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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Analgesics and Anesthetics	**Original Policy Date:**	July 1, 2018
Subject:	IR Opioid Combo Drugs	**Page:**	1 of 16

Last Review Date: March 12, 2021

IR Opioid Combo Drugs

Description

Apadaz* (benzhydrocodone-acetaminophen), Codeine-acetaminophen, Dvorah* (dihydrocodeine-caffeine-acetaminophen*), Hydrocodone-acetaminophen, Hydrocodone-acetaminophen solution 10-325mg*, Hydrocodone-ibuprofen, Nalocet* (oxycodone-acetaminophen*), Oxycodone-acetaminophen, Oxycodone-aspirin, Oxycodone-ibuprofen, Primlev*/Prolate* (oxycodone-acetaminophen*), Tramadol-acetaminophen, Trezix (dihydrocodeine-caffeine-acetaminophen)

*Prior authorization for certain non-covered formulations applies only to formulary exceptions

Background
Apadaz (benzhydrocodone-acetaminophen), codeine-acetaminophen, dihydrocodeine-caffeine-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 (1-24).

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 (1-20).

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 adults and a 3 day Pre-PA Allowance for pediatric patients 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 (1-20).

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 (1-20):

- 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: (1-25)

- 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.

- 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 (1-18).

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 (21).

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 (21). The FDA also states that benzodiazepines “are also commonly abused and misused, often together with opioid pain relievers and other medicines” (28).

The CDC Guideline for Prescribing Opioids for Chronic Pain states that when starting opioid therapy for pain, clinicians should prescribe immediate-release opioids instead of 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 patients to taper opioids to lower dosages or to taper and discontinue opioids (21).

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) (22).

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 (25).

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 (26).

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 (27).

The safety and effectiveness of immediate-release opioids in pediatric patients below the age of 18 have not been established (1-20).

Related policies
Abstral, Actiq, Butrans, Duragesic, Extended Release Opioid Drugs, Fentanyl Powder, Fentora, Immediate Release Opioid Drugs, Methadone, Opioid Injectables, Opioid Powders, Suboxone Drug Class, Subsys

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Immediate-release opioids may be considered **medically necessary** for the management of mild to moderately severe pain and if the conditions indicated below are met.

Immediate-release opioids may be considered **investigational** for all other indications.

Prior-Approval Requirements

Prior authorization is not required if prescribed by an oncologist and/or the member has paid pharmacy claims for an oncology medication(s) in the past 6 months

Age 12 years of age or older – Ultracet (tramadol and acetaminophen) and Codeine/APAP products **ONLY**
No age limit for all other opioids

Diagnoses

Patient must have **ONE** of the following:

1. Moderate to Severe Acute Pain (short term)
    a. **Age 18 or older:** Patient requires extended treatment beyond 7 days for ongoing management of ACUTE pain
    b. **Age 17 or under:** Patient requires extended treatment beyond 3 days for ongoing management of ACUTE pain
    c. Prescriber agrees to discontinue therapy after 30 days

2. Moderate to Severe Chronic Pain
    a. Prescriber agrees to assess the benefits of pain control (i.e. care plan, signs of abuse, severity of pain) after 3 months of therapy

AND ALL of the following:

a. **NO** dual therapy with other immediate-release opioid analgesic(s)
b. Alternative treatment options have been ineffective, not tolerated or inadequate for controlling the pain
    i. These include: non-opioid analgesics and other treatment modalities
c. Prescriber agrees to assess patient for signs and symptoms of serotonin syndrome
d. Prescriber agrees to participate in the Opioid Analgesic REMS program and to monitor for abuse, misuse, addiction, and overdose and discontinue if necessary (*https://opioidanalgesicrems.com*)
e. **NO** other opioid at prior authorization limits
f. **NO** dual therapy with opioid addiction treatment or methadone
g. **NO** dual therapy with an anti-anxiety benzodiazepine(s)
    i. Alprazolam (Xanax)
    ii. Clonazepam (Klonopin)
    iii. Diazepam (Valium)
    iv. Lorazepam (Ativan)
    v. Oxazepam (Serax)
    vi. Chlordiazepoxide (Librium)
    vii. Clorazepate dipotassium (Tranxene)
h. **NO** cumulative morphine milligram equivalent (MME) over 300 MME

