values for naltrexone HCl C_{max} were 1074 (1463) pg/mL and 1810 (2450) pg/mL respectively; the AUC_{0-2h} values were 1217 (1471) and

2010 (1839) pg·h/mL, and the AUC_{inf} values were 2877 (2834) pg·h/mL and 4695 (3714) pg·h/mL, respectively.

Oral administration of crushed 40 mg/4.8 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed 40 mg IR oxycodone HCl. Oral administration of crushed 60 mg/7.2 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking E_{max} compared to crushed 60 mg IR oxycodone HCl. The mean and median Take Drug Again E_{max} for crushed 60 mg/7.2 mg TROXYCA ER compared with crushed 60 mg IR oxycodone HCl was numerically lower; however, this finding did not reach statistical significance. The results from this study are summarized in Table 6.

Among the 31 subjects who received both TROXYCA ER and IR oxycodone by the oral route, 74% (23) and 77% (24) experienced some reduction in Drug Liking E_{max} with crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone, while 26% (8) and 23% (7) of subjects had no reduction in Drug Liking E_{max} for crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone. With crushed 40 mg/4.8 mg TROXYCA ER, 65% (20) of subjects had at least a 30% reduction and 55% (17) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 40 mg IR oxycodone. With crushed 60 mg/7.2 mg TROXYCA ER, 61% (19) of subjects had at least a 30% reduction and 45% (14) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 60 mg IR oxycodone.

Table 6. Summary Statistics of Abuse Potential Measures of Drug Liking (E_{max}) and Take Drug Again (E_{max}) following Oral Administration

Bipolar VAS Scale (100 point)		Placebo N=31	TROXYCA ER 40 mg/4.8 mg Crushed N=31	IR Oxycodone 40 mg Crushed N=31	TROXYCA ER 60 mg/7.2 mg Intact N=31	TROXYCA ER 60 mg/7.2 mg Crushed N=31	IR Oxycodone 60 mg Crushed N=31
Drug Liking (E_{max})*	Mean (SE)	51.6 (0.68)	69.5 (3.45)	85.6 (2.94)	59.3 (2.75)	74.3 (3.30)	90.0 (2.46)
	Median (range)	51.0 (50,68)	64.0 (50,100)	94.0 (50,100)	51.0 (50,100)	73.0 (50,100)	100.0 (57,100)
Take Drug Again (E_{max})*	Mean (SE)	45.5 (3.47)	56.7 (6.00)	82.9 (3.66)	47.7 (5.12)	71.1 (5.08)	80.6 (4.56)
	Median (range)	50.0 (0.92)	58.0 (0.100)	90.0 (30,100)	50.0 (0.100)	77.0 (0,100)	90.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Intranasal Abuse Potential Study

In this study, 27 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids received all four treatments by the intranasal route: crushed 30 mg/3.6 mg TROXYCA ER, crushed 30 mg IR oxycodone HCl, crushed placebo sugar spheres and crushed placebo lactose tablets. Placebo sugar spheres and placebo lactose tablets were weight matched to TROXYCA ER or IR oxycodone HCl. When TROXYCA ER was

crushed and taken intranasally, the geometric mean (SD) values for naltrexone HCl C_{max}, AUC_{0-2h}, and AUC_{inf} were 4372 (1409) pg/mL, 5481 (1472) pg·hr/mL, and 10710 (3213) pg·hr/mL, respectively.

Intranasal administration of crushed TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed IR oxycodone HCl (summary statistics for Drug Liking and Take Drug Again in Table 7).

Table 7. Summary Statistics of Abuse Potential Measures for Drug Liking and Take Drug Again with Intranasal Administration of Crushed TROXYCA ER Compared to Crushed IR Oxycodone HCl

VAS Scale (100 point)		Placebo for TROXYCA ER N=27	TROXYCA ER 30 mg/3.6 mg Crushed N=27	Placebo for IR Oxycodone N=27	IR Oxycodone 30 mg Crushed N=27
Drug Liking (E_{max})*	Mean (SE)	51.0 (0.23)	60.3 (2.36)	51.3 (0.65)	93.7 (2.11)
	Median (range)	51.0 (50,56)	55.0 (50,100)	51.0 (50,68)	100.0 (50,100)
Take Drug Again (E_{max})*	Mean (SE)	47.9 (2.92)	58.1 (6.27)	46.5 (3.67)	88.5 (5.18)
	Median (range)	50.0 (0.83)	51.0 (0,100)	50.0 (0.98)	100.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Among 27 subjects who received both TROXYCA ER and IR oxycodone by the intranasal route, 93% (25) experienced some reduction in Drug Liking Emax with crushed TROXYCA ER compared to crushed IR oxycodone, while 7% (2) of subjects had no reduction in Drug Liking Emax for crushed TROXYCA ER compared to crushed IR oxycodone. With crushed TROXYCA ER 93% (25) of subjects had at least a 30% reduction in Drug Liking Emax and 85% (23) of subjects had at least a 50% reduction in Drug Liking Emax compared to crushed IR oxycodone.

