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Section:	Prescription Drugs	**Effective Date:**	July 1, 2022
Subsection:	Analgesics and Anesthetics	**Original Policy Date:**	July 1, 2018
Subject:	IR Opioid Combo Drugs	**Page:**	1 of 15

Last Review Date: June 16, 2022

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*), Seglentis** (celecoxib-tramadol), Tramadol-acetaminophen, Trezix (dihydrocodeine-caffeine-acetaminophen)

*Prior authorization for certain non-covered formulations applies only to formulary exceptions
**This medication is currently pending tier determination and may not be available at this time

Background

Apadaz (benzhydrocodone-acetaminophen), codeine-acetaminophen, dihydrocodeine-caffeine-acetaminophen, hydrocodone-acetaminophen, hydrocodone-ibuprofen, oxycodone-acetaminophen, oxycodone-ibuprofen, oxycodone-aspirin, celecoxib-tramadol, 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 (1-21).

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 (1-21).

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.

Maximum daily limit of any combination of opioid medications without a PA is 90 MME/day. Maximum daily limit of any combination of opioid medications with a PA is 200 MME/day for patients age 18 and older, or 90 MME/day for patients age 17 and under.

Regulatory Status
FDA-approved indications: Immediate-release opioids are indicated for the management of mild to moderately severe pain (1-21).

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).

Seglentis is indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Seglentis is contraindicated in children younger than 12 years of age (21).

Immediate-release opioids have boxed warnings for the following (1-21):

- 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: (1-26)

- 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 (1-19).

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 (22).

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” (29).

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 (22).

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) (23).

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 (26).

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 (27).

The FDA has determined that a Risk Evaluation and Mitigation Strategy (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. Prescribers should counsel patients and caregivers about the use of naloxone for opioid overdose and consider prescribing naloxone if clinically indicated (28).

The safety and effectiveness of immediate-release opioids in pediatric patients below the age of 18 have not been established (1-21).

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 moderate to 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 18 years of age or older: Formulary Exception opioids
12 years of age or older: Seglentis (celecoxib/tramadol), Ultracet (tramadol/APAP) and codeine/APAP products **ONLY**
No age limit for all other opioids

Diagnoses

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

All medications

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

All medications except for Apadaz and Seglentis

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 for **ALL** medications:

a. Alternative treatment options have been ineffective, not tolerated or inadequate for controlling the pain (i.e., non-opioid analgesics and other treatment modalities)
b. Prescriber agrees to evaluate patient's response to therapy before changing dose or adding additional opioid medications

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** dual therapy with opioid addiction treatment or methadone
f. **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)
g. **NO** cumulative morphine milligram equivalent (MME) over:
    (e.g., https://www.mdcalc.com/morphine-milligram-equivalents-mme-calculator, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf, https://www.cdc.gov/opioids/providers/prescribing/app.html)
    i. 200 MME/day for patients 18 years of age or older
    ii. 90 MME/day for patients 17 years of age or under

Prior – Approval *Renewal* 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

All medications except for Apadaz and Seglentis

Age 18 years of age or older: Formulary Exception opioids
12 years of age or older: Ultracet (tramadol/APAP) 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. Prescriber agrees to continue to assess the benefits of pain control (i.e., care plan, signs of abuse, severity of pain) after 3 months of therapy
b. Prescriber agrees to evaluate patient's response to therapy before changing dose or adding additional opioid medications
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** dual therapy with opioid addiction treatment or methadone
f. **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)
g. **NO** cumulative morphine milligram equivalent (MME) over:
    (e.g., https://www.mdcalc.com/morphine-milligram-equivalents-mme-calculator, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf, https://www.cdc.gov/opioids/providers/prescribing/app.html)
    i. 200 MME/day for patients 18 years of age or older
    ii. 90 MME/day for patients 17 years of age or under

Policy Guidelines

Pre - PA Allowance

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/APAP) and Codeine/APAP products **ONLY**
No age limit for all other opioids

Quantity

- Patients age 18 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 or under will require a PA after they have filled a 3 day supply of the Pre-PA Allowance in the last 180 days.

- Patients with opioid addiction treatment or methadone in the last 30 days will NOT be eligible for Pre-PA Allowance.
- **The IR opioid combination products Pre-PA quantity limits are set for a 90 day limit that does not exceed 50 MME/day.**

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	
Celecoxib/tramadol	56/44 mg	None (reserved for acute pain with a PA only)

Maximum daily limit of any combination of opioid medications without a PA is 90 MME/day, without exceeding 50 MME per day of an IR combo product.

