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Extended-Release Hydrocodone: The Devil in Disguise or Just Misunderstood?

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Abstract

Opioid abuse in the United States increased significantly over the past decade, leading to opioid-related deaths. Approval of Zohydro ER, a product that lacks an abuse-deterrent formulation, has provoked media controversy and aggressive legislative action from multiple stakeholders. Only the American Academy of Pain Management has released a position statement on this medication, and individual opinion varies. Additional single-entity extended-release hydrocodone formulations are in the pipeline, and Zohydro ER's limited clinical utility may make the controversy associated with its approval a moot point. As with other opioids, providers will need to assess individual patient risk versus benefit when prescribing Zohydro ER.

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Abstract:

Opioid abuse in the United States increased significantly over the past decade leading to increased opioid related deaths. Approval of Zohydro™ ER, a product that lacks an abuse deterrent formulation, has provoked media controversy and aggressive legislative action from multiple stakeholders. Only the AAPM has released a position statement on this medication, and individual opinion varies. Additional single-entity extended release hydrocodone formulations are in the pipeline and Zohydro™ ER's limited clinical utility make the controversy associated with its approval a moot point. Similarly to other opioids, providers will need to assess individual patient risk versus benefit when prescribing Zohydro™ ER.

Public Health:

Opioid related deaths are a United States public health crisis. In 2012, the Substance Abuse and Mental Health Services Administration (SAMHSA) reported 4.9 million Americans used pain relievers recreationally compared with 4.5 million the previous year.¹ The National Center for Health Statistics noted that 75% of medication overdose deaths were related to opioid use in 2010.² For every one opioid related death there are 10 inpatient admissions for abuse, 32 emergency department visits for misuse, 130 addicted patients, and 825 nonmedical opioid users.³ The rise in opioid related deaths corresponds to a 300% increase in opioid sales between 1999-2010.⁴ This opioid volume is sufficient for each US adult to take one combination hydrocodone 5mg tablet every four hours for one month and costs health insurers \$72.5 billion annually. Approximately 131 million hydrocodone containing outpatient prescriptions were dispensed in 2011, illustrating both high usage and the potential unmet need for a long acting hydrocodone formulation.⁵

Zohydro™ ER Background:

Zohydro™ ER is a single entity hydrocodone bitartrate Schedule II controlled substance indicated for severe pain requiring around the clock management. Zohydro™ ER is available in 10mg, 15mg, 20mg, 30mg, 40mg and 50 mg strengths, and is intended to be dosed twice daily.⁶ Table 1 lists the conversion factors from other commonly used opioids to Zohydro™ ER. One randomized, double-blind, placebo controlled trial (n = 510) has been published demonstrating chronic back pain patients with a mean pain intensity (PI) score of 7 and a mean daily morphine equivalent usage of 83.8 mg had statistically greater increases in their average daily PI score when maintained on placebo versus those patients treated with extended-release hydrocodone (p

= 0.008).⁷ Additionally, a statistically greater number of patients maintained on placebo discontinued therapy due to lack of efficacy compared to patients treated with extended-release hydrocodone (p=0.001). Adverse effects reported in the study were consistent with opioid induced adverse effects. Serious adverse effects were not considered to be related to study drug, with the exception a case of reported anxiety.

Zohydro™ ER is formulated using Spheroidal Oral Drug Absorption System (SODAS®) technology.⁸ The extended-release properties are achieved by coating soluble beads with active drug which are further coated with a semi-permeable shell then encased in a hard gelatin capsule. The beads are slowly released as gastrointestinal fluid penetrates the semi-permeable shell. This formulation allows for biphasic drug distribution, however; this technology is not an abuse deterrent formulation (ADF) leading to abuse concerns.

Mainstream Media:

The absence of ADF has generated significant media coverage, provoked political intervention, and prompted a position statement from the American Academy of Pain Management (AAPM). The general public has been exposed to numerous stories inaccurately reflecting Zohydro™ ER's potency relative to other long-acting opioids and emphasizing abuse potential without providing context for the therapeutic benefit. While there have been a limited number of Zohydro™ ER editorials in the medical literature, the greatest volume of commentary is within the lay press. The additional volume of stories that the general public is exposed to serve as a how to guide for potential abusers of a product as well as promoting the ideas that everyone is doing it, lowering the threshold for new users to abuse a substance. A 2009 study published sought to determine the correlation between media reporting on abuse potential of prescriptions medications and the

increase in actual reports of abuse of these medications.⁹ The authors tracked overdose deaths associated with short acting opioids relative to the number of mentions the brand and generic medications received in the media. They determined that the increase in media mentions preceded the increase in opioid deaths by two to six months.

Political Action:

Significant political action (table 1) has occurred in response to the Food and Drug Administration's (FDA) ZohydroTM ER approval despite a negative recommendation from the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). Twenty-nine state Attorney Generals signed a letter to the FDA commissioner requesting revocation of ZohydroTM ER approval or requiring it to be reformulated as an abuse-deterrent product.¹⁰ They cited concern over the product's potential to exacerbate the current opioid abuse epidemic through aggressive marketing and sales, overprescribing, and potential opioid tampering by patients which may ultimately lead to overdose deaths. Similar appeals were made by five state Attorney Generals and eight congressional members in letters to the US Department of Health and Human Services Secretary.^{11,12} West Virginia Senator Joe Manchin and Massachusetts Representative Stephen Lynch both introduced bills (S. 2134 and H.R. 4241: Act to Ban ZohydroTM ER) requesting that it's FDA approval be withdrawn until an ADF is available.¹³ At the time of this writing, both bills were referred to their respective congressional committees for further review.

