OXYMORPHONE ER FORMULATIONS (brand and generic)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Oxymorphone ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Oxymorphone, a pure opioid agonist, is relatively selective for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. Oxymorphone extended release (ER) formulations (brand and generic) are available as 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets for oral administration. Doses are generally administered every 12 hours.

Pain is a subjective episode described as an unpleasant, multi-dimensional, sensory, and emotional experience associated with actual or potential tissue damage or described in relation to such damage. The perception of pain is further influenced by physical, psychological, social, cultural, and hereditary factors. Persistent pain will often require treatment with regularly scheduled analgesics and supplemental analgesics for breakthrough periods.
OXYMORPHONE ER FORMULATIONS (brand and generic) (cont.)

Chronic pain can be defined as any pain that persists beyond the anticipated time of normal tissue healing, which is generally assumed to be three months. Chronic pain may be caused by numerous medical conditions and syndromes with widely divergent pathophysiology.

Opioid analgesic medications relieve a wide variety of pain syndromes and are widely accepted for the treatment of severe acute pain and chronic pain related to active cancer. In contrast, the use of chronic opioid therapy to treat other types of chronic pain not associated with malignancy remains controversial. There is a large amount of clinical experience with opioids for the treatment numerous pain syndromes, yet there are limited data on the safety and efficacy of long-term opioid therapy for chronic non-cancer pain.

There are many agents available with brand and generic options for the treatment of pain. Several agents are available as both immediate (or short) acting and long acting formulations. There are clinically meaningful differences in potency, time to onset, elimination and duration of action among the various compounds.

Long-acting opioids are more convenient than short-acting opioids for the treatment of chronic pain conditions, although there is no reliable evidence of superiority. There is no reliable comparative evidence demonstrating that one long-acting opioid is more effective than another opioid analgesic, including immediate-release or other controlled-release formulations.

Specific central nervous system (CNS) opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of pain. Opioid receptors have also been identified within the peripheral nervous system (PNS). The primary site of therapeutic action of opioids is within the CNS. Opioid agonists are thought to reduce pain by acting primarily through interaction with opioid mu-opioid receptors located in the brain, spinal cord, and smooth muscle. Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center.

All opioids have the potential to cause respiratory depression, abuse and physical dependence. None have been proven to be safer than another. One method employed by manufacturers to mitigate abuse of opioids has been formulating products that are difficult to extract the main opioid ingredient from the original form.

Providers should individualize treatment of pain in every case, using non-opioid analgesics, opioids on an as needed basis, combination products, and when appropriate chronic opioid therapy in a progressive comprehensive plan of pain management.

The World Health Organization’s (WHO) guidelines for cancer pain management recommends a three-stepped approach with consideration for the type of pain and response to therapy. Initial therapy includes non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. For moderate to severe pain, opioid analgesics are recommended. Titration of dose and frequency is individualized to the patient’s response and development of adverse effects. For patients with inadequate pain relief and intolerable opioid-related toxicity/adverse effects, a switch to an alternative opioid may be an option for obtaining symptomatic relief.

The National Comprehensive Cancer Network (NCCN) 2015 Clinical Practice Guideline in Oncology: Adult Cancer Pain outlines numerous steps in managing opioid medications in cancer pain that can be adapted for non-cancer pain management. Examples of some of the recommendations include: use short-acting opioid medications for titration, for persistent pain initiate regular schedule of opioid with a rescue dose as needed, calculate opioid dose increase based on the total 24-hour dose (around the clock/scheduled and as needed
doses), when possible, use the same short-acting and long-acting opioid formulation, and simplify regimen for improved adherence.

In theory, opioids have no maximum or ceiling dose; however recent guidelines suggest close evaluation of individuals using large doses of opioid medications for unique opioid related adverse effects.