Prior – Approval *Renewal* Requirements

Age 12 years of age or older – Ultracet (tramadol and acetaminophen) and Codeine/APAP products **ONLY**
No age limit for all other opioids

Diagnosis

Patient must have the following:

Moderate to Severe Chronic Pain

AND ALL of the following:

a. **NO** dual therapy with other immediate-release opioid analgesic(s)
b. Prescriber agrees to continue to assess the benefits of pain control (i.e. care plan, signs of abuse, severity of pain)
c. Prescriber agrees to assess patient for signs and symptoms of serotonin syndrome
d. Prescriber agrees to participate in the Opioid Analgesic REMS program and to monitor for abuse, misuse, addiction, and overdose and discontinue if necessary
(*https://opioidanalgesicrems.com*)
e. **NO** other opioid at prior authorization limits
f. **NO** dual therapy with opioid addiction treatment or methadone
g. **NO** dual therapy with an anti-anxiety benzodiazepine(s)
    i. Alprazolam (Xanax)
    ii. Clonazepam (Klonopin)
    iii. Diazepam (Valium)
    iv. Lorazepam (Ativan)
    v. Oxazepam (Serax)
    vi. Chlordiazepoxide (Librium)
    vii. Clorazepate dipotassium (Tranxene)
h. **NO** cumulative morphine milligram equivalent (MME) over 300 MME

Policy Guidelines

Pre - PA Allowance

Age 1*2* years of age or older – Ultracet (tramadol and acetaminophen) and Codeine/APAP products

Quantity
Patients 18 years or older will be able to fill the Pre-PA Allowance after they have filled an initial 7 day supply of IR opioid therapy or if they have been on IR or ER opioid therapy in the last 180 days

Patients age 17 and under will require a PA after they have filled a 3 day supply of the Pre-PA Allowance

Patients with opioid addiction treatment or methadone in the last 30 days will not be eligible for Pre-PA Allowance

Immediate Release Tablets or Capsules ≤ 50 MME/day

Medication	Strength	Quantity Limit
Codeine/APAP soln	120-12 mg/5 mL	5400 mL per 90 days
Hydrocodone/APAP soln	7.5/325 mg/15 mL	
Hydrocodone/APAP elixir	10/300 mg/15 mL	
Oxycodone/APAP soln	5-325 mg/5 mL	3000 mL per 90 days
Hydrocodone/ibuprofen	5/200 mg, 7.5/200 mg, 10/200 mg	270 units per 90 days
Oxycodone/ibuprofen	5/400 mg	
Oxycodone/APAP	10/325 mg	
Codeine/APAP	60/300 mg	360 units per 90 days
Hydrocodone/APAP	7.5/300 mg, 7.5/325 mg, 10/300 mg, 10/325 mg	
Oxycodone/APAP	7.5/325 mg	
Dihydrocodeine/APAP/caffeine	16/320.5/30 mg	450 units per 90 days
Codeine/APAP	15/300 mg, 30/300 mg	540 units per 90 days
Hydrocodone/APAP	2.5/325 mg, 5/300 mg, 5/325 mg	
Oxycodone/APAP	2.5/325 mg, 5/325 mg	
Oxycodone/ASA	4.8355/325 mg	
Tramadol/APAP	37.5/325 mg	

