NDA 21-217 EXALGO™ (HYDROMORPHONE HYDROCHLORIDE) EXTENDED RELEASE TABLETS CII

Opioid Agonist

Mallinckrodt Inc., a Covidien Company
675 McDonnell Boulevard
Hazelwood, MO 63042

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of EXALGO.
2. To inform patients and healthcare professionals about the safe use of EXALGO.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each EXALGO prescription in accordance with 21 CFR§208.24. The following additional measures will be instituted:

1. Medication Guides will be included in the primary and secondary packaging of the commercial product.
2. One (1) Medication Guide will be affixed (spot glued) to each bottle of EXALGO
3. Additional Medication Guides (48) will be provided with each carton containing 12 bottles of EXALGO; partial cases will include four additional Medication Guides per bottle.
4. The Medication Guide also will be available through the EXALGO REMS web site (www.exalgorems.com), the product web site (www.exalgo.com), or through the toll-free Product Monitoring department number at 1-800-778-7898.
5. The Medication Guide also will be distributed with the EXALGO REMS Healthcare Professional Education Program Kit as part of the prescribing program.

Please see the appended Medication Guide.

B. Element to Assure Safe Use

1. Healthcare providers who prescribe EXALGO will receive training.
    a. Covidien will ensure that training will be provided to healthcare providers who prescribe EXALGO. To become trained, each prescriber will be provided with the materials in the EXALGO REMS Healthcare Professional Education Program Kit.

        The training includes the following:

        i. Proper patient selection
        ii. Appropriate EXALGO dosing and administration
        iii. General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
        iv. The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including EXALGO
        v. The risks of EXALGO including:
            1) The risk of overdose caused by exposure to an essentially immediate-release form of hydromorphone due to broken, chewed, crushed, or dissolved EXALGO
            2) The risk of addiction from exposure to EXALGO
            3) The risk of overdose with use in opioid non-tolerant individuals
        vi. Information to counsel patients on the need to store opioid analgesics safely out of the reach of children and household acquaintances
        vii. The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide

    b. Covidien will ensure that within 60 days of approval of EXALGO, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists; including pain specialists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of EXALGO as well as the need to complete the EXALGO REMS Education Program. This letter will also be available on both the product web site (www.exalgo.com) and the REMS web site (www.exalgorems.com) for 1 year.

    c. The mailing will also include the EXALGO Healthcare Professional Education Program Kit which will consist of the following:

        i. A copy of the full Prescribing Information (PI);
        ii. The Medication Guide;

iii. The EXALGO Prescribing Brochure;

iv. The EXALGO Essential Information Form.

d. Additional printed educational materials will be made available through field-force distribution and the toll-free Product Monitoring department number at 1-800-778-7898.

e. The educational materials will be available for download at www.exalgorems.com.

f. Covidien will maintain a list of all prescribers that have completed the EXALGO REMS Education Program.

g. Prescribers will be re-trained, including review of the educational material and completion of the EXALGO Essential Information Form, every two years or following substantial changes to the EXALGO REMS. Substantial changes may include, changes in the EXALGO Full Prescribing Information, EXALGO Medication Guide, or EXALGO REMS that require substantial modification of the educational materials.

The following materials are part of the REMS and are appended:

- Dear Healthcare Professional Letter
- EXALGO REMS Web site
- EXALGO REMS Healthcare Professional Education Program Kit
  - Full Prescribing Information
  - Medication Guide
  - EXALGO Essential Information Form
  - EXALGO Prescribing Brochure

C. Implementation System

Because EXALGO can be approved without the Elements to Assure Safe Use described under 505-1(f)(3)(B), (C), and (D) of the Food Drug & Cosmetic Act as amended an implementation system is not required.

D. Timetable for Submission of Assessments

Covidien will submit REMS Assessments to the U.S. Food and Drug Administration (FDA) every 6 months for the first year from the date of approval of the REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. Covidien will submit each assessment so that it will be received by the FDA on or before the due date.

COVIDIEN

[Month date, year]

Dear Healthcare Professional:

Mallinckrodt Inc., a Covidien company, is notifying you that EXALGO™ (hydromorphone hydrochloride) Extended Release Tablets CII has been approved for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. Patients considered opioid tolerant are those who are taking 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, for 1 week or longer. EXALGO is NOT intended for use as an as-needed analgesic.

Please see full prescribing information including BOXED WARNING.
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

Potential for Abuse

EXALGO contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. EXALGO can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Proper Patient Selection

EXALGO is an extended release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered opioid tolerant are those who are taking 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, for a week or longer.

EXALGO is for use in opioid tolerant patients only.

Fatal respiratory depression could occur in patients who are not opioid tolerant.

Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone.

Limitations of Use

EXALGO is not indicated for the management of acute or postoperative pain.

EXALGO is not intended for use as an as-needed analgesic.

EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved or crushed EXALGO or its contents leads to rapid release and absorption of a potentially fatal dose of hydromorphone.

675 McDonnell Blvd.
Hazelwood, MO
63042

314-654-2000 [T]

WWW.EXALGOREMS.COM

To ensure that the benefits of EXALGO outweigh the potential risks, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the U.S. Food and Drug Administration (FDA). The EXALGO REMS requires:

- Healthcare Professional (HCP) training on responsible EXALGO prescribing and use
- Distribution of REMS educational materials to HCPs
- Distribution of the Exalgo Medication Guide to patients and/or caregivers every time EXALGO is dispensed

The goals of this REMS are to:

- Inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of EXALGO
- Inform patients and healthcare professionals about the safe use of EXALGO.