The most aggressive legislative action was taken by in Massachusetts. They sought to ban its prescribing, stocking, and dispensing in Massachusetts until an ADF is available.¹⁴ In reaction, ZohydroTM ER's manufacturer Zogenix sued the governor and Department of Public Health

Commissioner seeking to overturn the ban. This sanction was overruled in US District Court , stating the governor had overstepped his authority which undermines the FDA's ability to make drugs available to promote and protect public health. Further, states are unable to force manufactures to make non-FDA approved formulations. In response, the Massachusetts Board of Registration in Medicine approved regulation 243 CMR 2.07(25) requiring prescribers to complete a risk assessment and pain treatment agreement with patients prior to Zohydro™ ER prescribing, participate in the state's prescription monitoring program, educate patients on Zohydro™ ER risks versus benefits, supply a letter of necessity, and document these actions in the patient's medical record.¹⁵ Similar proceedings are underway by Vermont Governor to prohibit the sale of Zohydro™ ER.¹⁶

Professional Organizations:

Most professional pain, addiction, hospice/palliative care, pharmacy, and physician organizations have not formally commented on Zohydro™ ER's role in pain management or abuse potential . Only the AAPM has released a formal statement outlining their viewpoints.¹⁷ They noted that patients with idiosyncratic responses to other opioids may respond to hydrocodone ER. Its abuse potential is similar than other immediate release (IR) and ER opioids, benzodiazepines, stimulants, barbiturates, alcohol, and nicotine. The Academy identified a 9:1 ratio of patients using to abusing opioids and commented that banning Zohydro™ ER would penalize the patients who take their opioids appropriately to safeguard a small percentage of patients with abuse disorders. AAPM noted that the 50mg Zohydro™ ER strength is less likely to be prescribed than the 10mg-40mg doses, is released over 12 hours when swallowed intact, and contains a lower equianalgesic dose than many other long-acting opioids. In an effort to balance

opioid abuse risk with the benefit of improved chronic pain management, AAPM advises prescribers to screen all patients for misuse and reassess risk at each encounter.

Pipeline/Future Directions:

In the NDA approval letter, the FDA acknowledges the limitations associated with voluntary post-marketing adverse event reporting are unlikely to accurately reflect the potential for “misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/long-acting opioid analgesics.....Zohydro™ ER”.⁵ Due to this concern, the FDA is requiring Zogenix to conduct at least one prospective study to quantify the above risks. This study, which is required to be completed by January 2018, should investigate the effect of the drug formulation in addition to other abuse risk factors.

The controversy surrounding Zohydro™ ER may be time-limited secondary to other manufacturers competing products. Purdue Pharma L.P. has submitted a New Drug Application (NDA) to the FDA for a once daily single entity extended-release hydrocodone product with abuse deterrent properties.¹⁸ Materials submitted to the FDA include data supporting efficacy, decreased enjoyment when insufflated or chewed compared to hydrocodone powder or solution, and lack of dose dumping. Teva Pharmaceutical Industries recently announced positive trial results for a similar abuse deterrent product. Single doses of up to 90 mg twice daily were studied. Teva anticipates filing an NDA by the end of 2014.¹⁹ Egalet Corporation has an extended release product in the preclinical stage, no details are available regarding a potential release date.²⁰

Role in Therapy:

We anticipate this drug will have marginal clinical utility in treating chronic pain. Similar to other brand name opioid products, Zohydro™ ER's cost will likely be a barrier to use and it does not offer a unique method of delivery such as administration through a feeding tube. Previously marketed long acting opioid ADF were not widely prescribed due to high cost and limited insurance coverage. Zohydro™ ER may have a defined niche in patients with poor response or idiosyncratic reactions to other opioids. Providers less familiar with prescribing long-acting opioids may be more comfortable converting patients from immediate release hydrocodone containing products to Zohydro™ ER than other long-acting opioid products.

Conclusion:

The increased number of opioid related deaths and lack of an ADF has caused significant concern over the FDA's Zohydro™ ER approval, creating an ethical conundrum for health care professionals who are trying to balance the product's abuse risk with potential clinical benefit in chronic pain patients. Despite its high cost and limited therapeutic niche, Zohydro™ ER has generated significant media attention and proposed legislative action to ban its prescribing, stocking, and dispensing until an ADF is available. However, the buildup surrounding Zohydro™ ER may be short lived as other manufacturers have ADF extended-release hydrocodone products in development. The product's narrow clinical utility is overstated by media reporting and the abuse potential cannot be quantified relative to other commercially available extended-release opioid products. To promote Zohydro™ ER patient safety, prescribers are encouraged to assess abuse risk at baseline and at each follow-up visit.

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Table 1: Potential conversion for transitioning to Zohydro™ ER*

Oral opioid dose (mg)	Oral conversion factor
Hydrocodone 10mg	1
Oxycodone 10mg	1
Hydromorphone 3.75mg	2.67
Morphine 15mg	0.67

*Adapted from reference 6