*Patients are only eligible for a combination of opioids not exceeding 300 MME

Prior - Approval Limits

Age 18 years of age or older

Quantity

Acute Pain

Medication / Strength	Quantity Limit for 30 days
Codeine/APAP soln 120-12 mg/5 mL	2100 mL per 30 days **OR**
Hydrocodone/APAP soln 7.5/325 mg/15 mL	2100 mL per 30 days **OR**
Hydrocodone/APAP elixir 10/300 mg/15 mL	2100 mL per 30 days **OR**
Oxycodone/APAP soln 5-325 mg/5 mL	1200 mL per 30 days **OR**
Codeine/APAP 15/300 mg	240 tablets per 30 days **OR**
Codeine/APAP 30/300 mg	240 tablets per 30 days **OR**
Codeine/APAP 60/300 mg	150 tablets per 30 days **OR**
Hydrocodone/APAP 2.5/325 mg	240 tablets per 30 days **OR**
Hydrocodone/APAP 5/300 mg	180 tablets per 30 days **OR**
Hydrocodone/APAP 5/325 mg	180 tablets per 30 days **OR**
Hydrocodone/APAP 7.5/300 mg	150 tablets per 30 days **OR**
Hydrocodone/APAP 7.5/325 mg	150 tablets per 30 days **OR**
Hydrocodone/APAP 10/300 mg	150 tablets per 30 days **OR**
Hydrocodone/APAP 10/325 mg	150 tablets per 30 days **OR**
Oxycodone/APAP 2.5/325 mg	240 tablets per 30 days **OR**
Oxycodone/APAP 5/325 mg	240 tablets per 30 days **OR**
Oxycodone/APAP 7.5/325 mg	180 tablets per 30 days **OR**
Oxycodone/APAP 10/325 mg	150 tablets per 30 days **OR**
Dihydrocodeine/APAP/Caffeine 16/320.5/30 mg	180 tablets per 30 days **OR**
Tramadol/APAP 37.5/325 mg	180 tablets per 30 days **OR**
Oxycodone/ASA 4.8355/325 mg	240 tablets per 30 days **OR**
Hydrocodone/ibuprofen 5/200 mg	150 tablets per 30 days **OR**
Hydrocodone/ibuprofen 7.5/200 mg	150 tablets per 30 days **OR**
Hydrocodone/ibuprofen 10/200 mg	150 tablets per 30 days **OR**
Oxycodone/ibuprofen 5/400 mg	120 tablets per 30 days

Medication / Strength with approved formulary exception only	**Quantity Limit for 30 days**
Apadaz 4.08/325 mg, 6.12/325 mg, 8.16/325 mg *Apadaz is indicated for short-term (no more than 14 days) management of acute pain	168 tablets per 30 days
Dvorah (dihydrocodeine/APAP/Caffeine) 16/325/30 mg	180 tablets per 30 days
Hydrocodone/APAP soln 10/325mg / 15 mL	1800 mL per 30 days
Nalocet tablets (oxycodone/APAP) 2.5/300 mg	240 tablets per 30 days
Primlev/Prolate (oxycodone/APAP) 5/300 mg	240 tablets per 30 days
Primlev/Prolate (oxycodone/APAP) 7.5/300 mg	180 tablets per 30 days
Primlev/Prolate (oxycodone/APAP) 10/300 mg	150 tablets per 30 days
Prolate soln (oxycodone/APAP) 10/300mg / 5 mL	900 mL per 30 days

Duration 1 month

Age 18 years of age or older

Quantity

Chronic Pain

Immediate Release Tablets or Capsules ≤90 MME/day (unless minimum FDA-labeled strength/dose/frequency exceeds 90 MME)

Medication / Strength	**Quantity Limit per 90 days**	**Morphine Milligram Equivalent Daily Dosing**
APAP/codeine soln 120-12 mg/5 mL	8100 mL per 90 days **OR**	32 MME/day
Hydrocodone/APAP soln 7.5/325 mg/15 mL	8100 mL per 90 days **OR**	45 MME/day
Hydrocodone/APAP elixir 10/300 mg/15 mL	8100 mL per 90 days **OR**	60 MME/day
Oxycodone/APAP soln 5-325 mg/5 mL	5400 mL per 90 days **OR**	90 MME/day