EXALGO should only be prescribed in accordance with the EXALGO REMS including HCP training on responsible EXALGO prescribing and use. HCPs should review the educational material in print or online at www.exalgorems.com. The printed materials are available as part of the EXALGO REMS Healthcare Professional Education Program Kit. Prior to prescribing, the training materials should be reviewed along with the Prescribing Information and Medication Guide. The Essential Information Form found in the kit should be completed and faxed to Covidien at 1-888-423-3511. A confirmation of receipt will be faxed or emailed.

Please see the enclosed Full Prescribing Information, including the boxed warning, Medication Guide, and EXALGO Prescribing Brochure for important safety information for EXALGO.

EXALGO contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. EXALGO can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion.

EXALGO is for use in opioid tolerant patients only. Administration of EXALGO to patients who are not opioid tolerant could result in fatal respiratory depression.

EXALGO is not indicated for the management of acute or postoperative pain and is not intended for use as an as-needed analgesic.

EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved, or crushed EXALGO or its contents can lead to rapid release and absorption of a potentially fatal dose of hydromorphone.

EXALGO contains hydromorphone, an opioid agonist and a schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders, and are subject to criminal diversion. Proper assessment of the patient, proper prescribing practices including careful titration for patients who are new to EXALGO, periodic re-evaluation of

therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse and misuse of opioid drugs.

Abuse of EXALGO by breaking, crushing, chewing, or dissolving the contents of the tablet can result in the uncontrolled delivery of the opioid and pose a significant risk of overdose and death.

Selection of patients for treatment with EXALGO is governed by the same principles that apply to the use of similar opioid analgesics. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as-needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as the guidelines outlined by the World Health Organization or the Federation of State Medical Boards Model Guidelines.

The dose range studied in clinical trials of EXALGO is 8 mg to 64 mg, once-daily. The tablets are to be administered every 24 hours with or without food. Discontinue all other extended release opioids when beginning EXALGO therapy.

Use caution to avoid medication errors when prescribing or dispensing EXALGO 8 mg tablets, as 8 mg tablets are also available as immediate-release hydromorphone tablets.

It is critical to initiate the dosing regimen individually for each patient. Overestimating the EXALGO dose when converting patients from another opioid medication can result in fatal overdose with the first dose.

In the selection of the initial dose of EXALGO, give attention to the following:

- Daily dose, potency, and specific characteristics of the opioid the patient has been taking previously
- Reliability of the relative potency estimate used to calculate the equivalent hydromorphone dose needed
- Patient's degree of opioid tolerance
- Age, general condition, and medical status of the patient
- Concurrent non-opioid analgesics and other medications, such as those with central nervous system (CNS) activity
- Type and severity of the patient's pain
- Balance between pain control and adverse effects
- Risk factors for abuse and addiction, including a prior history of abuse and addiction

In general, EXALGO should not be abruptly discontinued. When the patient no longer requires therapy with EXALGO, taper doses gradually, down to a dose of 8 mg before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the physically dependent patient.

In clinical trials, the most commonly reported (≥10%) adverse events associated with EXALGO were constipation, nausea, vomiting, somnolence, headache, fatigue, and dizziness. These adverse events should be expected and managed accordingly. For more information, please see accompanying Full Prescribing Information, including boxed warning.

It is important that you discuss the risks of EXALGO with your patients and their caregivers. Provide your patients with a Medication Guide and encourage them to read the Medication Guide (see enclosed copy). The Medication Guide provides important information on the safe and effective use of EXALGO and will be provided to patients with each prescription. Patients should be counseled on the need to store EXALGO safely out of the reach of children and household acquaintances.

Additional copies of the Medication Guide are available by download from www.exalgorems.com, by contacting our EXALGO Call Center at 1-888-9EXALGO (1-888-939-2546) or by asking your Covidien representative.

Please report all suspected adverse events associated with the use of EXALGO to Covidien Product Monitoring at 1-888-778-7898.

Adverse event information may also be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch.

Please take the time to review the enclosed Full Prescribing Information, Medication Guide and EXALGO Prescribing Brochure. If you have any questions or concerns, you may contact our Product Monitoring department at 1-888-778-7898 or visit www.exalgorems.com

Sincerely,

Herbert Neuman, MD
Chief Medical Officer
Vice President, Medical Affairs
Covidien Pharmaceuticals

Enclosures:

- Full Prescribing Information
- Medication Guide
- EXALGO Prescribing Brochure

Toll Free: 1.888.9EXALGO (1.888.939.2546) Fax: 1.888.423.3511

EXALGO™ (hydromorphone HCl) II
Extended-Release Tablets

Complete the EXALGO REMS Education Program. **Start here. >>**

Risk Evaluation and Mitigation Strategy

In order to ensure that the benefits of EXALGO outweigh the potential risks, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the U.S. Food and Drug Administration (FDA).

