Opioids ER
Prior Authorization and
Quantity Limit Program Summary

This prior authorization program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Opioids ER Prior Authorization (PA) and Quantity Limit (QL) program is to ensure appropriate selection of patients for treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment (for which alternative treatment options are inadequate) based on product labeling and/or clinical practice guidelines and/or clinical studies. The program will allow for approval for patients with diagnosis of pain due to active malignancies or who are in hospice care. The program will also allow for approval in chronic non-cancer pain when the prescriber has provided documentation for a formal consultative evaluation which includes diagnosis and complete medical history; and the requested agent is not prescribed as an as-needed (prn) analgesic; and the patient's medication history includes the use of an immediate acting opioid or the patient has a documented intolerance, FDA labeled contraindication(s), or hypersensitivity to immediate-acting opioid; the prescriber has confirmed that a patient-specific pain management plan is on file; and the prescriber has confirmed that the patient is not diverting. The program will check for concurrent use of target agents and buprenorphine or buprenorphine/naloxone products used for treatment of opioid dependence. If concurrent use is found, the program will approve concurrent use only when the prescriber provides documentation in support of the concurrent use. The program will not be approved for those with FDA labeled contraindication(s) to the requested agent. Quantity limits within this program encourage appropriate dosing. The program allows continuation of the requested agent when there is documentation that the patient is receiving an opioid ER product. Requests for opioid ER agents, including quantities above the allowed limit, will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS

Arymo ER (morphine sulfate ER)
Avinza (morphine sulfate ER)
Belbuca (buprenorphine buccal film)
Buprenorphine Transdermal System
Butrans (buprenorphine transdermal system)
Duragesic (fentanyl transdermal patch)
Embeda (morphine/naltrexone ER)
Exalgo (hydromorphone ER)[a]
Fentanyl transdermal patch
Hysingla ER (hydrocodone ER)
Kadian (morphine sulfate ER)[a]
Morphabond ER (morphine ER)
morphine sulfate ER
MS Contin (morphine sulfate ER)[a]
Opana ER (oxymorphone SR)[a]
Opana ER Crush Resistant (oxymorphone SR)
Oramorph SR (morphine ER)
OxyContin (oxycodone ER)
Xartemis XR (oxycodone/acetaminophen ER)
Xtampza ER (oxycodone ER)

Zohydro ER Abuse Deterrent (hydrocodone ER)
Nucynta ER (tapentadol ER)
Conzip (tramadol ER)
Tramadol ER[a]
Ultram ER (tramadol ER)[a]
a - generic available, and targeted by program

