

# First Script Prescription Benefit News for Workers' Compensation

July 2018

## Drug of the Month

### Apadaz<sup>®</sup>

Apadaz is a combination of benzhydrocodone and acetaminophen, and was approved by the U.S. Food and Drug Administration (FDA) in February of this year for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate. Apadaz immediate-release tablets contain the prodrug form of hydrocodone, meaning the active form of benzhydrocodone is not released until the tablets are converted to hydrocodone by enzymes in the intestinal tract. While the formulation was likely intended to deter abuse of the opioid component, abuse potential in vitro and human studies failed to show an advantage for Apadaz over the comparative hydrocodone/acetaminophen when using physical manipulation and extraction for abuse via intravenous route or smoking. It also did not support expectations of abuse deterrence through oral or nasal routes of administration.

The intended dosing for Apadaz is for oral use of 1 to 2 tablets every 4 to 6 hours as needed for pain, with a maximum daily dose of 12 tablets in a 24-hour period. Apadaz is available in a single strength of 6.12 mg benzhydrocodone/325 mg acetaminophen, and the lowest effective dose should be used for the shortest duration to minimize risk. As a point of reference, the hydrocodone content in 6.12 mg of benzhydrocodone is equivalent to that within 7.5 mg hydrocodone bitartrate, the form of hydrocodone found in traditional products such as Vicodin<sup>®</sup>.

Apadaz is a Schedule II controlled substance and, as with all opioids, carries a risk of abuse, misuse, addiction, and/or criminal diversion. Due to these concerns, providers are encouraged to assess the patient's risk of addiction, abuse, or misuse prior to prescribing Apadaz and regularly thereafter. For these reasons, it is recommended that the use of Apadaz be reserved for individuals for whom alternative therapies such as non-opioid analgesics are not tolerated or are insufficient to provide adequate pain relief, and for whom first-line immediate-release opioids, such as generic codeine, acetaminophen/codeine, hydrocodone/acetaminophen, oxycodone, oxycodone/acetaminophen, tramadol, tramadol/acetaminophen, morphine IR, or hydromorphone have been tried and failed or are not tolerated.

Reference: [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/)

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## Discontinued/Recalled Drugs

[AbbVie](#) plans to discontinue manufacturing Technivie<sup>®</sup> tablets and Viekira XR<sup>™</sup> extended-release tablets by year end due to business reasons, not safety or effectiveness. Prescribers have been encouraged to choose alternative treatment plans for Hepatitis C by July 1, 2018.

Hospira, Inc. is voluntarily recalling two lots of Naloxone Hydrochloride Injections from hospitals and institutions due to the potential presence of embedded and loose particulate matter on the syringe plunger. Check [here](#) to learn more.

For more information, please contact your Account Manager or Account Pharmacist.



## Ask The Pharmacist

To suggest a topic, send an email to:  
[AskThePharmacist@cvtv.us.com](mailto:AskThePharmacist@cvtv.us.com)

**I have been hearing a lot of buzz lately about non-opioid drugs or drugs that bypass concerns with addiction that are in development for the management of pain. Can you speak to what some of these products might be or what we can expect to see in the next few years?**

With all of the focus on the opioid epidemic and the related statistics on over-prescribing, substance use disorder, and general misuse, abuse, and risks of these medications, it should be no surprise that a number of research efforts are beginning to pursue additional non-opioid pain medication options. Specifically, research in this area has been honing in on so-called “euphoria-sparing” analgesics; in other words, drugs that effectively manage pain while avoiding many of the pathways that can lead to drug craving, physical dependence, and/or addiction. In order to better understand what new developments are on the horizon, it may be helpful to first review the various pain pathways within the body.