The goals of this REMS are to:

1. Inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of EXALGO
2. Inform patients and healthcare professionals about the safe use of EXALGO

Education Program: Training and REMS Information

The EXALGO REMS requires that EXALGO should only be prescribed in accordance with the EXALGO REMS, including healthcare professional training on responsible prescribing and use.

The EXALGO REMS education can be completed in 3 easy steps.

STEP 1
Review the Prescribing Brochure along with the Prescribing Information and Medication Guide

STEP 2
Complete and submit the EXALGO Essential Information Form online or via fax to 1.888.423.3511

STEP 3
You will receive confirmation via fax or email

You may download the EXALGO REMS information:

Dear Healthcare Professional Letter >>
EXALGO Full Prescribing Information >>
EXALGO Medication Guide >>
EXALGO Prescribing Brochure >>
EXALGO Essential Information Form >>

For additional information, please call Covidien at 1.888.9EXALGO (1.888.939.2546)

Please see full prescribing information including **BOXED WARNING.**
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

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Proper Patient Selection

EXALGO is an extended release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered opioid tolerant are those who are taking 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, for a week or longer.

EXALGO is for use in opioid tolerant patients only.

Fatal respiratory depression could occur in patients who are not opioid tolerant.

Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone.

Limitations of Use

EXALGO is not indicated for the management of acute or postoperative pain.

EXALGO is not intended for use as an as-needed analgesic.

EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved or crushed EXALGO or its contents leads to rapid release and absorption of a potentially fatal dose of hydromorphone.

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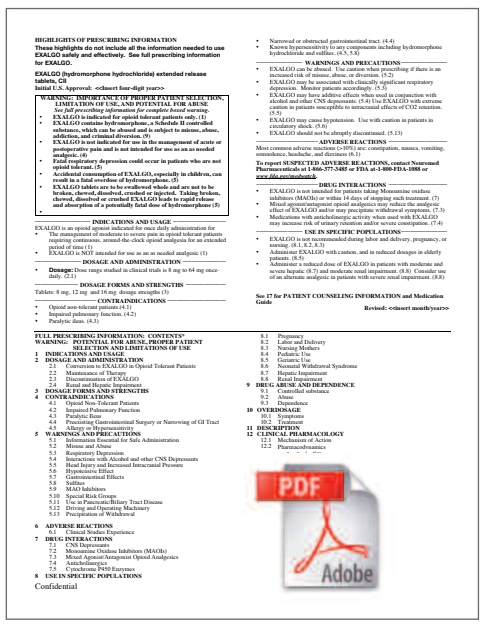
Toll Free: 1.888.9EXALGO (1.888.939.2546) Fax: 1.888.423.3511

EXALGO™ (hydromorphone HCl) CII

Extended-Release Tablets

Complete the EXALGO REMS Education Program. **Start here. >>**



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXALGO safely and effectively. See full prescribing information for EXALGO.

EXALGO (hydromorphone hydrochloride) extended release tablets, CII

Initial U.S. Approval: <<Insert four-digit year>>

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, LIMITATION OF USE, AND POTENTIAL FOR ABUSE
See full prescribing information for complete boxed warning.

- EXALGO is indicated for opioid tolerant patients only. (1)
- EXALGO contains hydromorphone, a Schedule II controlled substance, which can be abused and is subject to misuse, abuse, addiction, and criminal diversion. (9)
- EXALGO is not indicated for use in the management of acute or postoperative pain and is not intended for use as an as needed analgesic. (4)
- Fatal respiratory depression could occur in patients who are not opioid tolerant. (5.5)
- Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone. (5)
- EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved or crushed EXALGO leads to rapid release and absorption of a potentially fatal dose of hydromorphone (5)

INDICATIONS AND USAGE

EXALGO is an opioid agonist indicated for once daily administration for

- The management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time (1)
- EXALGO is NOT intended for use as an as needed analgesic (1)

DOSAGE AND ADMINISTRATION

- Dosage: Dose range studied in clinical trials is 8 mg to 64 mg once-daily. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 8 mg, 12 mg and 16 mg dosage strengths (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients (4.1)
- Impaired pulmonary function. (4.2)
- Paralytic ileus. (4.3)
- Narrowed or obstructed gastrointestinal tract. (4.4)
- Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites. (4.5, 5.8)

WARNINGS AND PRECAUTIONS

- EXALGO can be abused. Use caution when prescribing if there is an increased risk of misuse, abuse, or diversion. (5.2)
- EXALGO may be associated with clinically significant respiratory depression. Monitor patients accordingly. (5.5)
- EXALGO may have additive effects when used in conjunction with alcohol and other CNS depressants. (5.4) Use EXALGO with extreme caution in patients susceptible to intracranial effects of CO2 retention. (5.5)
- EXALGO may cause hypotension. Use with caution in patients in circulatory shock. (5.6)
- EXALGO should not be abruptly discontinued. (5.13)

ADVERSE REACTIONS

Most common adverse reactions (>10%) are: constipation, nausea, vomiting, somnolence, headache, and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurmed Pharmaceuticals at 1-866-377-5485 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- EXALGO is not intended for patients taking Monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment. (7)
- Mixed agonist/antagonist opioid analgesics may reduce the analgesic effect of EXALGO and/or may precipitate withdrawal symptoms. (7.3)
- Medications with anticholinergic activity when used with EXALGO may increase risk of urinary retention and/or severe constipation. (7.4)

USE IN SPECIFIC POPULATIONS

- EXALGO is not recommended during labor and delivery, pregnancy, or nursing. (8.1, 8.2, 8.3)
- Safety of EXALGO with caution, and in reduced dosages in elderly patients. (8.5)
- Administer a reduced dose of EXALGO in patients with moderate and severe hepatic (8.7) and moderate renal impairment. (8.8) Consider use of an alternate analgesic in patients with severe renal impairment. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: <<Insert month/year>>

FULL PRESCRIBING INFORMATION: CONTENTS*

Confidential

Full Prescribing Information

View the PDF >>

Download the PDF >>

Please see full prescribing information including **BOXED WARNING.**

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

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EXALGO is for use in opioid tolerant patients only.