PRIOR AUTHORIZATION AND QUANTITY LIMIT TARGET DRUGS - RECOMMENDED LIMITS

Brand (generic)	GPI	Quantity Per Day Limit
Narcotic Analgesics		
Arymo ER™ (morphine sulfate)		
15 mg extended release tablet	6510005510A620	3 tablets
30 mg extended release tablet	6510005510A630	3 tablets
60 mg extended release tablet	6510005510A640	3 tablets
Avinza®, morphine sulfate ER		
30 mg sustained-release capsule	65100055207020	1 capsule
45 mg sustained-release capsule	65100055207025	1 capsule
60 mg sustained-release capsule	65100055207030	1 capsule
75 mg sustained-release capsule	65100055207035	1 capsule
90 mg sustained-release capsule	65100055207040	1 capsule
120 mg sustained-release capsule	65100055207050	1 capsule
Belbuca™ (buprenorphine buccal film)		
75 mcg buccal film	65200010108210	2 films
150 mcg buccal film	65200010108220	2 films
300 mcg buccal film	65200010108230	2 films
450 mcg buccal film	65200010108240	2 films
600 mcg buccal film	65200010108250	2 films
750 mcg buccal film	65200010108260	2 films
900 mcg buccal film	65200010108270	2 films
Butrans®, Buprenorphine Transdermal System		
5 mcg/hour transdermal system	65200010008820	1 system/week
7.5 mcg/hour transdermal system	65200010008825	1 system/week
10 mcg/hour transdermal system	65200010008830	1 system/week
15 mcg/hour transdermal system	65200010008835	1 system/week
20 mcg/hour transdermal system	65200010008840	1 system/week
Duragesic® (fentanyl transdermal patch)		
12 mcg/hr transdermal patch	65100025008610	15 patches/month
25 mcg/hr transdermal patch	65100025008620	15 patches/month
50 mcg/hr transdermal patch	65100025008630	15 patches/month
75 mcg/hr transdermal patch	65100025008640	15 patches/month
100 mcg/hr transdermal patch	65100025008650	15 patches/month
Embeda® (morphine/naltrexone ER)		
20 mg/0.8 mg controlled-release capsule	65100055700220	2 capsules
30 mg/1.2 mg controlled-release capsule	65100055700230	2 capsules
50 mg/2 mg controlled-release capsule	65100055700240	2 capsules
60 mg/2.4 mg controlled-release capsule	65100055700250	2 capsules
80 mg/3.2 mg controlled-release capsule	65100055700260	2 capsules
100 mg/4 mg controlled-release capsule	65100055700270	2 capsules

Brand (generic)	GPI	Quantity Per Day Limit
Exalgo® (hydromorphone ER)		
8 mg extended-release tablet[a]	6510003510A820	1 tablet
12 mg extended-release tablet[a]	6510003510A830	1 tablet
16 mg extended-release tablet[a]	6510003510A840	1 tablet
32 mg extended-release tablet	6510003510A855	1 tablet
Fentanyl transdermal patch		
37.5 mcg/hr transdermal patch	65100025008626	15 patches/month
62.5 mcg/hr transdermal patch	65100025008635	15 patches/month
87.5 mcg/hr transdermal patch	65100025008645	15 patches/month
Hysingla ER™ (hydrocodone ER)		
20 mg extended-release tablet	6510003010A810	1 tablet
30 mg extended-release tablet	6510003010A820	1 tablet
40 mg extended-release tablet	6510003010A830	1 tablet
60 mg extended-release tablet	6510003010A840	1 tablet
80 mg extended-release tablet	6510003010A850	1 tablet
100 mg extended-release tablet	6510003010A860	1 tablet
120 mg extended-release tablet	6510003010A870	1 tablet
Kadian® (morphine sulfate ER)		
10 mg sustained-release capsule[a]	65100055107010	2 capsules
20 mg sustained-release capsule[a]	65100055107020	2 capsules
30 mg sustained-release capsule[a]	65100055107030	2 capsules
40 mg sustained-release capsule	65100055107035	2 capsules
50 mg sustained-release capsule[a]	65100055107040	2 capsules
60 mg sustained-release capsule[a]	65100055107045	2 capsules
70 mg sustained-release capsule[b]	65100055107047	2 capsules
80 mg sustained-release capsule[a]	65100055107050	2 capsules
100 mg sustained-release capsule[a]	65100055107060	2 capsules
130 mg sustained-release capsule[b]	65100055107070	2 capsules
150 mg sustained-release capsule[b]	65100055107074	2 capsules
200 mg sustained-release capsule	65100055107080	2 capsules
Morphabond ER™ (morphine ER)		
15 mg ER tablet	6510005510A720	2 tablets
30 mg ER tablet	6510005510A730	2 tablets
60 mg ER tablet	6510005510A740	2 tablets
100 mg ER tablet	6510005510A760	2 tablets
MS Contin® (morphine sulfate ER)		
15 mg sustained-release tablet[a]	65100055100415	3 tablets
30 mg sustained-release tablet[a]	65100055100432	3 tablets
60 mg sustained-release tablet[a]	65100055100445	3 tablets
100 mg sustained-release tablet[a]	65100055100460	3 tablets
200 mg sustained-release tablet[a]	65100055100480	3 tablets
Opana ER®, Oxymorphone SR		
5 mg sustained-release tablet[a]	65100080107405	2 tablets
7.5 mg sustained-release tablet[a]	65100080107407	2 tablets