Simulated IV Abuse Potential Study

This study in non-dependent recreational opioid abusers compared 20 mg IV oxycodone HCl in combination with 2.4 mg IV naltrexone HCl (to simulate parenteral use of crushed TROXYCA ER) to 20 mg of IV oxycodone HCl and placebo; 29 subjects received all three treatments. These doses were based on the assumption of the complete release of both oxycodone HCl and naltrexone HCl upon crushing TROXYCA ER. Intravenous administration of the combination of oxycodone HCl and naltrexone HCl was associated with statistically significantly lower mean and median Drug Liking and Take Drug Again Emax scores (median scores 51 and 50, respectively) compared with oxycodone alone (median scores 97 and 81, respectively). Among 29 subjects, 90% (26) experienced some reduction in Emax of Drug Liking with simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl, while 10% (3) of subjects had no reduction in Drug Liking Emax for simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl.

Summary

The in vitro and pharmacokinetic data demonstrate that crushing TROXYCA ER pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data along with results from the oral and intranasal human abuse potential studies indicate that TROXYCA ER has properties that are expected to reduce abuse via the oral and intranasal routes. However, abuse of TROXYCA ER by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of TROXYCA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

A human abuse potential study of intravenous oxycodone HCl and naltrexone HCl to simulate crushed TROXYCA ER demonstrated lower Drug Liking and Take Drug Again Emax compared with oxycodone HCl alone. However, it is unknown whether these results with simulated crushed TROXYCA ER predict a reduction in abuse by the IV route until additional postmarketing data are available.

TROXYCA ER contains oxycodone HCl, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol.

TROXYCA ER can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1)*].

ARYMO ER (morphine sulfate) extended-release tablets [NDA 208603]

Approval Date: January 9, 2017

Abuse Deterrence Studies

ARYMO ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.

To evaluate the ability of ARYMO ER to reduce the potential for misuse and abuse, a series of abuse-deterring in vitro laboratory physical manipulation, chemical extraction, and syringeability studies was conducted. An oral pharmacokinetic study and an oral clinical abuse potential study were also conducted.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the extended-release properties. The results of this testing demonstrated that ARYMO ER tablets, in comparison to morphine sulfate extended-release tablets, have increased resistance to cutting, crushing, grinding or breaking using a variety of tools. When subjected to a liquid environment, the manipulated ARYMO ER tablets form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Oral Pharmacokinetic Study

The pharmacokinetic profile of manipulated ARYMO ER was characterized following oral administration. The study was conducted in a randomized cross-over design. The pharmacokinetic profile of manipulated and intact ARYMO ER compared to crushed morphine sulfate extended-release was evaluated in 38 subjects after oral administration. The results are summarized in [Table 2](#) and demonstrate that oral ingestion of manipulated ARYMO ER resulted in a higher Cmax, but similar AUC, when compared to intact ARYMO ER. In addition, manipulated ARYMO ER had a lower Cmax and longer Tmax than crushed morphine sulfate extended-release tablets.

Table 2: Results from Oral Pharmacokinetic Study

PK Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 39)
	Manipulated (n = 38)	Intact (n = 38)	
<i>C</i> max (ng/mL)			
Mean (SD)	28.7 (9.1)	17.8 (6.6)	42.3 (14.3)
Median (Range)	29.2 (12.5, 47.8)	16.7 (8.5, 32.3)	42.2 (14.2, 79.0)
<i>T</i> max (h)			
Median (Range)	2.1 (0.9, 4.2)	4.1 (1.6, 6.1)	0.9 (0.6, 4.1)
<i>AUC</i> 0-∞ (h*ng/mL)			
Mean (SD)	159.3 (36.8)	168.0 (53.6)	182.1 (49.9)
Median (Range)	157.1 (94.5, 215.3)	159.4 (80.9, 274.8)	185.5 (61.8, 284.1)

*C*max = maximum observed plasma concentration; *T*max = time to achieve the maximum observed plasma concentration; *AUC*0-∞ = area under the curve, zero to infinity

Oral Clinical Abuse Potential Study

An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users; 38 subjects completed the study. Treatment arms included manipulated ARYMO ER 60 mg tablets (taken with juice), intact ARYMO ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate extended-release tablets (mixed in juice), and placebo.

The study demonstrated that the oral administration of manipulated ARYMO ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate extended-release tablets. However, the difference between manipulated ARYMO ER and crushed morphine sulfate extended-release tablets for Take Drug Again was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.

These results are summarized in [Table 3](#).

