OPIOID IR COMBO DRUGS

Apadaz (benzhydrocodone-acetaminophen), Codeine-acetaminophen, Dihydrocodeine-acetaminophen, Hydrocodone-acetaminophen, Hydrocodone-ibuprofen, Nalocet* (oxycodone-acetaminophen), Oxycodone-acetaminophen, Oxycodone-aspirin, Oxycodone-ibuprofen, Tramadol-acetaminophen

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RATIONALE FOR INCLUSION IN PA PROGRAM

Background
Apadaz (benzhydrocodone-acetaminophen), codeine-acetaminophen, dihydrocodeine-cafeine-acetaminophen, hydrocodone-acetaminophen, hydrocodone-ibuprofen, oxycodone-acetaminophen, oxycodone-ibuprofen, oxycodone-aspirin, and tramadol-acetaminophen are schedule narcotics. Immediate-release (IR) opioids are drugs that are indicated for the management of acute mild to moderately severe pain (1-23).

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Immediate-release opioids are indicated for the management of mild to moderately severe pain. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve immediate-release opioids for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (1-19).

Limits have been placed on naïve opioid patients based on CDC recommendations. The plan has set limits to patients who are naïve to opioids to a 7 day Pre-PA Allowance for immediate release (IR) combination opioids.

Regulatory Status
FDA-approved indications: Immediate-release opioids are indicated for the management of mild to moderately severe pain (1-19).

Apadaz is indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate (4).

Immediate-release opioids have boxed warnings for the following (1-19):
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- Respiratory depression is the chief hazard of opioid agonists, which if not immediately recognized and treated, may lead to respiratory arrest and death. Risk is increased in patients receiving concurrent CNS depressants (including alcohol), patients with chronic obstructive pulmonary disease, orthostatic hypotension, increased intracranial pressure, biliary tract diseases, and seizure disorders. To reduce the risk of respiratory depression, proper dosing, titration, and monitoring are essential.

- All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

- Accidental ingestion of immediate-release opioids, especially in children, can result in fatal opioid overdose.

- Prolonged use of opioid agonists during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening.

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

Other boxed warnings include the following: (1-24)

- Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 mg per day, and often involve more than one acetaminophen-containing product.
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- Ibuprofen or aspirin cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.
- Concomitant use with CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose of hydrocodone and oxycodone.

The FDA maximum 24-hour dose of acetaminophen is 4 grams (4000 mg), the maximum 24-hour dose of aspirin is 4 grams (4000 mg), and the maximum 24-hour dose of ibuprofen is 3200 mg (1-17).

The Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain recommends that when opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day. The Immediate-release opioid drug initial quantity limits are set to encompass the usual/starting dosage and frequency range recommendations in labeling without exceeding 90 MME per day (20).

CDC guidelines find that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%-61% of decedents (20).

The CDC Guideline for Prescribing Opioids for Chronic Pain states that when starting opioid therapy for pain, clinicians should prescribe immediate-release opioids instead extended-release opioids. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with...
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patients to taper opioids to lower dosages or to taper and discontinue opioids (20).

CDC has a new Opioid Guideline App, it is designed to help providers apply the recommendations of CDC’s Guideline for Prescribing Opioids for Chronic Pain into clinical practice by putting the entire guideline, tools, and resources in the palm of their hand. It can be accessed by this url: https://www.cdc.gov/drugoverdose/prescribing/app.html.

FDA warns that opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see Appendix 1 for list of drugs) (21).

In the SPACE randomized clinical trial showed that treatment with opioids was not superior to treatment with non-opioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain (24).

The FDA is restricting the use of tramadol in children. Tramadol carries serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children (25).

The FDA has determined that a REMS is necessary for all opioid analgesics intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks. The Opioid Analgesic REMS is a strategy to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics (26).

The safety and effectiveness of immediate-release opioids in pediatric patients below the age of 18 have not been established (1-19).
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Summary

Immediate-release opioids are schedule drugs that are indicated for the management of acute mild to moderately severe pain. Safety and effectiveness of immediate-release opioids in pediatric patients have not been established (1-21).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of immediate-release opioids while maintaining optimal therapeutic outcomes.

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