Brand (generic)	GPI	Quantity Per Day Limit
10 mg sustained-release tablet[a]	65100080107410	2 tablets
15 mg sustained-release tablet[a]	65100080107415	2 tablets
20 mg sustained-release tablet[a]	65100080107420	2 tablets
30 mg sustained-release tablet[a]	65100080107430	2 tablets
40 mg sustained-release tablet[a]	65100080107440	2 tablets
Opana ER® (oxymorphone SR, crush resistant ER)		
5 mg sustained-release tablet	6510008010A705	2 tablets
7.5 mg sustained-release tablet	6510008010A707	2 tablets
10 mg sustained-release tablet	6510008010A710	2 tablets
15 mg sustained-release tablet	6510008010A715	2 tablets
20 mg sustained-release tablet	6510008010A720	2 tablets
30 mg sustained-release tablet	6510008010A730	2 tablets
40 mg sustained-release tablet	6510008010A740	2 tablets
Oramorph SR® (morphine sulfate ER)		
15 mg sustained-release tablet[b]	65100055107415	3 tablets
30 mg sustained-release tablet[b]	65100055107430	3 tablets
60 mg sustained-release tablet[b]	65100055107445	3 tablets
100 mg sustained-release tablet[b]	65100055107460	3 tablets
OxyContin® (oxycodone ER)		
5 mg extended release tablet	6510007510A705	2 tablets
10 mg extended release tablet	6510007510A710	2 tablets
15 mg extended release tablet	6510007510A715	2 tablets
20 mg extended release tablet	6510007510A720	2 tablets
30 mg extended release tablet	6510007510A730	2 tablets
40 mg extended release tablet	6510007510A740	2 tablets
60 mg extended release tablet	6510007510A760	4 tablets
80 mg extended release tablet	6510007510A780	4 tablets
Xartemis XR™ (oxycodone/acetaminophen ER)		
7.5 mg/325 mg extended release tablet	65990002200430	4 tablets
Xtampza ER™ (oxycodone ER)		
9 mg capsule	6510007500A310	2 capsules
13.5 mg capsule	6510007500A315	2 capsules
18 mg capsule	6510007500A320	2 capsules
27 mg capsule	6510007500A330	2 capsules
36 mg capsule	6510007500A340	2 capsules
Zohydro® ER Abuse Deterrent (hydrocodone ER)		
10 mg sustained-release capsule	6510003010A310	2 capsules
15 mg sustained-release capsule	6510003010A315	2 capsules
20 mg sustained-release capsule	6510003010A320	2 capsules
30 mg sustained-release capsule	6510003010A330	2 capsules
40 mg sustained-release capsule	6510003010A340	2 capsules
50 mg sustained-release capsule	6510003010A350	2 capsules

Brand (generic)	GPI	Quantity Per Day Limit
Tramadol, Tapentadol		
ConZip® (tramadol SR biphasic ER)		
100 mg sustained-release capsule	65100095107070	1 capsule
200 mg sustained-release capsule	65100095107080	1 capsule
300 mg sustained-release capsule	65100095107090	1 capsule
Nucynta ER® (tapentadol ER)		
50 mg extended-release tablet	65100091107420	2 tablets
100 mg extended-release tablet	65100091107430	2 tablets
150 mg extended-release tablet	65100091107440	2 tablets
200 mg extended-release tablet	65100091107450	2 tablets
250 mg extended-release tablet	65100091107460	2 tablets
tramadol ER		
100 mg sustained-release tablet[a]	65100095107560	1 tablet
200 mg sustained-release tablet[a]	65100095107570	1 tablet
300 mg sustained-release tablet[a]	65100095107580	1 tablet
Tramadol ER (tramadol SR biphasic)		
150 mg sustained-release capsule	65100095107075	1 capsule
Ultram ER® (tramadol ER)		
100 mg sustained-release tablet[a]	65100095107520	1 tablet
200 mg sustained-release tablet[a]	65100095107530	1 tablet
300 mg sustained-release tablet[a]	65100095107540	1 tablet

a – generic available, included in quantity limit program
b - discontinued

PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL
Opioids ER agents and quantities above the quantity limit will be approved when ALL of the following are met:

1. ONE of the following:
    a. There is documentation that the patient is currently using the requested agent
    OR
    b. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed
    OR
    c. ONE of the following:
        i. The patient has a diagnosis of chronic cancer pain due to an active malignancy
        OR
        ii. The patient is eligible for hospice care
        OR
        iii. The patient is undergoing treatment of chronic non-cancer pain and ALL of the following are met:
            1. The prescriber provides documentation of a formal, consultative evaluation including:
                a. Diagnosis
                AND

b. A complete medical history which includes previous and current pharmacological and non-pharmacological therapy

AND

2. The requested agent is not prescribed as an as-needed (prn) analgesic

AND

3. ONE of the following:
   a. The patient's medication history includes a trial of at least 7 days of an immediate-acting opioid

   OR

   b. The patient has a documented intolerance, FDA labeled contraindication(s), or hypersensitivity to immediate-acting opioid

AND

4. The prescriber has confirmed that a patient-specific pain management plan is on file for the patient

AND

5. The prescriber has confirmed that the patient is not diverting the requested medication, according to the patient's records in the state's prescription drug monitoring program (PDMP), if applicable

AND

2. ONE of the following:
   a. The patient is not concurrently using a buprenorphine or buprenorphine/naloxone for opioid dependence treatment

   OR

   b. The prescriber has submitted documentation supporting concurrent use of an opioid and the requested buprenorphine product due to one of the following:
      i. Dental procedure with dates
      ii. Surgery with dates
      iii. Acute injury with dates

AND

3. The patient does not have any FDA labeled contraindication(s) to the requested agent

AND

4. ONE of the following:
   a. The requested dose is within the program quantity limit

   OR

   b. The requested dose is above the program quantity limit AND BOTH of the following:
      i. The requested dose cannot be achieved using a lesser quantity of a higher strength

      AND

      ii. The prescriber has submitted documentation in support of therapy with a higher dose (quantity) for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 6 months

treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE[10,15-30,33,34,36,37]

Brand/Generic Name	Dosing Frequency (Maximum Labeled Dose)	Indication and Usage
Narcotics		
Arymo ER™ (morphine sulfate ER) 15, 30, 60 mg	Two or three times daily	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product 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. • Product is not indicated as an as-needed (prn) analgesic.
Avinza® **morphine sulfate ER** 30, 45, 60, 75, 90, 120 mg	Once daily (1600 mg daily)	
Belbuca™ (buprenorphine buccal film) 75, 150, 300, 450, 600, 750, 900 mcg	Twice daily (1800 mcg daily)	
Butrans® **Buprenorphine Transdermal** 5, 7.5, 10, 15, 20 mcg/hour system	1 transdermal system weekly (20 mcg/hr)	
Duragesic® (fentanyl transdermal patch) 12, 25, 50, 75, 100 mcg/hour	15 patches per month	
Embeda® (morphine/naltrexone ER) 20-0.8, 30-1.2, 50-2, 60-2.4, 80-3.2, 100-4 mg	Once or twice daily	
Exalgo® (hydromorphone ER) [a] 8, 12, 16, 32 mg	Once daily	
Fentanyl transdermal patch 37.5, 62.5, 87.5 mcg/hour	15 patches per month	
Hysingla ER™ (hydrocodone ER) 20, 30, 40, 60, 80, 100, 120 mg	Once daily	
Kadian® [a] (morphine ER) 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200 mg	Once or twice daily	