Table 3: Summary of Maximum Scores (E_{max}) for Drug Liking and Take Drug Again VAS¹ Following Oral Administration of Manipulated and Intact ARYMO ER and Crushed Morphine Sulfate Extended-Release in Non-Dependent Recreational Opioid Users

Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 38)	Placebo (n = 38)
	Manipulated (n = 38)	Intact (n = 38)		
Maximum Drug Liking (E_{max})				
Mean (SD)	68.3 (12.3)	63.2 (10.1)	73.3 (9.8)	53.3 (7.8)
Median (Q1, Q3)	67.0 (61.0, 75.0)	62.0 (56.0, 68.0)	74.0 (68.0, 79.0)	50.0 (50.0, 52.0)
Take Drug Again (E_{max})				
Mean (SD)	62.9 (19.6)	54.8 (20.8)	70.1 (17.5)	51.0 (10.2)
Median (Q1, Q3)	61.5 (51.0, 71.0)	56.0 (50.0, 65.0)	68.0 (56.0, 80.0)	50.0 (50.0, 50.0)

¹ 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)

Summary

The in vitro data demonstrate that ARYMO ER has physical and chemical properties expected to make abuse by injection difficult.

Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that ARYMO ER has physical and chemical properties that are expected to reduce abuse via the oral route.

Abuse of ARYMO ER by injection, as well as by the oral and nasal routes, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of ARYMO ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

VANTRELA ER (hydrocodone bitartrate) extended-release tablets [NDA 207975]

Approval Date: January 17, 2017

Abuse Deterrence Studies

VANTRELA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results

support that VANTRELA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When VANTRELA ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.

Pharmacokinetics of Manipulated Tablets

The pharmacokinetic profile of manipulated VANTRELA ER tablet contents was characterized following oral and intranasal administration. The studies were conducted in a randomized, crossover design and are described in the section on Clinical Abuse Potential Studies. In the oral study assessing manipulation by crushing, the most effective crushing method identified in previous *in vitro* studies was applied to the product(s). For the intranasal study, VANTRELA ER tablets were manipulated to produce a powder suitable for nasal insufflation.

Oral Pharmacokinetic Data

The effect of product manipulation (crushing) on VANTRELA ER pharmacokinetics was measured in an oral clinical abuse potential study. VANTRELA ER tablets were crushed prior to oral administration in healthy, nondependent recreational opioid users. The two comparators in this study were intact VANTRELA ER tablets and an immediate-release hydrocodone powder.

The pharmacokinetic data displayed in Table 4 illustrate the findings from this study. The data demonstrated that crushing VANTRELA ER tablets prior to administration increased the maximum observed plasma concentration (C_{max}) but not the total exposure (AUC_{0-inf}) relative to dosing the intact product. Relative to immediate-release hydrocodone, the C_{max} for all VANTRELA ER treatments was significantly lower and the T_{max} significantly longer, consistent with an extended-release profile.

Table 4: Hydrocodone Pharmacokinetic Parameters, Oral Administration (45 mg)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-inf} (hr*ng/mL)
45 mg Vantrela ER intact	28.77 (6.1)	7.1 (6.1 - 12.0)	584 (124.8)
45 mg Vantrela ER finely crushed	40.78 (10.2)	4.0 (1.8 - 7.0)	586 (138.5)
45 mg immediate- release hydrocodone powder	91.46 (16.8)	0.8 (0.3 - 4.1)	625 (137.3)

Values shown for C_{max} and AUC_{0-inf} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Data

The pharmacokinetic profile following intranasal administration of manipulated VANTRELA ER tablet contents was characterized in a nasal clinical abuse potential study. VANTRELA ER tablets were finely milled and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. Two comparators in this study were intact VANTRELA ER tablets (oral) and immediate-release hydrocodone powder (intranasal) at an equivalent dose.

The results of the study demonstrated that intranasal administration of manipulated VANTRELA ER tablet contents resulted in higher peak plasma concentration (C_{max}) and shorter time to peak concentration (T_{max}) than taking VANTRELA ER orally and lower C_{max} and longer T_{max} than taking hydrocodone powder intranasally. The pharmacokinetic data from this nasal clinical abuse potential study are displayed in Table 5 to represent these findings.

Table 5: Hydrocodone Pharmacokinetic Parameters, Nasal and Oral Administration

Treatment	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-inf} (hr*ng/mL)
45 mg intact Vantrela ER Tablets (oral)	25.05 (7.18)	9.11 (4.10 -12.12)	568 (172)
45 mg Vantrela ER finely milled (nasal)	56.84 (15.1)	2.62 (1.33 - 7.02)	572 (150)
45 mg immediate-release hydrocodone powder (nasal)	71.28 (30.5)	1.38 (0.60 - 7.07)	579 (163)

Values shown for C_{max} and AUC_{0-inf} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Abuse Potential Studies

Two randomized, double-blind active- and placebo-controlled studies were conducted in nondependent opioid abusers to characterize the abuse potential of oral or intranasal administration of VANTRELA ER following physical manipulation. For both studies, Drug Liking was measured on a bipolar drug-liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would Take Drug Again was measured on a bipolar scale of 0 to 100 where 0 represents the strongest negative response (“definitely would not take drug again”), 50 represents a neutral response, and 100 represents the strongest positive response (“definitely would take drug again”).