Fatal respiratory depression could occur in patients who are not opioid tolerant.

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Limitations of Use

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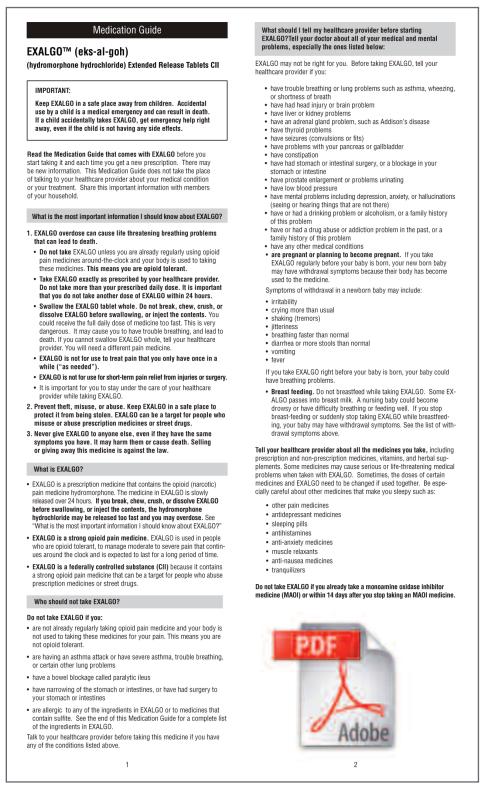
EXALGO™
(hydromorphone HCl) CII
Extended-Release Tablets

Complete the EXALGO REMS Education Program. **Start here. >>**



Medication Guide

EXALGO™ (eks-al-goh)
(hydromorphone hydrochloride) Extended Release Tablets CII

IMPORTANT:
Keep EXALGO in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes EXALGO, get emergency help right away, even if the child is not having any side effects.

Read the Medication Guide that comes with EXALGO before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household.

What is the most important information I should know about EXALGO?

1. **EXALGO overdose can cause life threatening breathing problems that can lead to death.**
   - **Do not take** EXALGO unless you are already regularly using opioid pain medicines around-the-clock and your body is used to taking these medicines. **This means you are opioid tolerant.**
   - **Take EXALGO exactly as prescribed by your healthcare provider. Do not take more than your prescribed daily dose. It is important that you do not take another dose of EXALGO within 24 hours.**
   - **Swallow the EXALGO tablet whole. Do not break, chew, crush, or dissolve EXALGO before swallowing, or inject the contents.** You could receive the full daily dose of medicine too fast. This is very dangerous. It may cause you to have trouble breathing, and lead to death. If you cannot swallow EXALGO whole, tell your healthcare provider. You will need a different pain medicine.
   - **EXALGO is not for use to treat pain that you only have once in a while ("as needed").**
   - **EXALGO is not for use for short-term pain relief from injuries or surgery.**
   - It is important for you to stay under the care of your healthcare provider while taking EXALGO.
2. **Prevent theft, misuse, or abuse. Keep EXALGO in a safe place to protect it from being stolen. EXALGO can be a target for people who misuse or abuse prescription medicines or street drugs.**
3. **Never give EXALGO to anyone else, even if they have the same symptoms you have. It may harm them or cause death. Selling or giving away this medicine is against the law.**

What is EXALGO?

- EXALGO is a prescription medicine that contains the opioid (narcotic) pain medicine hydromorphone. The medicine in EXALGO is slowly released over 24 hours. **If you break, chew, crush, or dissolve EXALGO before swallowing, or inject the contents, the hydromorphone hydrochloride may be released too fast and you may overdose.** See "What is the most important information I should know about EXALGO?"
- **EXALGO is a strong opioid pain medicine.** EXALGO is used in people who are opioid tolerant, to manage moderate to severe pain that continues around the clock and is expected to last for a long period of time.
- **EXALGO is a federally controlled substance (CII)** because it contains a strong opioid pain medicine that can be a target for people who abuse prescription medicines or street drugs.

Who should not take EXALGO?

Do not take EXALGO if you:
- are not already regularly taking opioid pain medicine and your body is not used to taking these medicines for your pain. This means you are not opioid tolerant.
- are having an asthma attack or have severe asthma, trouble breathing, or certain other lung problems
- have a bowel blockage called paralytic ileus
- have narrowing of the stomach or intestines, or have had surgery to your stomach or intestines
- are allergic to any of the ingredients in EXALGO or to medicines that contain sulfite. See the end of this Medication Guide for a complete list of the ingredients in EXALGO.