Brand/Generic Name	Dosing Frequency (Maximum Labeled Dose)	Indication and Usage
Morphabond ER™ (morphine ER) 15, 30, 60, 100 mg	Twice daily	
MS Contin® [a] (morphine sulfate ER) 15, 30, 60, 100, 200 mg	Twice daily with some patients requiring three times daily	
Opana ER® [a] (oxymorphone ER) 5, 7.5, 10, 15, 20, 30, 40 mg	Twice daily	
Opana ER crush-resistant® (oxymorphone ER) 5, 7.5, 10, 15, 20, 30, 40 mg	Twice daily	
Oramorph SR® (morphine ER) 15, 30, 60, 100 mg	Twice daily with some patients requiring three times daily	
OxyContin® (oxycodone ER)	Twice daily	
Xtampza ER™ (oxycodone ER) 9, 13.5, 18, 27, 36 mg capsules	Twice daily (288 mg)	
Zohydro ER® Abuse Deterrent (hydrocodone ER) 10, 15, 20, 30, 40, 50 mg capsules	Twice daily	

Brand/Generic Name	Dosing Frequency (Maximum Labeled Dose)	Indication and Usage
Xartemis XR™ (oxycodone/acetaminophen ER) 7.5 mg/325 mg tablet	Twice daily	Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, reserve oxycodone/acetaminophen ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate

Brand/Generic Name	Dosing Frequency (Maximum Labeled Dose)	Indication and Usage
Tapentadol, Tramadol		
Nucynta ER® (tapentadol ER) 50, 100, 150, 200, 250 mg	Twice daily (500 mg daily)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve tapentadol ER for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Tapentadol ER is not indicated as an as-needed (prn) analgesic.
Conzip® (tramadol SR biphasic) 100, 200, 300 mg	Once daily (300 mg daily)	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time
tramadol ER [a] 100, 200, 300 mg	Once daily (300 mg daily)	
Tramadol SR Biphasic (tramadol SR biphasic) 150 mg	Once daily (300 mg daily)	

Brand/Generic Name	Dosing Frequency (Maximum Labeled Dose)	Indication and Usage
Ultram ER® [a] (tramadol ER) 100, 200, 300 mg	Once daily (300 mg daily)	

CLINICAL RATIONALE[1,2]
Narcotic analgesics and combinations are indicated for the treatment of mild to moderate to severe pain. Immediate release products may be administered on an as needed basis whereas extended release agents are used in the treatment of chronic pain. Morphine remains the prototype opioid; as newer agents are introduced, their efficacy and safety are compared to morphine as the gold standard. Morphine is considered the drug of choice for severe pain.[3] There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.[9] Tramadol has been found to be efficacious in several randomized trials for the treatment of neuropathic pain, chronic non-cancer pain, and osteoarthritis pain.[11]

Patients who are opioid tolerant/experienced are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Current Guidelines
Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.[35]

When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week.[35]

Scientific research has identified high-risk prescribing practices that have contributed to the overdose epidemic (e.g., high-dose prescribing, overlapping opioid and benzodiazepine prescriptions, and extended-release/long-acting [ER/LA] opioids for acute pain).[35]

The National Comprehensive Cancer Network (NCCN) Guidelines: Adult Cancer Pain v 2.2015 recommends that in a patient who has not been exposed to opioids in the past morphine is generally considered the standard starting drug of choice. Oral administration is the preferred route. Patients presenting with severe pain needed urgent relief should be treated with parenteral opioids.