In general, pain typically begins with some sort of harmful physical stimulus (e.g., heat or pressure) or disease process (e.g., inflammation) that can lead to tissue damage and the release of a myriad of chemicals. These various chemical mediators work within the body to relay messages, activate pain receptors, and influence effects back and forth through the central nervous system (CNS). Essentially, “pain signals” are transmitted to the brain through the nerves and spinal cord where they are processed. It is important to understand that because of this, all pain has an affective-emotional component that influences the individual’s behavioral responses and perception of pain. In essence, the body strives for balance and can respond to pain signals by a process known as descending modulation where chemical mediators are released back down the pathway to reduce signal transmission or can work to begin relieving the pain.

Examples of some of these chemical mediators include N-methyl-D-aspartate (NMDA), g-aminobutyric acid (GABA), acetylcholine (ACh), dopamine (DA), norepinephrine (NE), serotonin (5-HT), substance P, the body’s own natural opioids (e.g., endorphin, enkephalin, dynorphin), and prostaglandins, to name a few. Many of our currently-available non-opioid analgesics or pharmacologic options for pain target one or more of these neurotransmitters for analgesia. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen can interfere with the production of prostaglandins, chemical mediators that activate or sensitize pain receptors in response to injury, thus reducing the conversion of the harmful stimulus to a pain signal. Drugs thought to enhance descending inhibition of pain signals include antidepressants such as the tricyclics or selective norepinephrine reuptake inhibitors (SNRIs) which block the reuptake of serotonin and norepinephrine, thus allowing for improvements in neuropathic (nerve-related) and chronic pain.

Opioids work in the CNS by binding to and activating opioid receptors and essentially altering the perception of pain through effects on both descending modulation and a decrease in the release of some of the neurotransmitters responsible for pain signal transmission. Feelings of euphoria result because opioids activate reward or pleasure centers in the brain, and this effect can be addictive to some people. Several future pharmacologic developments for pain management have thus looked to avoid opioid receptors altogether. While there are several areas of research underway, including topical drug delivery formulations and the exploding area of medical cannabis, a handful of different research drug categories will be highlighted here. The goal for many of these drugs is to create effective pain medications without the “high” thus achieving production of “safer” painkillers.

## **Future Pharmacologic Developments for Pain – “Euphoria-sparing” analgesics**

### **Nerve Growth Factor (NGF) Inhibitors**

Tanezumab is a novel biologic specialty drug (humanized monoclonal antibody) being developed by Pfizer in partnership with Eli Lilly for osteoarthritis, chronic low back pain, and cancer pain. The drug works by selectively binding to nerve growth factor (NGF), a chemical mediator whose levels are known to elevate in response to injury or inflammation in chronic pain patients. This binding inhibits the NGF protein from activating pain-signaling neurons. The drug is currently in Phase 3 Clinical Trials with results expected in the second half of this year. If tanezumab is approved by the Food and Drug Administration (FDA), this may be expected to have a relatively significant impact in the workers’ comp space as biologic specialty medications typically come with a hefty price tag.

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## Kappa Opioid Receptor Agonists (KORAs)

“Traditional” opioids primarily target mu receptors; however, Cara Therapeutics is investigating an experimental drug that binds primarily to kappa opioid receptors thus bypassing many of the negative effects associated with opioid medications. According to the drug manufacturer’s website, their drug “CR845” mainly targets peripheral kappa opioid receptors and will not cross the blood-brain barrier. Thus, they claim it provides comparable opioid analgesia but does not exhibit detrimental intestinal effects, life-threatening respiratory depression, addiction, or euphoria.

## G Protein-Coupled Receptor Drugs (GPCRs)

GPCRs represent an area of research into new drug design as they play key roles in cells’ signaling and response. In fact, the opioid receptors fall within this class. Researchers are using crystallography and x-ray lasers to help them better study and map the function of opioid drugs and other GPCRs to understand key structures that may contribute to particular effects. Oliceridine, a G protein-based ligand, is one such drug that is subject to research. While oliceridine binds at the mu opioid receptor, it works in a slightly different pathway when compared to traditional mu opioid agonists such as morphine. In animal studies, oliceridine’s pathway specificity appeared to enhance the analgesic benefits and safety profile of the drug while reducing typical opioid-related adverse effects.