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

1

What should I tell my healthcare provider before starting EXALGO?Tell your doctor about all of your medical and mental problems, especially the ones listed below:

EXALGO may not be right for you. Before taking EXALGO, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have had head injury or brain problem
- have liver or kidney problems
- have an adrenal gland problem, such as Addison's disease
- have thyroid problems
- have seizures (convulsions or fits)
- have problems with your pancreas or gallbladder
- have constipation
- have had stomach or intestinal surgery, or a blockage in your stomach or intestine
- have prostate enlargement or problems urinating
- have low blood pressure
- have mental problems including depression, anxiety, or hallucinations (seeing or hearing things that are not there)
- have or had a drinking problem or alcoholism, or a family history of this problem
- have or had a drug abuse or addiction problem in the past, or a family history of this problem
- have any other medical conditions
- **are pregnant or planning to become pregnant.** If you take EXALGO regularly before your baby is born, your new born baby may have withdrawal symptoms because their body has become used to the medicine.

Symptoms of withdrawal in a newborn baby may include:

- irritability
- crying more than usual
- shaking (tremors)
- jitteriness
- breathing faster than normal
- diarrhea or more stools than normal
- vomiting
- fever

If you take EXALGO right before your baby is born, your baby could have breathing problems.

- **Breast feeding.** Do not breastfeed while taking EXALGO. Some EXALGO passes into breast milk. A nursing baby could become drowsy or have difficulty breathing or feeding well. If you stop breast-feeding or suddenly stop taking EXALGO while breastfeeding, your baby may have withdrawal symptoms. See the list of withdrawal symptoms above.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with EXALGO. Sometimes, the doses of certain medicines and EXALGO need to be changed if used together. Be especially careful about other medicines that make you sleepy such as:

- other pain medicines
- antidepressant medicines
- sleeping pills
- antihistamines
- anti-anxiety medicines
- muscle relaxants
- anti-nausea medicines
- tranquilizers

Do not take EXALGO if you already take a monoamine oxidase inhibitor medicine (MAOI) or within 14 days after you stop taking an MAOI medicine.

2

Medication Guide

View the PDF >>
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Please see full prescribing information including **BOXED WARNING.**

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

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Proper Patient Selection

EXALGO is an extended release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered opioid tolerant are those who are taking 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, for a week or longer.

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Fatal respiratory depression could occur in patients who are not opioid tolerant.

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Limitations of Use

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EXALGO is not intended for use as an as-needed analgesic.

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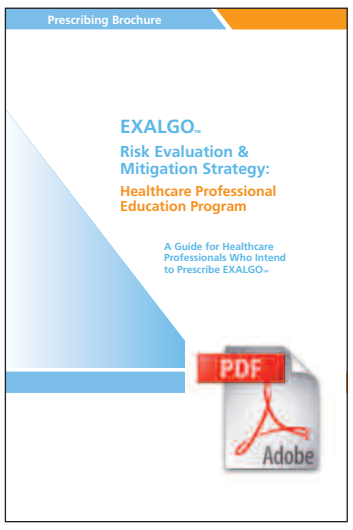
EXALGO™
(hydromorphone HCl) II
Extended-Release Tablets

Complete the EXALGO REMS Education Program. **Start here. >>**



Prescribing Brochure

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EXALGO™

Risk Evaluation & Mitigation Strategy

Healthcare Professional Education Program Kit

EXALGO™
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Extended-Release Tablets

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EXALGO Risk Evaluation and Mitigation Strategy (REMS) Healthcare Professional (HCP) Education Program

- EXALGO was approved with a REMS in order that the benefits outweigh the potential risks
- EXALGO should only be prescribed in accorda with the EXALGO REMS including HCP educat on responsible EXALGO prescribing and use
- The education can be completed in 3 easy ste

STEP 1
Review the Prescribing Brochure along with the Prescribing Information and Medication Guide

STEP 2
Complete and submit the EXALGO Essential Information Form electronically on www.exalgorems.com or via fax to 1-888-423-3511

STEP 3
You will recieve confirmation via fax or email

Ways to Complete Your Training

- The above steps can be completed using the resources included in this kit
- Or online at www.exalgorems.com

EXALGO™
(hydromorphone HCl) Ⓘ
Extended-Release Tablets

EXALGO Essential Information Form

Please complete and submit this form electronically on www.exalgorems.com or via fax to 1.888.423.3511.
For additional educational information, go to www.exalgorems.com or call 1.888.9EXALGO (1.888.939.2546).
Completion of this form does not affect your ability to prescribe EXALGO.

EXALGO™ (hydromorphone HCl) Extended-Release Tablets

Prescriber Information (please fill in all fields completely)

Prescriber Name, Credentials _____

DEA Registration Number _____ Specialty _____

Affiliation _____

Address _____

City _____ State _____ Zip _____

Office Phone _____ Office Fax _____

E-mail _____ Office Manager Name _____

How do you want to be confidentially informed of the results of your Essential Information Form?