The Evidence-based Guideline: Treatment of painful diabetic neuropathy (DPN) from the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation state the following:[11] Dextromethorphan, morphine, tramadol, and oxycodone should be considered for the treatment of DPN, but data is insufficient to recommend one

agent over the other, but are not considered as first line therapy.[11] Tapentadol has a similar mechanism of action as tramadol, with indications for treatment of moderate to severe pain in adults as well as for the treatment of diabetic peripheral neuropathy, but is not recommended by any guidelines.[2,11]

The AAN states that although there is evidence for significant pain relief with opioids in the short term (average duration of trials 5 weeks, range 1-16 weeks), there is no substantial evidence for maintenance of pain relief over longer periods of time, or significant evidence for improved physical function.[31]

The World Health Organization (WHO) Pain Relief Ladder states:[6]
If pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and acetaminophen); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain.

The American Society for Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012) states the following: While there is significant short-term evidence available for all opioids, the evidence for long-term effectiveness is inconclusive due to relatively short (3 months) duration of studies and lack of quality studies. The ASIPP also recommends the following when prescribing opioids for chronic use:[13]

- Before initiating opioid therapy, a comprehensive assessment and documentation which includes comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history.
- Screening for opioid use.
- Implement prescription monitoring program.
- Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating therapy.
- Establish medical necessity for initiating and maintaining therapy.
- Establish treatment goals.
- Establish a robust agreement with patient to prevent overuse, misuse, abuse, and diversion.
- A pain management consultation, may assist non-pain physicians, if high-dose opioid therapy is utilized.

The CDC guideline for opioid prescribing states that although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should continue to use non-pharmacologic and non-opioid pharmacologic pain treatments as appropriate and consider consulting a pain specialist as needed to provide optimal pain management.[35]

Safety
Adverse effects to opioid analgesics include respiratory depression, nausea, vomiting, urinary retention, mental clouding, tolerance and dependence, sedation, ileus, constipation, euphoria, pruritus, and biliary spasms.

Patients should receive FDA approved dosing as excessive narcotic administration may lead to coma or death. Patients that develop opioid tolerance may need increased doses or additional therapies to manage pain. Tramadol and tramadol containing products have been associated with adverse events including seizures that may be dose related.[1,2]

In September 2013 the FDA issued a safety bulletin. In an effort to combat the rising rate of opioid-related deaths, the FDA will require safety label changes on all extended release and

long-acting opioid analgesics (extended-release and long-acting opioids include hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol).[13]

- The new safety information will emphasize that the drugs are only to be used for patients requiring continuous treatment when other treatment options, including non-opioid analgesics or immediate-release opioids, are ineffective or intolerable. The labels will also indicate that the drugs should not be used on an "as-needed" pain relief basis.
- The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts.
- In addition, the FDA is notifying ER/LA opioid analgesic application holders of the need for changes to the following sections of drug labeling: Dosage and Administration; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Patient Counseling Information, and the Medication Guide.[13]
- Once the safety labeling changes are finalized, modifications will also be made to the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), to reflect the updated information.
- The FDA will also require drug companies to conduct longer studies and trials of extended-release and long-acting opioid painkillers that are already on the market. The studies will assess known risks associated with the drugs, including increased sensitivity to pain, misuse, abuse, addiction, overdose, and death.[13]

Hydrocodone combination products have been reclassified to Schedule II by the Drug Enforcement Administration (DEA) effective October 2014. This change followed the recommendation out of the FDA Advisory Committee meeting that occurred in January 2013 where the committee voted 19 to 10 to reschedule these products.[18]

Concomitant use of tramadol with MAO inhibitors or selective serotonin reuptake inhibitors (SSRIs) increases the risk of adverse events such as seizures and serotonin syndrome. Withdrawal symptoms may occur if tramadol is discontinued abruptly.[11]

For additional clinical information see the Prime Therapeutics Formulary Chapters 10.1: Non-Narcotic Analgesics; 10.2A: Narcotic Agonists + Mixed; 10.2B: Tramadol; 10.2C: Narcotic Combinations; and Prime Therapeutics Formulary Monograph: Nucynta (tapentadol)