Oral Abuse Potential Study

In a randomized, double-blind, placebo- and active-controlled, 4-period crossover study in nondependent opioid abusers, 35 of the 49 enrolled subjects completed all treatment conditions: 45 mg VANTRELA ER (intact), 45 mg VANTRELA ER (finely crushed), 45 mg hydrocodone bitartrate powder (immediate release (IR) condition), and placebo.

The oral administration of finely crushed VANTRELA ER was associated with statistically significantly lower mean scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 6.

Table 6: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Oral Administration

Measure	Statistic	Placebo (N=35)	Hydrocodone IR 45 mg (N=35)	VANTRELA ER 45 mg (finely crushed) (N=35)	VANTRELA ER 45 mg (intact) (N = 35)
Drug Liking	Mean (SE)	53.4 (1.80)	85.0 (2.31)	65.6 (2.46)	54.5 (1.02)
Measure	Statistic	Placebo (N=35)	Hydrocodone IR 45 mg (N=35)	VANTRELA ER 45 mg (finely crushed) (N=35)	VANTRELA ER 45 mg (intact) (N = 35)
	Median (Range)	51.0 (50-100)	88.0 (50-100)	60.0 (50-98)	51.0 (50-70)
Take Drug Again	Mean (SE)	46.3 (2.88)	75.1 (3.04)	55.9 (3.53)	48.5 (2.77)
	Median (Range)	50.0 (0-98)	74.0 (42-100)	56.0 (2-97)	50.0 (1-100)

Intranasal Abuse Potential Study

In a randomized, double-blind, placebo-and active-controlled, 5-period crossover study in nondependent opioid abusers, 34 of the 45 subjects enrolled completed all treatment conditions: intranasal administration of 45 mg VANTRELA ER (finely milled), intranasal administration of 45 mg hydrocodone bitartrate powder (immediate release condition), oral administration of 45 mg VANTRELA ER (intact), and intranasal administration of placebo.

The intranasal administration of finely milled VANTRELA ER was associated with statistically significantly lower mean and median scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone administered intranasally, as summarized in Table 7.

Table 7: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal Insufflation

Measure	Statistic	Placebo IN (N=34)	Hydrocodone IR 45 mg (N=34)	VANTRELA ER 45 mg Finely Milled (N=34)
Drug Liking	Mean (SE)	58.6 (1.94)	80.2 (2.16)	72.8 (2.35)
	Median (Range)	52.0 (50-90)	79.0 (57-100)	72.5 (50-100)
Take Drug Again	Mean (SE)	56.4 (2.13)	75.5 (2.57)	67.5 (3.45)
	Median (Range)	50.0 (34-90)	76.5 (43-100)	67.0 (30-100)

The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to make intravenous abuse difficult. The data from the in vitro studies and clinical abuse potential studies indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route and the intranasal route. However, abuse of VANTRELA ER by the intravenous, nasal, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of VANTRELA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

VANTRELA ER contains hydrocodone bitartrate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. VANTRELA ER can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)*].



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

MEMORANDUM

DATE: January 20th, 2017

FROM: Xiaobin Shen, Ph.D., Review Chemist
Julia Pinto, Ph.D., Branch Chief

TO: Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Open Session Study Results Document: In Vitro Studies of Proposed Abuse-Deterrence Properties, April 5, 2017 AADPAC/DSaRM Meeting to Discuss NDA 209-777

1. Overview of the Proposed Product Abuse Deterrent Formulation (ADF) Features

The drug product is an oral immediate-release (IR) tablet formulation containing 5, 15 and 30 mg oxycodone hydrochloride. All strengths have the same formulation design, comprising a multilayer coated tablet. The comparator was Roxicodone® 30 mg tablet.

The coding for specific in vitro conditions discussed below and in the closed session of the AC meeting briefing document is provided by the applicant for easier data correlation and assessment.

2. In Vitro Study Results

Among the in vitro abuse-deterrent studies conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties, only the methodologies that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below.

A. Physical Manipulation (Size Reduction) (Study Report: ARS-122-06)

Roxicodone tablets are efficiently crushed into a fine insufflatable powder with Tool E.

Oxycodone ARIR tablets are harder and comparatively more difficult to be crushed or ground into a fine insufflatable powder. The time it took and the difficulty to particle size reduced Oxycodone ARIR are summarized in the Table 1 below.

Table 1. Mean Time and Difficulty of Manipulation (N = 5)

Oxycodone ARIR 30 mg		
Tools used to manipulate	Time to Manipulate (Seconds)	Difficulty to Manipulate
Tool A	300	10
Tool B	300	9
Tool C	300	6.6
Tool D	60	6.2
Tool E	119.8**	7.4
Tool F	300	8.4
Tool G	32.2*	1.4

1 = very easy to adulterate, 10 = impossible (impractical) to adulterate; maximum time allowed = 300 seconds.