APAP/codeine 15/300 mg	1080 tablets per 90 days **OR**	27 MME/day
APAP/codeine 30/300 mg	1080 tablets per 90 days **OR**	54 MME/day
APAP/codeine 60/300 mg	540 tablets per 90 days **OR**	54 MME/day
Hydrocodone/APAP 2.5/325 mg	1080 tablets per 90 days **OR**	30 MME/day
Hydrocodone/APAP 5/300 mg	720 tablets per 90 days **OR**	40 MME/day
Hydrocodone/APAP 5/325 mg	720 tablets per 90 days **OR**	40 MME/day
Hydrocodone/APAP 7.5/300 mg	540 tablets per 90 days **OR**	45 MME/day
Hydrocodone/APAP 7.5/325 mg	540 tablets per 90 days **OR**	45 MME/day
Hydrocodone/APAP 10/300 mg	540 tablets per 90 days **OR**	60 MME/day
Hydrocodone/APAP 10/325 mg	540 tablets per 90 days **OR**	60 MME/day
Oxycodone/APAP 2.5/325 mg	1080 tablets per 90 days **OR**	45 MME/day
Oxycodone/APAP 5/325 mg	1080 tablets per 90 days **OR**	90 MME/day
Oxycodone/APAP 7.5/325 mg	720 tablets per 90 days **OR**	90 MME/day
Oxycodone/APAP 10/325 mg	540 tablets per 90 days **OR**	90 MME/day
Dihydrocodeine/APAP/Caffeine 16/320.5/30 mg	900 capsules per 90 days **OR**	40 MME/day
Tramadol/APAP 37.5/325 mg	720 tablets per 90 days **OR**	30 MME/day
Oxycodone/ASA 4.8355/325 mg	1080 tablets per 90 days **OR**	87 MME/day
Hydrocodone/ibuprofen 5/200 mg	450 tablets per 90 days **OR**	25 MME/day
Hydrocodone/ibuprofen 7.5/200 mg	450 tablets per 90 days **OR**	38 MME/day
Hydrocodone/ibuprofen 10/200 mg	450 tablets per 90 days **OR**	50 MME/day
Oxycodone/ibuprofen 5/400 mg	360 tablets per 90 days	30 MME/day

Medication / Strength with approved formulary exception only	**Quantity Limit for 90 days**	**Morphine Milligram Equivalent Daily Dosing**
Dvorah (dihydrocodeine/APAP/Caffeine) 16/325/30 mg	900 tablets per 90 days	40 MME/day

Hydrocodone/APAP soln 10/325mg / 15 mL	5400 mL per 90 days	40 MME/day
Nalocet tablets (oxycodone/APAP) 2.5/300 mg	1080 tablets per 90 days	30 MME/day
Primlev/Prolate (oxycodone/APAP) 5/300 mg	1080 tablets per 90 days **OR**	90 MME/day
Primlev/Prolate (oxycodone/APAP) 7.5/300 mg	720 tablets per 90 days **OR**	90 MME/day
Primlev/Prolate (oxycodone/APAP) 10/300 mg	540 tablets per 90 days **OR**	90 MME/day
Prolate soln (oxycodone/APAP) 10/300mg / 5 mL	2700 mL per 90 days	90 MME/day

Duration 6 months

Age 12 – 17 years of age – **Ultracet (tramadol and acetaminophen) and Codeine/APAP products ONLY**
17 years old or under for all other opioids