**Definitions:**

**Sustained release (SR) and extended release (ER) and controlled release (CR) formulation:**
A dose form where active drug is released slowly over a prolonged period of time thereby allowing for less frequent administration throughout the day

Also known as long-acting formulation

**Immediate release formulation:**
A dose form where active drug is released quickly over a short period of time and usually requires more frequent/multiple administration throughout the day

Also known as short-acting formulation

**Drug related events:**

- **Ineffective / failure**
  Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

  A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

- **Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance
  Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

  **Allergic reaction / hypersensitivity** – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.
If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

*Contraindication*

Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

*Non-adherence*

Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

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**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

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**Criteria:**

See “Resources” section for FDA-approved dosage.

- Precertification for Oxymorphone extended release formulation (brand and generic) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Oxymorphone extended release formulation (brand and generic) is considered *medically necessary* with medical record documentation of ALL of the following:
1. Individual is 18 years of age or older

2. Documented diagnosis of pain severe enough to require daily, around-the-clock, long-term opioid treatment AND for which alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain

3. Used in conjunction with a comprehensive pain management regimen that includes (where clinically appropriate):
   - Immediate release opioid
   - Acetaminophen (APAP)
   - Non-steroidal anti-inflammatory drug (NSAID)
   - Combination product of acetaminophen or NSAID with an opioid
   - Gastrointestinal ulcer protection
   - Adjuvant pain medication

4. Absence of ALL of the following contraindications:
   - Respiratory depression
   - Acute or severe bronchial asthma
   - Known or suspected paralytic ileus or other GI obstruction
   - Moderate to severe hepatic impairment
   - Known hypersensitivity to Oxymorphone, Morphine, or Morphine analogs such as Codeine

5. Absence of ALL of the following exclusions:
   - Simultaneous use with another long-acting opioid drug
   - Used on an as needed basis
   - Used during immediate post-operative period
   - Used for the treatment of mild pain
   - Used for pain not expected to persist for an extended period of time
   - Simultaneous use with opioid antagonist or opioid agonist-antagonist

- Oxymorphone extended release formulation (brand and generic) for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

History:
- Pharmacy and Therapeutics review 07-21-2016
- Director Pharmacy Mgmt. review 06-25-2016
- Pharmacy and Therapeutics review 07-16-2015
- Director Pharmacy Mgmt. review 06-14-2015

Date: Activity:
- 07-21-2016 Approved
- 06-25-2016 Criteria revisions
- 07-16-2015 Approved
- Added to Description section to include NCCN guideline for opioid use, added to Definitions section to include ER,
OXYMORPHONE ER FORMULATIONS (brand and generic) (cont.)

<table>
<thead>
<tr>
<th>Date</th>
<th>Criteria Revisions</th>
<th>Revisions</th>
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<tbody>
<tr>
<td>06-25-2016</td>
<td>4. Absence of ALL of the following contraindications:</td>
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<tr>
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<td>▪ Acute or severe bronchial asthma or at risk for hypercarbia or CO₂ retention</td>
<td>▪ Acute or severe bronchial asthma</td>
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<tr>
<td>06-25-2016</td>
<td>5. Absence of ALL of the following, where Oxymorphone ER formulations (brand and generic) will be used:</td>
<td>5. Absence of ALL of the following exclusions:</td>
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<td>▪ With another long-acting opioid drug</td>
<td>▪ Simultaneous use with another long-acting opioid drug</td>
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<td>▪ On an as needed basis</td>
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<td></td>
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<td>▪ For mild pain</td>
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<td>▪ With opioid antagonist or opioid agonist-antagonist</td>
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<td>06-14-2015</td>
<td>Used in conjunction with a comprehensive pain management regimen that includes (where clinically appropriate:</td>
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<tr>
<td></td>
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<td>▪ Combination product of APAP or</td>
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SR, CR and immediate release definitions, added item in Criteria #2, divided Criteria #3 into two separate sections
Approved
Description section rewritten, added Definitions section to define drug related events, Criteria #1 changed (see below)
Title changed from Opana ER to Oxymorphone ER formulations (brand and generic), this change was made throughout the coverage guide, Description section updated on available strengths, minor correction in criteria for paralytic ileus and known hypersensitivities

Pharmacy and Therapeutics review 07-19-2012 Adopted guideline
Director Pharmacy Mgmt. review 07-19-2012 Development
PHARMACY COVERAGE GUIDELINES

SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 08/10/12
LAST REVIEW DATE: 07/21/16
LAST CRITERIA REVISION DATE: 06/25/16
ARCHIVE DATE:

NEXT REVIEW DATE: 3rd QUARTER 2017

OXYMORPHONE ER FORMULATIONS (brand and generic) (cont.)

opioid
- Gastrointestinal ulcer protection
- Adjuvant pain management

NSAID with an opioid
- Gastrointestinal ulcer protection
- Adjuvant pain management

06-14-2015
3. All of the following circumstances and/or conditions have been ruled out and/or assessed:
   - Oxymorphone sustained release formulations (brand and generic) use with other long acting opioid drugs
   - Oxymorphone sustained release formulations (brand and generic) use on an as needed basis
   - Oxymorphone sustained release formulations (brand and generic) use during immediate post-operative period
   - Mild pain
   - Pain not expected to persist for an extended period of time
   - Respiratory depression
   - Acute or severe bronchial asthma or at risk for hypercarbia or CO₂ retention
   - Known or suspected paralytic ileus or other GI obstruction
   - Moderate to severe hepatic impairment
   - Known hypersensitivity to Oxymorphone, Morphine, or Morphine analogs such as Codeine

Concurrent use of opioid antagonist or opioid agonist-antagonist

3. Absence of ALL of the following contraindications:
   - Respiratory depression
   - Acute or severe bronchial asthma or at risk for hypercarbia or CO₂ retention
   - Known or suspected paralytic ileus or other GI obstruction
   - Moderate to severe hepatic impairment
   - Known hypersensitivity to Oxymorphone, Morphine, or Morphine analogs such as Codeine

4. Absence of ALL of the following, where Oxymorphone ER formulations (brand and generic) will be used:
   - With another long-acting opioid drug
   - On an as needed basis
   - During immediate post-operative period
   - For mild pain
   - For pain not expected to persist for an extended period of time

With opioid antagonist or opioid agonist-antagonist

08-07-2014
Adult members (18 years of age and older) with documented diagnosis of moderate to severe pain requiring continuous around-the-clock opioid treatment for an extended period of time

Adult members (18 years of age and older) with documented diagnosis of pain severe enough to require daily, around-the-clock, long-term opioid treatment AND for which alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain

07-31-2013
And all of the following circumstances and/or conditions have been ruled out:
- Paralytic ileus

Known hypersensitivity to Oxymorphone or other Morphine analogs

And all of the following circumstances and/or conditions have been ruled out and/or assessed:
- Paralytic ileus or other GI obstruction
- Known hypersensitivity to Oxymorphone, Morphine, Morphine analogs such as Codeine
OXYMORPHONE ER FORMULATIONS (brand and generic) (cont.)

Resources:

Opana® ER package insert revised by manufacturer on 04/2014, reviewed on 08-07-2014

Opana® ER package insert revised by manufacturer on 08/2012, reviewed on 07-31-2013

Opana® ER package insert revised by manufacturer on 01/2012, reviewed on 06-16-2012

National Comprehensive Cancer Network Clinical Practice Guideline in Oncology: Adult Cancer Pain version 2.2015

Institute for Clinical Systems Improvement Health Care Guideline: Assessment and management of chronic pain. 5th edition, November 2011


Cancer pain relief: with a guide to opioid availability. World Health Organization 1996

Refer to package insert for complete dosing information.

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>OPANA ER is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. Not intended for use as an as needed analgesic. Not indicated in the immediate post-operative period or if the pain is mild or not expected to persist for an extended period of time.</td>
<td>Individualize treatment; titrate to effective and tolerable dose. Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating. Use symmetrical dosing, every 12h dosing is appropriate for the majority of patients. Opioid-Naïve Patients: Initiate treatment with 5 mg every 12 hours. Opioid-Experienced Patients: Ratios as a guide to convert only from other opioids to OPANA ER. Safety and effectiveness of OPANA ER in pediatric patients below the age of 18 years have not been established</td>
</tr>
</tbody>
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