Drug and Alcohol Dependence xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Development and impact of prescription opioid abuse deterrent formulation technologies

Louis Alexander[a], Richard O. Mannion[b], Brianne Weingarten[c,*], Richard J. Fanelli[d], Gary L. Stiles[e]

[a] Department of Risk Management and Epidemiology, Purdue Pharma L.P., United States
[b] Department of Pharmaceutics, Purdue Pharma L.P., United States
[c] Department of Program Management, Purdue Pharma L.P., United States
[d] Department of Regulatory Affairs, Purdue Pharma L.P., United States
[e] Research and Development, Purdue Pharma L.P., United States

ARTICLE INFO

Article history:
Received 5 November 2013
Received in revised form 3 February 2014
Accepted 3 February 2014
Available online xxx

Keywords:
Abuse deterrent formulation
Opioid analgesic
Pain relief
Non-medical use
Unintended misuse

ABSTRACT

Background: Millions of patients are treated with opioid analgesics (OpAs) to relieve pain. Unfortunately, these medications are subject to abuse and/or unintended misuse. Abuse deterrent formulations (ADFs) represent an intervention strategy to decrease abuse/misuse without affecting patient access. The Food and Drug Administration (FDA) has issued Draft Guidance "Abuse deterrent opioids, Evaluation and Labeling" and is currently actively pursuing scientific input on this issue.
Methods: The development of ADF technologies was reviewed using peer reviewed journals describing OpA post marketing studies, web sites containing FDA announcements on product approvals and manufacturer product use profiles.
Results: Reviewed is the FDA recent approval of a product label describing the abuse deterrent characteristics of OxyContin® (physical barrier formulation), and the FDA determination that studies were insufficient for an Opana® (physical barrier) ADF label. Additional reviewed marketed OpAs with ADF technologies include: Suboxone® and Embeda® (opioid agonist/antagonist combinations), Oxecta® (aversion technology), and Nucynta® (physical barrier). Reviewed ADF technologies currently in development include: new physical barrier and aversion technologies, an innovative extended release formulation as well as novel polymer–opioid conjugates. As ADF technologies are part of a comprehensive intervention strategy to promote safe OpA use, additional components including governmental, community, and educational initiatives are reviewed.
Conclusions: The outcomes of the recent ADF labeling applications for OxyContin® (Tier 3 approval) and Opana® (non-approval) suggest that the threshold for ADF labeling will be appropriately high. The presented findings indicate that ADF technologies can be a critical component of a comprehensive strategy to promote the safe and effective use of OpAs.

© 2014 Elsevier Ireland Ltd. All rights reserved.

Contents

* Corresponding author at: Department of Program Management, Purdue Pharma L.P., One Stamford Forum, Stamford, CT 06901, United States. Tel.: +1 203 588 7565; fax: +1 203 588 6255.
E-mail address: brianne.weingarten@pharma.com (B. Weingarten).

http://dx.doi.org/10.1016/j.drugalcdep.2014.02.006
0376-8716/© 2014 Elsevier Ireland Ltd. All rights reserved.

Please cite this article in press as: Alexander, L., et al., Development and impact of prescription opioid abuse deterrent formulation technologies. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.02.006

1. Implications of non-medical opioid analgesic (OpA) use

It has been estimated that approximately 100 million adults in the U.S. are currently afflicted with chronic pain (Committee on Advancing Pain Research, Care and Education et al., 2011). The rising rate of chronic pain has been accompanied by substantial increases in the use of drugs, particularly opioid analgesics (OpAs; Rosenblum et al., 2008). Unfortunately, this rise has been accompanied by a rapid escalation in the prevalence of non-medical use (Substance Abuse and Mental Health Services, 2011) segregated into three categories based on distinct characteristics and attendant groups: (1) intentional abuse, (2) therapeutic error and (3) accidental exposure (Havens et al., 2007; Katz et al., 2008; National Drug Intelligence Center, 2001). Intentional abuse describes the use of the drug to stimulate an associated high, euphoric or other psychotropic effect. Historically, the majority of chronic opioid abusers tamper with tablets in order to achieve these effects, and accordingly, the reported attractiveness of an OpA to abusers is linked to its tampering susceptibility (Butler et al., 2006; Katz et al., 2011; Passik et al., 2006). Extended release (ER) formulations are favored by abusers as they contain a high dose of active opioid and ER properties are readily neutralized by crushing or dissolving (Butler et al., 2010, 2011). Non-oral abuse is a serious public health issue as it significantly increases the risk of opioid overdose and death (Jones et al., 2013; Okie, 2010; U.S. Food and Drug Administration (FDA), 2012; Warner et al., 2009).