* This represents the average time at which the product appeared to be significantly adulterated.

** It is difficult to particle size reduce using this tool. The result may depend on the individual's strength.

Physical manipulation using most of the tools tested are difficult to impractical to particle size reduce the Oxycodone ARIR tablets, except Tool G can quickly grind it into insufflatable powder with ease. Tools D and E can also be used to particle size reduce the Oxycodone ARIR tablets, but not to the extent of mostly an insufflatable powder.

Particle size distribution data shown in Figure 1 identified Tool G, under the given testing conditions, as the only tool to produce a fine, relatively homogeneous powder sufficient for intranasal insufflation. Varying the manipulation time did not markedly change the particle size distribution profile.

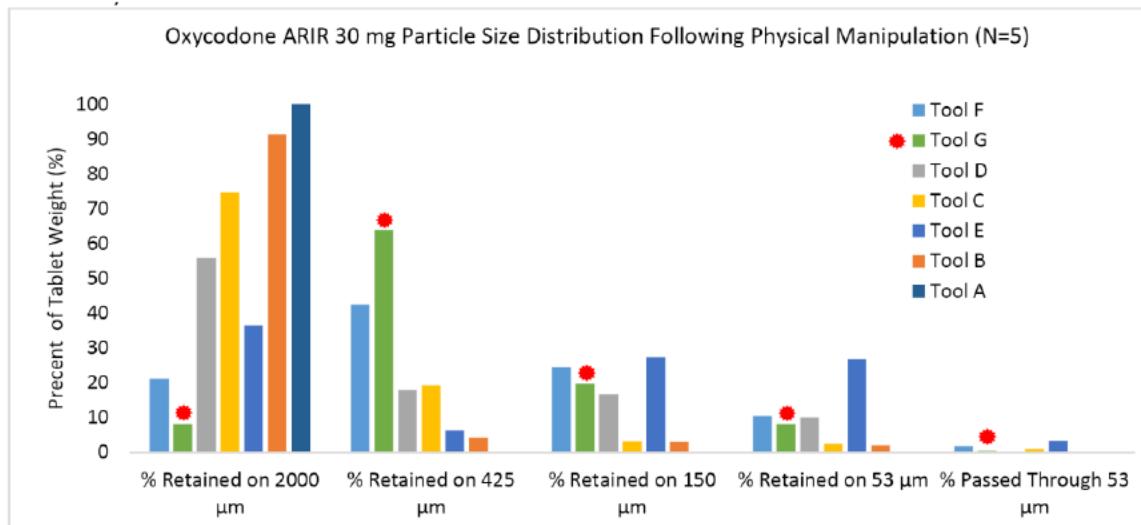


Figure 1: Particle size distribution following manipulation of non-pretreated Oxycodone ARIR tablets with household tools

Pretreatment with Pre-Treatment A, B, C, and D did not detectably render the Oxycodone ARIR tablets easier to physical manipulation for particle size reduction; Nor did it significantly affect the particle size of the obtained powder. Pre-treatment E and F were found not suitable as the product was significantly altered after the treatments.



B. Large Volume Extraction Studies

Test 1 – Effect of ^{(b) (4)} on Extraction over Time Course

Roxicodone tablets crushed using Tool E released oxycodone completely (~ 100%) within 1 minute in Solvent A with Agitation B and at Temperature A. Solvent A is the simplest and most common solvent used; hence Roxicodone was not tested in additional solvents and temperatures.

In contrast, Oxycodone ARIR tablets did not dose dump oxycodone even in Solvents H & I, the most efficient solvents in extraction, with Agitation B and long incubation times. Intact and (Tool G) crushed tablets released a maximum of 25% and 66% within 30 minutes and 60 minutes, respectively, at Temperature A (Figure 3). At Temperature B and with Agitation B, as high as 86% oxycodone can be extracted from the Oxycodone ARIR tablets in 15 minutes; the extraction reaches as high as 94% in 30 minutes (Figure 4).

The extractions performed in Solvent H resulted in the highest levels of oxycodone released from Oxycodone ARIR tablets. Grinding increases extraction in early time points, up to an identified 15 minutes. With further increase in extraction time in excess of 30 minutes, grinding then slows down extraction significantly when compared to the intact tablets. Such effect is most pronounced at Temperature A with Agitation A, as shown by the 17.9% recovery from ground samples vs 66.3% recovery from intact tablets at 60 minutes. Agitation B and Temperature B reduced the difference of grinding, for example, 77.7% recovery was observed from ground samples vs 93.4% recovery from intact tablets at 60 minutes.

A combination of Solvent H, Temperature B and Agitation B represents the most efficient extraction condition for Oxycodone ARIR, with greater than 80% extracted by 15 minutes from the intact tablets (Figure 4).



(b) (4)

Figure 3.



(b) (4)



(b) (4)

Figure 4.