## N-methyl-D-aspartate (NMDA) Receptor-Blocking Drugs

The substance NMDA is thought to play a role in pain signal sensitization through the descending pathway. Several currently-available medications have NMDA-blocking ability, including ketamine, magnesium, methadone, and dexamethasone. This area is thought to be a promising avenue for research into new pain medications; however, more studies are required.

## Transient Receptor Potential Vanilloid Type 1 (TRPV1) Inhibitors

TRPV1 is thought to play a role in acute injury response as well as in chronic pain. The substance can lead to conversion of harmful stimuli into pain signals and can be sensitized by prostaglandins and other inflammatory mediators released in response to tissue injury. Capsaicin, currently on the market in over-the-counter topical form, works to alleviate chronic or nerve-related pain through inhibition of this particular pathway. Interestingly, the non-psychoactive marijuana constituent cannabidiol (CBD) also has activity at TRPV1 receptors.

In the pharmacology of pain management, targeting non-opioid pathways has the potential to provide a positive therapeutic response while avoiding some of the negative effects associated with traditional opioid medications. The utility of these investigational “euphoria-sparing” therapies cannot be fully understood until the drugs complete clinical trials and receive regulatory approval by the FDA. However, current research has been promising and is likely to continue and expand. The potential benefits of such drugs are encouraging, and novel evolutions in pain management approaches will certainly be something to watch over the coming years.

### References:

<http://projects.hsl.wisc.edu/GME/PainManagement/session2.2.html>  
[https://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_and\\_lilly\\_receive\\_fda\\_fast\\_track\\_designation\\_for\\_tanezumab](https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_lilly_receive_fda_fast_track_designation_for_tanezumab)  
<https://www.caratherapeutics.com/pipeline-technology/kappa-opioid-receptor-agonists/>  
<https://www.painmedicineneeds.com/Monographs-and-Whitepapers/Article/10-17/The-Promise-of-Opioids-Targeting-G-Protein-Signaling/44958> (subscription required)  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5710326/>  
<https://www.painmedicineneeds.com/Clinical-Pain-Medicine/Article/08-15/Human-Nociceptor-Model-May-Lead-to-Customized-Pain-Treatment/33229>  
<https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf>. Accessed: May 31, 2018.

# Regulatory Update

## Arkansas

[Rule 099.41](#) establishes a workers' comp drug formulary effective July 1, 2018. The rule includes guidelines for opioid treatment limitations and requirements for pharmacy/physician staffing.

## Colorado

[Senate Bill 22](#) imposes a seven-day limit on opioid prescribing for first-time opioid users effective May 21, 2018.

## Connecticut

[Senate Bill 302](#) regarding Telehealth became effective July 1, 2018. The bill includes definitions for medication-assisted treatment, establishes prescriber limitations for Schedule I, II, or III controlled substances, and requires electronic subscriptions for Schedule II or III controlled substances.

## Rhode Island

[RI 216-RICR-20-20-4](#) has adopted an opioid prescribing rule establishing requirements for pain management and opioid prescribing, and requires registration of all who manufacture, distribute, prescribe, administer, or dispense any controlled substance within Rhode Island. The rule became effective July 2, 2018.

## New York

In 2017, New York State signed subject number [046-1012 legislation](#) to establish a prescription drug formulary. The proposed effective date was set for July 1, 2018; however, to date there has been no confirmed implementation date.

## Tennessee

[House Bill 1831](#) has enacted opioid prescribing rules including a three-day supply limitation and Morphine Equivalent Dosing (MED) restrictions. The law became effective July 1, 2018.

[Senate Bill 2025](#) regarding partial fills for controlled substance prescriptions became effective May 21, 2018; however, the opioid provision becomes effective January 1, 2019.

**Coventry's Regulatory and Legislative Affairs (RLA) group will continue to monitor further discussion on these topics. If you have questions regarding these changes, please contact your First Script Account Manager.**

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