EXALGO® (hydromorphone hydrochloride) extended-release oral tablet
HYDROMORPHONE HYDROCHLORIDE extended-release oral tablet

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:

Exalgo (hydromorphone) and Hydromorphone hydrochloride ER are indicated for the management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which 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. Exalgo (hydromorphone) Hydromorphone hydrochloride ER are not indicated as an as-needed (prn) analgesic.

Hydromorphone, a semi-synthetic morphine derivative, is an agonist of mu-opioid receptors. The precise mechanism of action of opioid analgesics is not known but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS).

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. 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 generally 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 also 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 their superiority. There is no reliable comparative evidence demonstrating that one long-acting opioid is more effective than another opioid analgesic, including immediate-acting or other long-acting 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-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.
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HYDROMORPHONE HYDROCHLORIDE extended-release oral tablet (cont.)

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 to identify unique opioid related adverse effects.

Definitions:

Opioid Risk Assessment Tool:

<table>
<thead>
<tr>
<th>Score each that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
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<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rx drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Personal history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Rx drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Age between 16-45 years</td>
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<td>1</td>
</tr>
<tr>
<td>History of preadolescent sexual abuse</td>
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<td>0</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Total score</td>
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<td></td>
</tr>
</tbody>
</table>

Assessment of risk

| Low risk for abuse                   | ≤ 3    |
| Moderate risk for abuse              | 4-7    |
| High risk for abuse                  | ≥ 8    |

Definitions of risk

Low = unlikely to abuse
Moderate = as likely will as will not abuse
High = likely to abuse
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HYDROMORPHONE HYDROCHLORIDE extended-release oral tablet (cont.)

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 prescribe 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.

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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Exalgo (brand) and hydromorphone HCl ER (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.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Exalgo (brand) and hydromorphone HCl ER (generic) is considered medically necessary when ALL of the following criteria are met:

  1. Individual is 18 years of age or older
  2. Individual is opioid-tolerant with medical record documentation 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 inadequate
  3. Individual is determined opioid-tolerant with medical record documentation of **ONE** of the following:
     - At least 60 mg oral morphine per day for one week or longer
     - At least 25 mcg transdermal fentanyl/hour for one week or longer
     - At least 30 mg oral oxycodone/day for one week or longer
     - At least 8 mg oral hydromorphone/day for one week or longer
     - At least 25 mg oral oxymorphone/day for one week or longer
     - An equianalgesic dose of another opioid for one week or longer
  4. Used in conjunction with a comprehensive pain management regimen that includes:
     - Immediate release opioid
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- Combination product of acetaminophen or non-steroidal anti-inflammatory drug with an opioid
- Gastrointestinal ulcer protection (where clinically appropriate)
- Adjuvant pain medication (where clinically appropriate)

5. Individual is unable to use **ALL** of the following due to ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain:
   - Morphine sustained release tablet, generic
   - Morphine extended release capsule, generic
   - Avinza ER capsule
   - Embeda ER capsule
   - Kadian ER capsule
   - Nucynta ER tablet
   - Oxycodone ER tablet
   - Fentanyl transdermal
   - Tramadol ER tablet, non-biphasic
   - Tramadol ER capsule, non-biphasic

6. Absence of **ALL** of the following contraindications:
   - Opioid non-tolerant patients
   - Significant respiratory depression
   - Acute or severe bronchial asthma
   - Known or suspected gastrointestinal obstruction, including paralytic ileus
   - Individuals who have had surgical procedures and/or underlying diseases resulting in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum
   - Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites

7. Absence of **ALL** of the following exclusions:
   - Simultaneous use of Exalgo (brand) or hydromorphone HCl ER (generic) with mixed agonist/antagonist and partial agonist opioid analgesics
   - Simultaneous use of Exalgo (brand) or hydromorphone HCl ER (generic) with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping an MAOI
   - Use in patients with impaired consciousness or coma who are susceptible to intracranial effects of carbon dioxide retention
   - Woman who is breast feeding an infant or child
   - Severe hepatic (Child Pugh Class C) impairment
   - Severe renal impairment (creatinine clearance < 30 mL/min)
   - Short-term treatment of pain
   - Simultaneous use with another long-acting opioid drug

- **Continuation of coverage (renewal request):** Exalgo (brand) or hydromorphone HCl ER (generic) is considered **medically necessary** with documentation of **ALL** of the following:
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1. The individual has benefited from therapy but remains at high risk
2. The condition has not progressed or worsened while on therapy
3. Individual has not developed any contraindications or other exclusions to its continued use

➢ Exalgo (brand) and hydromorphone HCl ER (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.

This includes but is not limited to the following:
- Management of intermittent pain (such as use on an as-needed (prn) basis)
- Management of mild or moderate pain

Resources:


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

FDA-approved indication and dosage:
### Indication

EXALGO® is an opioid agonist indicated in opioid-tolerant patients 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.

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

#### 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 EXALGO 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.

- EXALGO is not indicated as an as-needed (prn) analgesic.

### Recommended Dose

- For once daily administration
- Instruct patients to swallow EXALGO tablets intact.
- Do not abruptly discontinue EXALGO.
- To convert to EXALGO from another opioid, use available conversion factors to obtain estimated dose.
- Dose may be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.

### Hydromorphone HCl ER

Hydromorphone HCl ER is an opioid agonist indicated in opioid-tolerant patients 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.

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

#### 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 Hydromorphone HCl ER 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.

- Hydromorphone HCl ER is not indicated as an as-needed (prn) analgesic.

### Recommended Dose

- For once daily administration
- Instruct patients to swallow Hydromorphone HCl ER tablets intact.
- Do not abruptly discontinue Hydromorphone HCl ER.
- To convert to Hydromorphone HCl ER from another opioid, use available conversion factors to obtain estimated dose.
- Dose may be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.