PAIN MATTERS

Abuse-Deterrent Opioids: Product Labeling

(Part 3 of a 3-Part Series)

Introduction

In April 2015, the FDA released a Guidance for Industry outlining recommendations for evaluation and labeling of abuse-deterrent (AD) opioids.[1] The first 2 installments of this 3-part series discussed various topics within this guidance. Part 1 reviewed the advances in technological approaches to development of AD formulations and Part 2 discussed recommended studies to evaluate these products. The final installment of this series focuses on translating data from studies into AD product labeling.

Abuse-Deterrent Labeling

The inclusion of AD information in product labeling can help inform health care providers and patients of the abuse-deterrence potential of an approved product. According to the guidance document, the FDA encourages pharmaceutical manufacturers to propose labeling that not only explains the results of completed studies with the AD formulation (as described in Part 2 of this series), but also describes the AD product features.[1] Key concepts regarding labeling of AD opioids include:

- The AD properties of the formulation, supported by study data, should be clearly stated in the labeling while acknowledging that abuse of the product is still possible (ie, AD does not equal abuse-proof).[1]
- In addition to the specific AD properties of the formulation, the product labeling should specify the routes of abuse that the product intends to discourage.[1]
- Currently, published data demonstrating a strong association between AD properties of an opioid formulation and reduction in abuse or adverse events (AEs) after approval are limited. Proposed labeling should reflect the "predictive quality of premarket studies" and include results from relevant postmarket studies if available.[1]
- Labeling revisions may be necessary if postmarket studies conclude that the AD properties of the formulation do not reduce abuse and AEs or reveal a shift in routes of abuse (eg, from oral to IV).[1]
- The FDA may require revisions if it determines that abusers have overcome a technology such that it no longer meaningfully deters abuse.[1]

The FDA plans to take a "flexible, adaptive approach" to evaluating AD product labeling.[1] In so doing, the agency expects pharmaceutical manufacturers to conduct studies that assess proposed formulations relative to the same opioids with currently approved AD labeling, and to continually update formulations as deterrence technology advances.[1] The FDA will assess the appropriateness of the labeling based on the data provided, but the agency cannot provide guidance on the "magnitude of effect that would be sufficient to support" each potential type of claim that could be proposed by a sponsor.[1]

Labeling Based on Study Categories

Labeling statements for an AD opioid formulation are derived from premarket investigations including in vitro data (Category 1), pharmacokinetic data (Category 2), clinical abuse potential (CAP) studies (Category 3), and postmarket studies (Category 4).[1] According to the guidance document, "the data necessary to support AD labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse." For most products, the data needed to support labeling text derive from study results in more than one study category.[1] The product labeling should not only discuss the results that support the deterrence claim, but also comment on the design and conduct of Category 2 and 3 studies. Category 1 studies should be described in more general terms to avoid creating a "road map" for individuals attempting to bypass or defeat the AD properties of an opioid formulation.[1] The guidance document provides examples of potential labeling statements supported by various study category data. These are summarized in the Table.

Labeling statements may not be the same across different administration routes. For example, it may be possible to obtain labeling approval based on Category 3 data for the intranasal but not for the oral route of abuse and vice versa.[1] Likewise, the same labeling statements may not apply to all methods of abuse within the same administration route. For example, one opioid formulation may receive a Category 3 labeling claim for potential to reduce abuse through demonstration of reduced liking of "chewed" data versus a comparator and another opioid may receive a Category 3 labeling claim for the potential to reduce abuse through demonstration of reduced liking of "finely milled" data versus a comparator. "Finely milled" data may represent a more rigorous test of potential abuse deterrence, as the product is "defeated" to the extent of how recreational abusers may treat the product. Despite this, it is important to note that abuse via the route studied is still possible.[1] Additionally, a statement that "data from laboratory and clinical studies may not fully predict abuse potential in the postapproval setting" should be included. Postmarket data (Category 4) from appropriately designed and conducted studies also can be used to support labeling statements by demonstrating that the AD properties of the opioid formulation lead to relevant and persistent deterrence.[1]

As part of the approved prescribing information for a product, AD labeling claims for opioids appear in Section 9.2, Abuse. Based on the FDA guidance document, the following are examples of information for inclusion in labeling for different types of AD properties based on the category of study:

Category 1

"For this product, in vitro data demonstrated that an AD 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. 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."[1]

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."[1]

This article is sponsored by Teva Pharmaceuticals.

Table. Information To Support Proposed Labeling for Abuse-Deterrent Formulations Based on Study Category Data[1]

Study Category Data	Potential Information To Include in Labeling
Category 1 data involving an oral AD formulation	• Discuss types of in vitro studies performed, such as physical and/or chemical manipulation studies of the product in general terms. • Explain the goal of the studies. For example, the goal is to demonstrate the inability of various extraction methods to bypass the AD formulation to allow for a sufficient volume of medication for abuse via the injectable route. • Include results from the studies that support the AD formulation, such as the product resists crushing, breaking, or dissolution via different methods while retaining its ER properties. • In vitro data may be sufficient to support deterrence via the IV route of administration.
Category 1 and 2 data involving an oral AD formulation	• Discuss types of in vitro studies performed, such as physical and/or chemical manipulation studies of the product in general terms. • Discuss pharmacokinetic studies of the product via the oral and intranasal routes, including design and conduct of the studies. • Explain the goal of the studies. For example, the goal is to demonstrate the inability of various extraction methods to bypass the AD formulation (Category 1 data) and to determine the effect of manipulation on drug release (Category 2 data). • Include results from the studies that support claims that the AD formulation is expected to deter oral, nasal, and IV abuse.
Category 2 and 3 data involving an oral formulation that releases an opioid antagonist following manipulation	• Discuss pharmacokinetic (Category 2) and CAP (Category 3) studies performed on the agonist/antagonist combination product, including design and methodology. • Explain the goal of the studies. In this case, the goal is to demonstrate the release of the opioid antagonist following attempted manipulation and that the presence of the antagonist resulted in a reduction in "drug liking" compared with a similar amount of opioid administered orally and intranasally. • Include results from the studies that support claims that the AD formulation is expected to deter oral and intranasal abuse.

AD, abuse deterrent; **CAP,** clinical abuse potential; **ER,** extended release

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. Possible labeling text:

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."[1]

Category 4

"Postmarket data from a variety of sources can demonstrate that a product's abuse-deterrent 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. 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-deterrent 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."[1]

Conclusion

The FDA guidance document on AD opioids provides pharmaceutical manufacturers with direction on translating data from in vitro, pharmacokinetic, CAP, and postmarket studies into information to include in product labeling. The FDA will assess the appropriateness of proposed labeling based on the data provided to the agency from the sponsor. When prescribing opioid medications, clinicians should be mindful that AD information in the labeling does not mean that a product is abuse-proof and that labeling may not be consistent across various routes of administration.

Reference

1. US Food and Drug Administration. Abuse-deterrent opioids – evaluation and labeling. Guidance for industry. April 2015. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. Accessed June 30, 2015.

BB159 PAIN-40307

Teva Pharmaceuticals reviewed and edited the content prior to publication.