(b) (4)

When the Oxycodone ARIR tablet is physically manipulated using Tool G and then pretreated using Pre-Treatment D, E and F, the overall extraction did not appear to be affected.

When the Oxycodone ARIR Tablet Form B is pretreated using Pre-Treatment D, E and F, the overall extraction is higher compared to Tablet Form A for two of solvents (A and H) respectively. The extraction reached an average of 51% (Figure 5). The study conducted at Temperature A and Agitation B.



(b) (4)

Figure 5.



(b) (4)

Test 2 – Extraction with other Solvents ((b) (4), Study Report: ARS-122-07)

Supporting with a study that abusers tend not to spend more than 10 to 16 minutes in trying to manipulate a product for abuse, and complemented with up to 60 minute of extraction results reported in the prior section, the applicant then performed the rest of extraction studies at 30 minutes only.

At Temperature A and with Agitation B, Solvent H and Solvent I extracted the most oxycodone relative to all other solvents after 30 minute. The maximum extraction was 25% from Solvent H. This is a big contrast from the almost 100% extraction from the Roxicodone tablets. The extraction decreased as the solvent changed from Solvent H to Solvent K in both intact and manipulated samples. Solvent A extracted very low amounts of oxycodone in both intact and manipulated samples (< ~ 5%). All tested solvents (Solvents B to G) extracted less than Solvent H, with only Solvent E extracting more than 5% after 30 minutes with Agitation B (Figure 6).



(b) (4)

Figure 6

Two factors have significant effect on oxycodone extraction from the Oxycodone ARIR tablets. Using Solvent H, at Temperature B, and with Agitation B, up to 94% of oxycodone can be extracted from the intact Oxycodone ARIR tablets over 30 minutes.

C. Syringeability and Small Volume Extractability (Study Report: ARS-122-08)

At Temperature A, manipulated Roxicodone was easily drawn into a syringe through Needle Gauge A in all tested volumes and conditions, recovering over 92% of oxycodone within 1 minute. All results are shown in Figure 7.

In contrast, powder from manipulated Oxycodone ARIR tablets (particle size reduced using Tool C or Tool G) formed a material that was difficult to syringe and only produced a small amount of injectable liquid. The recoveries ranged from 2.5 to 18.9% even with Needle Gauge C when prepared using both Volume A and Volume B of Solvent A extracted up to 30 minutes.

Doubling the number of tablets per sample was as easy to syringe the Roxicodone samples but it resulted in slightly lower recoveries ranging from 85 to 91%. But it was more difficult to syringe the Oxycodone ARIR samples and the recoveries were even lower than single tablet sample.

Oxycodone ARIR tablets manipulated with Tool C had higher syringed sample recoveries than the intact and Tool G manipulated samples.

When extracted at Temperature B, the oxycodone recovery increased but still at not more than 33%.

(b) (4)

Figure 7.

(b) (4)

The Tablet Form B, manipulated using Tool G and then pretreated using Pre-Treatment D was found to have lower extractions to be syringed in Solvents H, L and M when compared to the intact Oxycodone ARIR tablets.



M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 1, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Silvia Calderon, Ph.D., Pharmacologist
James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: OPEN SESSION BACKGROUND DOCUMENT on NDA 209-777 for Oxycodone Hydrochloride (Oxycodone HCl) Abuse Deterrent Immediate-Release (ARIR) Tablets. Prepared for the FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee Meeting, April 5, 2017.

Background Document

Under NDA 209-777, Inspiration Delivery Sciences, LLC conducted an intranasal human abuse potential (HAP) study designated O-ARIR-002 in support of Oxycodone HCl ARIR Tablets. HAP studies, under the designation of Category 3 studies, are used to assess the potential abuse-deterrent effects of pharmaceutical products. Study O-ARIR-002 is briefly described below along with the observed findings.

Study O-ARIR-002 entitled “A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Four-Way Crossover Study to Assess the Relative Bioavailability and Abuse Potential of Intranasal Administration of Ground Oxycodone ARIR Tablets (Abuse Deterrent) versus an Equivalent Dose of Crushed Roxicodone in Nondependent Recreational Opioid Users.”

Description of Study O-ARIR-002

Study O-ARIR-002 was a randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover, single-center study. The study consisted of a

Screening Period, Qualification Period, Treatment Period, and Follow-up Period. The pharmacodynamic completer population consisted of 29 opioid-experienced, non-dependent subjects with experience in intranasal drug administration.

In order to advance to the Treatment Period subjects were required to successfully pass a naloxone challenge test and to complete a drug discrimination test. In a 3-way crossover, 1:1:1 ratio, double-blind, randomized design, subjects received a single intranasal dose each of Roxicodone (15 mg crushed tablet), Roxicodone (30 mg crushed tablet) and placebo powder (microcrystalline cellulose powder). There was a 24 hour washout between treatments. Subjects were required to discriminate the subjective effects produced from crushed Roxicodone (15 mg and 30 mg) from placebo.