Quantity

Immediate Release Tablets or Capsules ≤ 50 MME/day

Medication	Strength	Quantity Limit for Chronic Pain	Quantity Limit for Acute Pain
Codeine/APAP soln	120-12 mg/5 mL	5400 mL per 90 days	1800 mL per 30 days
Hydrocodone/APAP soln	7.5/325 mg/15 mL		
Hydrocodone/APAP elixir	10/300 mg/15 mL		
Oxycodone/APAP soln	5-325 mg/5 mL	3000 mL per 90 days	1000 mL per 30 days
Hydrocodone/ibuprofen	5/200 mg, 7.5/200 mg, 10/200 mg	270 units per 90 days	90 units per 30 days
Oxycodone/ibuprofen	5/400 mg		
Oxycodone/APAP	10/325 mg		
Codeine/APAP	60/300 mg	360 units per 90 days	120 units per 30 days
Hydrocodone/APAP	7.5/300 mg, 7.5/325 mg, 10/300 mg, 10/325 mg		
Oxycodone/APAP	7.5/325 mg		

Dihydrocodeine/APAP/caffeine	16/320.5/30 mg	450 units per 90 days	150 units per 30 days
Codeine/APAP	15/300 mg, 30/300 mg	540 units per 90 days	180 units per 30 days
Hydrocodone/APAP	2.5/325 mg, 5/300 mg, 5/325 mg		
Oxycodone/APAP	2.5/325 mg, 5/325 mg		
Oxycodone/ASA	4.8355/325 mg		
Tramadol/APAP	37.5/325 mg		

Duration 1 month for acute pain
6 months for chronic pain

Prior – Approval *Renewal* Limits

Same as above
NO renewal for Acute Pain

Rationale

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 (1-22).

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

References

1. Acetaminophen and Codeine Phosphate Solution [package insert]. Huntsville, AL: Qualitest Pharmaceuticals; May 2015.
2. Acetaminophen and Codeine Phosphate Suspension [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals; October 2014.
3. Acetaminophen and Codeine Phosphate Tablet [package insert]. Webster Groves, MO: Mallinckrodt Pharmaceuticals, Inc; August 2017.
4. Apadaz [package insert]. Newtown, PA: KVK-Tech, Inc.; October 2019.
5. Endocet [package insert]. Chestnut Ridge, NY: Endo Pharmaceuticals ; August 2019.
6. Endodan [package insert]. Chadds Ford, PA: Endo Pharmaceuticals; May 2011.
7. Hycet [package insert]. South Plainfield, NJ: G&W Laboratories, Inc; September 2014.
8. Hydrocodone Bitartrate and Acetaminophen Tablets [package insert]. Parsippany, NJ: Actavis Pharma, Inc; April 2016.

9. Hydrocodone Bitartrate and Ibuprofen Tablet [package insert]. Hauppauge, NY: Amneal Pharmaceuticals of NY; August 2015.
10. Lorcet [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; August 2018.
11. Lortab Elixir [package insert]. Lake Forest, IL: Akorn, Inc.; March 2015.
12. Oxycodone and Acetaminophen [package insert]. Atlanta, GA: Mikart, Inc; September 2006.
13. Oxycodone and Ibuprofen [package insert]. Elizabeth, NJ: Actavis Pharma, Inc.; March 2016.
14. Primlev [package insert]. Cranford, NJ: Akrimax Pharmaceuticals, LLC; October 2018.
15. Prolate [package insert]. Las Vegas, NV: Forte Bio-Pharma LLC; February 2020.
16. Roxicet Tablet and Solution [package insert]. Columbus, OH: Roxane Laboratories, Inc.; August 2016.
17. Ultracet [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2018.
18. Norco [package insert]. Parsippany, NJ. Actavis Pharma, Inc.; July 2017.
19. Panlor [package insert]. Canton, MS: Skylar Laboratories, LLC; December 2017.
20. Trezix [package insert]. Ridgeland, MS: WraSer Pharmaceuticals LLC; July 2011.
21. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain. CDC Guidelines 2016.
22. FDA Safety Release. FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016.
23. Chou R, Fanciullo G, Fine P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain The Journal of Pain 2009;10:113-130.
24. Hooten W, Timming R, Belgrade M, et al. Institute for Clinical Systems Improvement. Assessment and Manage-ment of Chronic Pain. Updated November 2013.
25. Krebs E, Gravely A, et al. Effect of Opioid vs Non-opioid medications on pain-related function in patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA March 6, 2018 Volume 319, Number 9; pg. 872 -882.
26. FDA Safety Release. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. December 11, 2017.
27. Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). Drug Safety and Availability: U.S. Food & Drug Administration. September 19, 2018.
28. FDA News Release. FDA Drug Safety Communication: FDA requiring labeling changes for benzodiazepines. September 23, 2020.