Via E-mail _____ Via Fax _____

Date the form was completed _____

1. Which are the primary risks of EXALGO? (check all that apply)

- ❑ Misuse
- ❑ Abuse
- ❑ Overdose
- ❑ Nausea
- ❑ Addiction

2. For which of the following conditions should EXALGO be prescribed?

- ❑ Pain that lasts only for a short time (acute)
- ❑ For moderate-to-severe chronic pain in opioid tolerant patients
- ❑ Pain after injury or surgery
- ❑ Mild pain
- ❑ Sudden or occasional pain that requires treatment on an as-needed basis

3. The EXALGO Full Prescribing Information defines opioid tolerance as patients taking. (check all that apply)

- ❑ At least 60 mg oral morphine/day
- ❑ At least 30 mg oral oxycodone/day
- ❑ At least 25 mg oral oxymorphone/day
- ❑ At least 8 mg oral hydromorphone/day
- ❑ At least 25 mcg transdermal fentanyl/hour

4. Please check the appropriate steps for proper EXALGO dosing. (check all that apply)

- ❑ Sum the total daily dose of current opioid therapy then multiply by the conversion ratio to calculate the approximate total daily dose of EXALGO, using conversion ratios in the EXALGO Full Prescribing Information
- ❑ Determine the approximate starting dose (approximately 50% of the calculated total daily EXALGO dose)
- ❑ Adjust the starting dose individually for each patient
- ❑ Individually titrate to adequate pain relief with tolerable side effects no more frequently than every 3-4 days

5. What is the only safe way to take EXALGO?

- ❑ Swallowing the tablet after it has been crushed
- ❑ Chewing the tablet
- ❑ Swallowing the tablet whole or intact
- ❑ Dissolving the tablet in a glass of water before swallowing
- ❑ Injecting the dissolved contents

6. Which of the following statements are true about the safe storage of EXALGO? (check all that apply)

- ❑ EXALGO should be kept out of reach of children and in a childproof container
- ❑ EXALGO should be kept in a convenient location accessible to anyone
- ❑ EXALGO should be kept hidden and inaccessible to household acquaintances
- ❑ EXALGO should be protected from theft from anyone for whom it was not prescribed

7. Patients should be counseled to read the EXALGO Medication Guide that they receive with every prescription as important information may have changed.

- ❑ True
- ❑ False

8. Which of the following are risk factors for addiction? (check all that apply)

- ❑ Active substance use disorder
- ❑ History of major untreated psychopathology
- ❑ Positive urine drug test for illicit drugs
- ❑ Egregious aberrant drug-taking behaviors, like selling prescription drugs

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Prescribing Brochure

EXALGO™

Risk Evaluation & Mitigation Strategy:

Healthcare Professional Education Program

A Guide for Healthcare Professionals Who Intend to Prescribe EXALGO

EXALGO™
(hydromorphone HCl) Ⓘⓘ
Extended-Release Tablets

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Limitations of Use

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Table of Contents

Introduction

EXALGO™ (hydromorphone HCl) Extended Release Tablets CII is an opioid agonist indicated for once daily administration for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. Patients considered opioid tolerant are those who are taking 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, for a week or longer. EXALGO is not intended for use as an as-needed analgesic and is not indicated for the management of acute or postoperative pain.[1]

In order to ensure that the benefits of EXALGO outweigh the potential risks, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the U.S. Food and Drug Administration (FDA). A REMS is a strategy to manage a known or potentially serious risk associated with a medicine.

The EXALGO REMS requires:

- Healthcare Professional (HCP) training on responsible EXALGO prescribing and use
- Distribution of REMS educational materials to HCPs
- Distribution of the EXALGO Medication Guide to patients and/or caregivers every time EXALGO is dispensed

The goals of this REMS are to:

- Inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of EXALGO
- Inform patients and healthcare professionals about the safe use of EXALGO

This brochure includes information on:

- Proper patient selection
- Appropriate product dosing and administration
- General opioid use, including information about opioid abuse and how to identify those at risk for addiction

- The risk of abuse, misuse, overdose, and addiction from exposure to opioids, including EXALGO
- The risks of EXALGO including:
  - The risk of overdose caused by exposure to an essentially immediate-release form of hydromorphone due to broken, chewed, crushed, or dissolved EXALGO
  - The risk of addiction from exposure to EXALGO
  - The risk of overdose with use in opioid non-tolerant patients
- Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances
- The importance of providing each patient the EXALGO Medication Guide with each prescription and instructing the patient to read it

General Opioid Use: Risks

Misuse, Abuse and Addiction of Prescription Opioids

Patients have a right to proper, respectful, informed, and nondiscriminatory pain management and care. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids, including EXALGO, 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.[1]

Addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation and proper use and handling are appropriate measures that help to minimize abuse and addiction of opioid drugs.[2]

Overdose of Prescription Opioids

Respiratory depression is the chief hazard of opioids, including EXALGO. Fatal respiratory depression could occur in individuals who are not opioid tolerant or in patients who use too much EXALGO. Proper patient selection, good prescribing practices as well as proper use and handling can significantly reduce the risk of overdose of opioid drugs.[1]

This brochure contains the most important information you should know to responsibly prescribe EXALGO.