During the Treatment Period, subjects received each of 4 treatments in a randomized, four-way crossover, double-blind, double-dummy, 1:1:1:1 ratio design. Each dose was separated by at least a 72-hour period. The treatments are listed below.

- Placebo (microcrystalline cellulose) Intranasal + Oral Placebo
- Crushed Roxicodone 30 mg Intranasal + Oral Placebo
- Ground Oxycodone ARIR 30 mg Intranasal + Oral Placebo
- Intact Oxycodone ARIR 30 mg Oral + Intranasal Placebo

For each treatment, the intact tablet taken orally preceded the crushed tablet administered intranasally. The subject swallowed the tablet directly from the amber vial with approximately 240 mL of room temperature water. The lights in the room were then turned off, the light box was turned on, and the privacy screen removed from the light box. Subjects were instructed to inhale directly from the vial using a 3 inch clear plastic straw. All dosing procedures were to be completed within 5 minutes, however an additional 5 minutes was allowed, if needed.

Some of the important subjective measures in the Qualification Period and Treatment Period included the primary measure of Drug Liking Visual Analog Scale (VAS), as well as the secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS. These scales are briefly described below.

- Drug Liking VAS is scored using a 0-100 point bipolar VAS anchored, on the left with "Strong Disliking" (score of 0), in the center with a neutral anchor of "Neither Like nor Dislike" (score of 50) and on the right with "Strong Liking" (score of 100). Subjects responded to the question "Do you like the drug effect you are feeling now?"
- High VAS was scored using a 0 to 100 point unipolar VAS anchored on the left by "None" (score of 0) and on the right by "Extremely" (score of 100). Subjects rated the statement "How high are you now?"
- Take Drug Again VAS was scored using a 0-100 point bipolar VAS anchored on the left with "Definitely Would Not" (score of 0); "Do Not Care" (score of 50); and anchored on the right with "Definitely Would" (score of 100). Subjects responded to the statement "Would you want to take the drug you just received again, if given the opportunity?"
- Overall Drug Liking VAS was scored using a 0 to 100 point bipolar VAS anchored on the left with "Strong Disliking" (score of 0); "Neither Like nor Dislike" (score of 50) in the

middle; and anchored on the right with “Strong Liking” (score of 100). Subjects completed the statement “Overall, my liking for this drug is:”

During the Treatment Period, Drug Liking VAS and High VAS were evaluated post-dose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours. In the case of High VAS, there was also a pre-dose measurement. Overall Drug Liking and Take Drug Again VAS were administered at 12 and 24 hours post-dose in the Treatment Period. Important parameters included maximum effect, designated Emax, and time to maximum effect, designated TEmax.

To evaluate the pharmacokinetics of oxycodone in plasma, blood samples were obtained during each Treatment Period within 1 hour pre-dose and at 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose. For purposes of this review, the pharmacokinetic parameters evaluated for plasma oxycodone included maximum achieved oxycodone plasma concentration (Cmax) and the time to achieve Cmax (Tmax).

Statistical analyses for the pharmacodynamic measures of Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking were conducted by the FDA CDER/Office of Translational Science/Office of Biostatistics. Statistical analyses were conducted using a mixed-effect model, with period, sequence, and treatment as fixed effects and subject nested within treatment sequence as a random effect. The normality assumption was satisfied with respect to Drug Liking VAS and High VAS allowing comparisons of Least Square (LS) means between treatments. For Overall Drug Liking VAS and Take Drug Again VAS, the normality assumption was not met, thereby requiring a non-parametric method for statistical analysis, with use of difference in median values of the various treatments.

The primary comparison was intranasal crushed 30 mg Roxicodone versus intranasal ground Oxycodone ARIR 30 mg. Validation of each measure was determined by comparing intranasal crushed 30 mg Roxicodone to placebo.

Findings from Study O-ARIR-002

- For the four subjective measures of Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS, statistical analyses demonstrated that the maximum responses (Emax) produced by intranasal crushed Roxicodone 30 mg (positive control) was significantly ($p<0.0001$) greater than that produced by placebo, thereby validating all four measures.
- The means and standard deviations (SD) of Emax of Drug Liking, the primary endpoint, following the intranasal treatments of placebo, crushed Roxicodone 30 mg, and ground Oxycodone ARIR 30 mg, were 53.41 (6.34) mm, 82.86 (11.55) mm, and 71.14 (12.01) mm, respectively. Statistical analyses demonstrated that intranasal Oxycodone ARIR 30 mg produced significantly ($p<0.0001$) lower maximum Drug Liking than that produced by intranasal crushed Roxicodone but significantly ($p<0.0001$) higher maximum Drug Liking compared to placebo. These data predict a possible deterrent effect of Oxycodone ARIR Tablets to abuse by intranasal administration, while, at the same time, indicating at least some abuse potential associated with intranasal Oxycodone ARIR Tablets