OpA tablet tampering can also increase the risk of a serious adverse outcome for patients through unintended misuse by non-therapeutic means (therapeutic error). This is exemplified by the application of crushed ER tablets into food to facilitate ingestion, exposing the subject to highly concentrated active opioid (Centers for Disease Control and Prevention, 2007). Accidental exposures of non-patients are also an important health consideration. Recent data (RADARS® System Poison Control Center Program) shows that very young children (ages 1–2.5) represent the majority of such exposures for OxyContin®, who may chew the tablets prior to swallowing, thereby increasing adverse event risk (Coplan et al., 2013).

2. Development of abuse-deterrent formulations

An intervention that addresses the public health implications of non-medical OpA use is the development of an abuse-deterrent formulation (ADF), which balances risk mitigation with appropriate patient access (Butler et al., 2010; Moorman-Li et al., 2012; Raffa and Pergolizzi, 2010; Romach et al., 2013). The FDA supports the development of innovations that promote the safe use of OpAs, including ADFs (FDA, 2013). Abuse deterrent properties cannot compromise the attributes that all pharmaceutical products require (e.g., chemical stability, correct release rate, reproducible manufacture at commercial scale, as well as clinical efficacy and safety) and consequently, their incorporation reduces formulation options. Moreover, ADFs must account for circumstances associated with real-world abuse. In addition to protecting against non-oral abuse, a controlled release oral product would ideally deter oral abuse via neutralization of the controlled release mechanism (e.g., through chewing or breaking).

The issuance of the Draft Guidance document "Guidance for Industry – Abuse deterrent opioids, Evaluation and Labeling" in January, 2013 has provided insight on the Agency's current thinking, which includes seeking additional scientific information (FDA, 2013). In the Draft Guidance, ADF claims are divided into four tiers as follows: Tier (1) the product is formulated with physicochemical barriers of abuse, Tier (2) the product is expected to reduce or block the effect of the opioid when the product is manipulated, Tier (3) the product is expected to result in a meaningful reduction in abuse and Tier (4) the product has demonstrated reduced abuse in the community. Some products developed with abuse deterrent properties and approved prior to issuance of the Draft Guidance document do not include any mention of abuse deterrence properties or attributes in their label. These include Opana® and Nucynta®. Others, such as Embeda® and Oxecta®, include references to clinical studies performed to assess abuse deterrence, but do not make specific claims of such properties.

This review will examine the role of ADFs to ensure the safe and effective use of OpAs for the relief of chronic pain as part of a comprehensive public health strategy that also includes governmental, community and educational initiatives. Recently (April, 2013), the FDA approved the first Tier 3 claim for an OpA (reformulated OxyContin®; FDA, 2013), which also determined that generic versions of this medication without an ADF could not be marketed due to safety concerns. The following section will review the clinical/real-world results associated with the development and implementation of this and other marketed approaches designed to confer abuse deterrence, which will be followed by a review of formulations designed to deter abuse that are in development.

3. Marketed abuse deterrent formulations

There are three types of developed ADF methodologies that will be covered in this review: (1) physical barriers conferring resistance to tablet tampering (crushing, chewing or dissolving); and imparting viscosity to prevent intravenous abuse. Examples include OxyContin® (ER oxycodone), Opana® (ER oxymorphone), and Nucynta® (ER tapentadol); (2) combining an opioid agonist with an antagonist. The antagonist may be sequestered, and not released in a concentration that produces a clinical effect unless

Please cite this article in press as: Alexander, L., et al., Development and impact of prescription opioid abuse deterrent formulation technologies. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.02.006

Download English Version:

https://daneshyari.com/en/article/7506307

Download Persian Version:

https://daneshyari.com/article/7506307

Daneshyari.com