General Opioid Use: Risk Factors

Risk Factors for Abuse

- Personal or family history of substance abuse[3]
- History of preadolescent sexual abuse[3]
- Mental disease[3]
- Social patterns of drug use[4]
- Psychological stress[4]

Risk Factors for Addiction

- Active substance use disorder[5]
- Major, untreated psychopathology[5]
- Positive urine drug test for illicit drugs[6]
- Behaviors suggestive of addiction may include[2]:
  - taking multiple doses together
  - frequent reports of lost or stolen prescriptions
  - doctor shopping
  - isolation from family and friends

Risk Factors for Overdose[1]

- Opioid non-tolerant individuals
- Children and elderly
- Impaired respiratory function
- Debilitated health
- Concomitant sedating agents that depress respiration
- Not taking as directed (e.g., misuse)
- Abuse, especially
  - if broken, chewed, dissolved, crushed, or injected
  - with concurrent abuse of alcohol or other sedating substances (e.g., benzodiazepines)

EXALGO Risks

Treatment with EXALGO carries certain risks of which prescribers should be aware.

Misuse, Abuse, and Addiction

EXALGO contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics, legal or illicit. Misuse or abuse by breaking, crushing, chewing, dissolving, or injecting EXALGO or its contents poses a hazard of overdose and death. This risk is increased by concurrent abuse of EXALGO with alcohol and other sedating substances.[1]

Overdose

Fatal respiratory depression could occur in individuals who are not opioid tolerant. Taking broken, crushed, chewed or dissolved EXALGO or its contents leads to rapid release and absorption of a potentially fatal dose of hydromorphone. Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone. Overestimating the EXALGO dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Titrating more frequently than every 3-4 days can lead to an overdose once steady-state concentrations are achieved.[1]

Information Essential for Safe Administration

- EXALGO tablets are to be swallowed whole, and are not to be broken, chewed, crushed, dissolved or injected. Taking broken, chewed, crushed, or dissolved EXALGO or its contents leads to the rapid release and absorption of a potentially fatal dose of hydromorphone.
- EXALGO is for use only in opioid tolerant patients. Ingestion of EXALGO may cause fatal respiratory depression when administered to patients who are not opioid tolerant.
- EXALGO tablets must be kept in a secure place out of the reach of children. Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone.

Proper Patient Selection

Proper patient selection is integral to responsible prescribing and use. Selection of patients for treatment with EXALGO is governed by the same principles that apply to the use of similar opioid analgesics. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as-needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as the guidelines outlined by the World Health Organization[7] or the Federation of State Medical Boards Model Guidelines.[8]

Before initiating treatment, clinicians should conduct and document in the medical record an effective patient evaluation, including an assessment of risk of substance misuse, abuse, or addiction.

Components of effective patient evaluation[9]

- Conduct a comprehensive physical examination including appropriate diagnostic testing
- Conduct a complete patient history, including comprehensive pain history, nature and intensity of pain, the effect of pain on physical and psychological function, as well as current and past treatments for pain
- Assess pain using validated pain assessment tools such as the Numeric Rating Scale (NRS) or the Brief Pain Inventory (BPI)
- Assess risk of abuse and addiction using patient history of substance abuse and validated risk assessment tools
- Evaluate the patient's environmental risk factors for opioid misuse, abuse, overdose, and addiction, including:
  - Presence of young children
  - Presence of adolescents or young adults
  - Presence of individuals with a history of substance misuse, abuse, or addiction, psychiatric issues, or drug-seeking behavior
  - Improper medication handling, storage, or disposal

Weigh the risks and benefits before initiating treatment with EXALGO and on an ongoing basis.[1]

Selection of patients for treatment with EXALGO is governed by the same principles that apply to the use of similar opioid analgesics[1]

- Screen and stratify patients according to risk factors for abuse and addiction
- Monitor for signs of abuse and addiction

RISK ASSESSMENT FOR ABUSE AND ADDICTION

Lower Risk	Moderate Risk	Higher Risk
• No past or current history of substance use disorder[5] • No family history of past or current substance use disorders[5] • No major psychopathology[5]	• May be a past history of a treated substance use disorder[5] • May be significant family history of problematic drug use[5] • May have a past or concurrent psychiatric disorder[5] • Not actively addicted[5]	• Active substance use disorder[5] • Major, untreated psychopathology[5] • Actively addicted[5] • Positive urine drug test for illicit drugs[6]

For patients with a history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors, consider[10]:

- Frequent and stringent monitoring
- Consulting with a mental health or addiction specialist
- Evaluating for appropriateness of treatment
- Restructuring therapy
- Referral for assistance in management
- Discontinuing treatment

Proper Patient Selection

- Appropriate patients for once-daily EXALGO must:
  - be opioid tolerant. Patients considered opioid tolerant are those who are taking 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, for a week or longer
  - have moderate to severe pain
  - require continuous, around-the-clock opioid analgesia for an extended period of time
- EXALGO is not intended for use as an as-needed analgesic
- EXALGO is not indicated for the management of acute or postoperative pain

Dosing and Administration[1]

- EXALGO will be available in the following tablet strengths: 8 mg, 12 mg, and 16 mg
- The approved dosage range is 8 mg to 64 mg
- It is important to consider the following for proper administration:
  - EXALGO should be taken once every 24 hours
  - EXALGO must be swallowed whole and should not be broken, crushed, chewed, dissolved, or injected
  - Discontinue all other around-the-clock opioids before starting EXALGO
  - Avoid concurrent use of alcohol and sedating medicines
  - Avoid medication errors when prescribing or dispensing 8 mg tablets, as 8 mg tablets are also available as immediate-release hydromorphone tablets
  - Follow all proper dosing and administration procedures (see below)