- The means (SD) of Emax of High following the intranasal treatments of placebo, crushed Roxicodone 30 mg, and ground Oxycodone ARIR 30 mg, were 7.52 (14.93) mm, 66.34 (25.67) mm, and 39.38 (25.88) mm, respectively. Based on statistical analyses, intranasal Oxycodone ARIR 30 mg produced significantly ($p<0.0001$) lower maximum High than that produced by intranasal crushed Roxicodone, thereby providing further support for a possible deterrent effect of Oxycodone ARIR Tablets to intranasal abuse. Considering that intranasal ground Oxycodone ARIR resulted in significantly ($p<0.0001$) higher maximum High compared to placebo, there appears to still be some abuse potential associated with intranasal Oxycodone ARIR tablets.
- The means (SD) of Emax of Take Drug Again following the intranasal treatments of placebo, crushed Roxicodone 30 mg, and ground Oxycodone ARIR 30 mg, were 41.89 (20.09) mm, 82.14 (16.44) mm, and 62.24 (24.51) mm, respectively. Based on nonparametric statistical analyses, intranasal Oxycodone ARIR 30 mg was associated with significantly ($p<0.0001$) lower maximum Take Drug Again than that produced by intranasal crushed Roxicodone. These data indicate that subjects were less willing to intranasally administer ground Oxycodone HCl ARIR than to intranasally administer crushed Roxicodone, thereby providing further support for a possible deterrent effect of Oxycodone ARIR Tablets to intranasal abuse.
- The means (SD) of Emax of Overall Drug Liking following the intranasal treatments of placebo, crushed Roxicodone 30 mg, and ground Oxycodone ARIR 30 mg, were 47.59 (15.73) mm, 80.86 (14.60) mm, and 64.21 (21.64) mm, respectively. Based on nonparametric statistical analyses, the maximum Overall Drug Liking experience following intranasal ground Oxycodone HCl ARIR 30 mg was significantly ($p=0.0004$) less than that produced by intranasal crushed Roxicodone 30 mg. These data also suggest an abuse deterrent effect of Oxycodone HCl ARIR Tablets to intranasal abuse.
- Upon oral administration of intact Oxycodone HCl ARIR 30 mg, the mean (SD) Emax values for Drug Liking, High, Take Drug Again, and Overall Drug Liking were 81.48 (11.49) mm, 66.66 (25.92) mm, 77.31 (18.11) mm, and 78.55. Statistical analyses of the comparison of intact Oxycodone HCl ARIR 30 mg given orally versus intranasal crushed Roxicodone 30 mg demonstrated no statistically significant differences with respect to Drug Liking ($p = 0.53$), High ($p=0.95$), Take Drug Again ($p=0.2587$), and Overall Drug Liking ($p=0.6313$).
- Intranasal ground Oxycodone HCl ARIR 30 mg and crushed Roxicodone 30 mg produced mean plasma oxycodone Cmax of 42.7 ng/mL and 56.5 ng/mL, respectively. Both treatments were not bioequivalent with respect to Cmax, with intranasal Oxycodone ARIR resulting in an approximate 28% lower Cmax of oxycodone compared to intranasal Roxicodone. The time to achieve Cmax was longer following intranasal Oxycodone ARIR compared to following intranasal Roxicodone (2.3 hours versus 1.7 hours, respectively).
- Oral administration of Oxycodone HCl ARIR 30 mg resulted in an oxycodone plasma Cmax of 58.4 ng/mL. This was bioequivalent to the Cmax produced by intranasal ground Roxicodone 30 mg, but represented a 30% increase in Cmax compared to intranasal Oxycodone HCl ARIR. Of interest was the shorter time to achieve Cmax following oral Oxycodone HCl ARIR (median Tmax of 1.3 hours) compared to following intranasal administration of either Oxycodone ARIR (median Tmax of 2.3 hours) or Roxicodone (median Tmax of 1.7 hours).
- Both the pharmacokinetic data and the pharmacodynamic data suggest that Oxycodone HCl ARIR will be subject to oral abuse.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: March 8, 2017

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Postmarketing Requirements (PMRs) for Opioid Analgesics Labeled with Abuse-Deterrent Properties

Postmarketing Requirements (PMRs) for Opioid Analgesics Labeled with Abuse-Deterrent Properties

The following PMRs are currently required for all approved opioid analgesics labeled with abuse-deterrent properties, in order to assess the known serious risks of misuse and abuse by determining whether the properties intended to deter misuse and abuse of the product actually result in a meaningful decrease in misuse and abuse, and their consequences of addiction, overdose, and death, in the community. The following studies are conducted according to a schedule agreed upon with the Agency.

1. In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2 (below), conduct a descriptive study that analyzes data on the following:
 - 1) Utilization of oxycodone ARIR and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND
 - 2) Abuse of oxycodone ARIR and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and

patterns of abuse for oxycodone ARIR as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
 - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.
 - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.
2. Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of oxycodone ARIR actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of oxycodone ARIR and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's Guidance for Industry and FDA Staff: *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.