REFERENCES

1. Facts and Comparisons 4.0, online edition. Accessed December 8, 2014.
2. Clinical Pharmacology. http://www.clinicalpharmacology-ip.com/Default.aspx Accessed on December 8, 2014.
3. Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev*. 2008;17:CD003868.
4. W. L. Lanie, E. D. Kharasch. Contemporary Clinical Opioid Use: Opportunities and Challenges *Mayo Clin Pro.* 2009;84(7):572-575.
5. National Comprehensive Cancer Network (NCCN) Guidelines: Adult Cancer Pain v.2.2015 Available @ www.NCCN.org. Accessed November 2015.
6. The World Health Organization. Pain relief Ladder. Available @ http://www.who.int/cancer/palliative/painladder/en/. Accessed October 2011.
7. FDA. Safety Communication APAP Combination Products. 1/13/2011 @ Safety Communication: APAP 1/13/2011 @ http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm
8. US Food and Drug Administration. Organ-specific warnings; internal analgesic, antipyretic, and antirheumatic drug productus for over-the-counter human use.

Federal Register. 2009 Apr 29;74(81). Available at http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf 20
9. World Health Organization (WHO). WHO guidelines on the pharmacological treatment of persisting pain in children with medical illness 2012. Accessed 10/31/2012 @ http;//apps.who.int/medicinedocs/en/m/abstract/Js1911en/
10. Ultram prescribing information. Janssen Pharmaceuticals. December 2016
11. Bril V, England j, Franklin GM, et al. Evidenced-based guideline:treatment of painfl diabetic neuropathy (report from the American Academy of Neurology, the American Assoc of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation).*Neurology* 2011;76:1758-1765
12. FDA. News Release. Long Acting Oral Opioids. 9/10/2013. Available @ http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm
13. Manchikanti l, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain. *Pain Physician* 2012;15:S1-S66.
14. DEA: DEA to Publish Final Rule Rescheduling Hydrocodone Combination Products. Accessed 21 November 2014 at http://www.dea.gov/divisions/hq/2014/hq082114.shtml
15. Avinza prescribing information. Pfizer Inc. June 2015.
16. Butrans prescribing information. Purdue Pharma LP. October 2017.
17. Embeda prescribing information. Pfizer Inc. December 2016.
18. Exalgo prescribing information. Mallinckrodt Inc. December 2016.
19. Hysingla ER prescribing information. Purdue Pharma LP. December 2016.
20. Kadian prescribing information. Actavis Kadian LLC. December 2016.
21. MS Contin prescribing information. Purdue Pharma LP. December 2016.
22. Opana ER prescribing information. Endo Pharmaceuticals Inc. December 2016.
23. Zohydro ER prescribing information. Zogenix Inc. November 2017.
24. Nucynta ER prescribing information. Janssen Pharmaceuticals Inc. December 2016.
25. Conzip prescribing information. Vertical Pharmaceuticals Inc. December 2016.
26. Ryzolt prescribing information. Purdue Pharma. September 2011.
27. Tramadol SR biphasic prescribing information. Stat Rx USA. October 2009.
28. Ultram ER prescribing information. Janssen Pharmaceuticals Inc. August 2017.
29. OxyContin prescribing information. Purdue Pharma L.P. December 2016.
30. Xartemis XR prescribing information. Mallinkrodt LLC. November 2017.
31. Opioids for chronic noncancerpain: a position paper of the American Academy of Neurolog. Neurology. September 2014. Accessed at www.neurology.org/content/83/14/1277.full.html
32. Duragesic prescribing information. Janssen Pharmaceuticals. June 2017.
33. Belbuca prescribing information. Endo Pharmaceutical, Inc. December 2016.
34. Xtampza prescribing information. Collegium Pharmaceuticals, Inc. December 2016.
35. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep. ePub: 15 March 2016. DOI: https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
36. Arymo ER prescribing information. Egalet. January 2017.
37. Morphabond ER prescribing information. Inspirion Delivery Technologies LLC. April 2017.