Policy History

Date	Action

June 2018	Addition to PA Annual review
July 2018	Changed 7 day step edit look back from 90 days to 180 days
October 2018	Addition of Opioid Analgesic REMS requirement
November 2018	Annual review and reference update. Addition of Opioid Analgesic REMS link per SME
February 2019	Addition of Nalocet to drug list and statement to Nalocet: **Prior authorization for the brand formulation applies only to formulary exceptions due to being a non-covered medication
March 2019	Annual review. Addition of Apadaz new strengths 4.08/325 mg and 8.16/325 mg
December 2019	Annual review. Addition of requirement of no cumulative MME over 300. Addition of 3 day limit Pre-PA for patients age 17 or under. Age 17 or under now require PA for any fill greater than 3 days. Moved Apadaz and hydrocodone/apap 10/325mg solution to MFE with PA only
February 2020	Added generic Nalocet (oxycodone/APAP) to MFE with PA only. Removed MFE opioids from pediatrics table. Updated Opioid Analgesic REMS link
March 2020	Annual review
April 2020	Addition of Primlev and Prolate to MFE + PA only
June 2020	Annual review
December 2020	Dvorah requires formulary exception + PA
March 2021	Annual review and reference update. Addition of Prolate solution 10/300mg/5 mL to formulary exception table

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

Appendix 1 - List of Serotonergic Medications

Selective Serotonin Reuptake Inhibitors (SSRIs)

paroxetine	Paxil, Paxil CR, Pexeva, Brisdelle
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Prozac Weekly, Sarafem, Selfemra, Symbyax
sertraline	Zoloft
citalopram	Celexa
escitalopram	Lexapro

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

venlafaxine	Effexor XR
desvenlafaxine	Pristiq, Khedezla
duloxetine	Cymbalta
milnacipran	Savella

Tricyclic Antidepressants (TCAs)

amitriptyline	No brand name currently marketed
desipramine	Norpramin
clomipramine	Anafranil
imipramine	Tofranil, Tofranil PM
nortriptyline	Pamelor, Aventyl
protriptyline	Vivactil
doxepin	Zonalon, Silenor
trimipramine	Surmontil

Monoamine Oxidase Inhibitors (MAOIs)

isocarboxazid	Marplan
phenelzine	Nardil
selegiline	Emsam, Eldepryl, Zelapar
tranylcypromine	Parnate

Other Psychiatric Medicines

amoxapine	No brand name currently marketed
maprotiline	No brand name currently marketed
nefazodone	No brand name currently marketed
trazodone	Oleptro
buspirone	No brand name currently marketed
vilazodone	Viibryd
mirtazapine	Remeron, Remeron Soltab
llthium	Lithobid

Migraine Medicines

almotriptan	Axert
frovatriptan	Frova
naratriptan	Amerge
rizatriptan	Maxalt, Maxalt-MLT
sumatriptan	Imitrex, Imitrex Statdose, Alsuma, Sumavel Dosepro, Zecuity, Treximet
zolmitriptan	Zomig, Zomig-ZMT

Antiemetics

ondansetron	Zofran, Zofran ODT, Zuplenz
granisetron	Kytril, Sancuso
dolasetron	Anzemet
palonosetron	Aloxi

Other Serotonergic Medicines

dextromethorphan	Bromfed-DM, Delsym, Mucinex DM, Nuedexta
linezolid	Zyvox
cyclobenzaprine	Amrix
methylene blue	
St. John’s wort	
tryptophan	