Prior - Approval Limits

Quantity

- **Tramadol IR: Maximum daily dose limit of any tramadol/APAP combination should NOT exceed 400 mg/day.**
- **Seglentis (celecoxib/tramadol) (56/44 mg): Maximum daily dose limit is 4 tablets/day.**
- **18 years of age or older**: Maximum daily limit of any combination of opioid medications with a PA is 200 MME/day.
- **17 years of age or under**: Maximum daily limit of any combination of opioid medications with a PA is 90 MME/day.

Immediate Release Tablets or Capsules
≤ 200 MME/day (age 18 and older) or ≤ 90 MME/day (age 17 or under)

Medication / Strength	Morphine Milligram Equivalent (MME) per unit
APAP/codeine soln 120-12 mg/5 mL	0.36 MME (per mL)
Hydrocodone/APAP soln 7.5-325 mg/15 mL	0.5 MME (per mL)
Hydrocodone/APAP elixir 10-300 mg/15 mL	0.66 MME (per mL)
Oxycodone/APAP soln 5-325 mg/5 mL	1.5 MME (per mL)
APAP/codeine 300/15 mg	2.25 MME
APAP/codeine 300/30 mg	4.5 MME
APAP/codeine 300/60 mg	9 MME
Hydrocodone/APAP 2.5/325 mg	2.5 MME
Hydrocodone/APAP 5/300 mg	5 MME
Hydrocodone/APAP 5/325 mg	5 MME
Hydrocodone/APAP 7.5/300 mg	7.5 MME
Hydrocodone/APAP 7.5/325 mg	7.5 MME
Hydrocodone/APAP 10/300 mg	10 MME
Hydrocodone/APAP 10/325 mg	10 MME
Oxycodone/APAP 2.5/325 mg	3.75 MME
Oxycodone/APAP 5/325 mg	7.5 MME
Oxycodone/APAP 7.5/325 mg	11.25 MME
Oxycodone/APAP 10/325 mg	15 MME
Dihydrocodeine/APAP/Caffeine 16/320.5/30 mg	4 MME
Tramadol/APAP 37.5/325 mg	3.75 MME
Oxycodone/ASA 4.8355/325 mg	7.25 MME
Hydrocodone/ibuprofen 5/200 mg	5 MME
Hydrocodone/ibuprofen 7.5/200 mg	7.5 MME
Hydrocodone/ibuprofen 10/200 mg	10 MME
Oxycodone/ibuprofen 5/400 mg	7.5 MME

*Seglentis (celecoxib/tramadol) 56/44mg	4.4 MME

***Seglentis is indicated for management of acute pain only.**

Medication / Strength with Approved Formulary Exception only (Age 18 and older only)	**Morphine Milligram Equivalent (MME) per unit**
Apadaz* (benzhydrocodone/APAP) 4.08/325 mg	5 MME
Apadaz* (benzhydrocodone/APAP) 6.12/325 mg	7.5 MME
Apadaz* (benzhydrocodone/APAP) 8.16/325 mg	10 MME
Dvorah (dihydrocodeine/APAP/Caffeine) 16/325/30 mg	4 MME
Hydrocodone/APAP soln 10-325mg/15 mL	0.67 MME (per mL)
Nalocet tablets (oxycodone/APAP) 2.5/300 mg	3.75 MME
Primlev/Prolate (oxycodone/APAP) 5/300 mg	7.5 MME
Primlev/Prolate (oxycodone/APAP) 7.5/300 mg	11.25 MME
Primlev/Prolate (oxycodone/APAP) 10/300 mg	15 MME
Prolate soln (oxycodone/APAP) 10-300mg/5 mL	3 MME (per mL)

***Apadaz is indicated for short-term (no more than 14 days) management of acute pain. Maximum daily limit of any combination of opioid medications should NOT exceed 200 MME/day for patients age 18 and older.**

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 (1-23).

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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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
December 2021	Per FEP, decreased the requirement for adults that cumulative MME cannot exceed 200 MME/day from 300 MME/day. Removed requirements “no other opioid at PA limits” and “no dual therapy with other immediate release opioids” due to blanket MME. Added requirement “Prescriber agrees to evaluate patient’s response to therapy before changing dose or adding additional opioid medications.” Revised PA quantity charts to remove quantity limits and add MME per unit. Combined the adult and pediatric PA quantity charts. Added 90 MME/day PA limit for patients 17 and under. Added 400 mg/day PA quantity limit for tramadol IR to align with the PI max daily dose.
February 2022	Updated Pre-PA allowance with oncology step edit statement. Per FEP: added “Prescribers should counsel patients and caregivers about the use of naloxone for opioid overdose” under regulatory status, and added MME calculating links
March 2022	Annual review
June 2022	Annual review. Addition of Seglentis to policy per FEP. Per SME, addition to regulatory status that prescriber should consider prescribing naloxone if clinically indicated

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 16, 2022 and is effective on July 1, 2022.

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	