STEP 1
Calculate the equivalent dose*

1. Sum the total daily current opioid therapy
2. Multiply by the conversion ratio to calculate the approximate total daily dose of EXALGO
3. Use 5:1 oral morphine:oral hydromorphone conversion ratio
   - 12 mg for every 60 mg total daily oral morphine equivalent
   - 12 mg for every 30 mg of total daily oral oxycodone
   - 12 mg for every 25 mcg/hr of transdermal fentanyl

STEP 2
Determine approximate starting dose*

1. 50% of calculated total daily EXALGO dose
2. Adjust individually for each patient
3. Administer once daily

STEP 3
Individually titrate*

1. Titrate to adequate pain relief with tolerable side effects
2. Assess pain relief and adverse reactions frequently
3. Titrate no more frequently than every 3 to 4 days
4. Consider increases of 25%-50%
5. Continue to administer once daily

*** Give attention to the following:**

- ☑ Daily dose, potency, and specific characteristics of the previous opioid
- ☑ Reliability of the relative potency estimate
- ☑ Degree of opioid tolerance
- ☑ Age, general condition, and medical status
- ☑ Concurrent medications
- ☑ Type and severity of the patient's pain
- ☑ Balance between pain control and adverse effects
- ☑ Risk factors for abuse, addiction, or diversion

Hydromorphone Conversion Table[1]

Previous Opioid	Approximate Equivalent Oral Dose	Oral Conversion Ratio[a]
Hydromorphone	12 mg	1
Codeine	200 mg	0.06
Hydrocodone	30 mg	0.4
Methadone[b]	20 mg	0.6
Morphine	60 mg	0.2
Oxycodone	30 mg	0.4
Oxymorphone	20 mg	0.6

Select opioid, sum the total daily dose, and then multiply the dose by the conversion ratio to calculate the approximate oral hydromorphone equivalent.

a. Ratio for conversion of oral opioid dose to approximate hydromorphone equivalent dose.
b. It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

Sample Conversion and Starting Dose

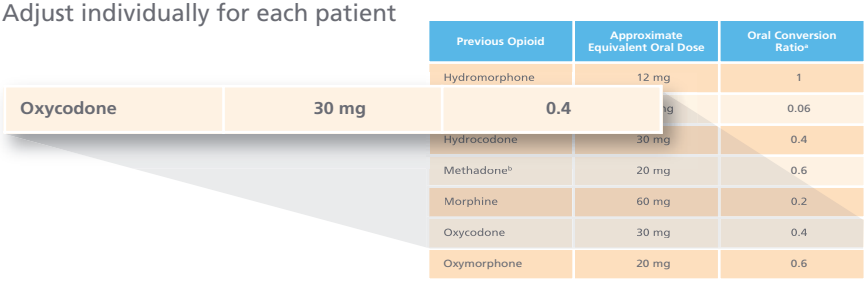
From oxycodone 30 mg q12h to EXALGO

Step 1: Calculate the equivalent dose

- 30 mg oxycodone q12h = 60 mg/day x 0.4 = 24 mg EXALGO

Step 2: Calculate approximate starting dose (50% of calculated total daily EXALGO dose)

- 24 mg/ 2 = 12 mg EXALGO once-daily
- Adjust individually for each patient



1. **Periodic Review of Chronic Therapy with EXALGO**
   During chronic therapy with EXALGO, assess the continued need for around-the-clock opioid therapy periodically. Continue to assess patients for their clinical risks for opioid abuse, addiction, or diversion particularly with high-dose formulations.

2. **Periodic review should include documentation of:**
   - ☑ Pain intensity and level of functioning using validated assessment tools
   - ☑ Progress toward achieving therapeutic goals
   - ☑ Presence of adverse events
   - ☑ Adherence to prescribed therapies and medication agreement, including periodic urine drug testing (UDT), tablet counts, or other information to confirm adherence to the treatment plan and agreement
   - ☑ Evidence of aberrant drug-related behaviors, addiction, or diversion
   - ☑ Changes in psychiatric or medical co-morbidities
   - ☑ Changes in environmental risk factors

3. **Discontinuing EXALGO Therapy**
   When the patient no longer requires therapy with EXALGO, taper doses gradually, by 25%–50% every 2 to 3 days down to a dose of 8 mg before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the physically dependent patient.

Patient Counseling[1]

Before initiating treatment with EXALGO, counsel patients and caregivers on EXALGO risks and safe use, including:

- EXALGO risks, including
  - The risk for overdose in opioid non-tolerant individuals
  - The importance of swallowing the EXALGO tablet whole
  - The importance of taking once-daily EXALGO exactly as prescribed
- The need to read the EXALGO Medication Guide each time EXALGO is dispensed
- The need to store opioid analgesics, including EXALGO, safely out of reach of children and household acquaintances

See the EXALGO Full Prescribing Information for a complete list of patient counseling messages.

The FDA requires that a Medication Guide be dispensed each time EXALGO is dispensed. Instruct patients to read the Medication Guide each time EXALGO is dispensed because new information may be available.

Glossary of Terms[1,2]

Aberrant drug-related behavior: A behavior outside the boundaries of the agreed upon treatment plan that is established as early as possible in the doctor-patient relationship.

Abuse: Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, for example, getting high.

Addiction: A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Diversion: The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.

Doctor Shopping: Visiting multiple doctors to obtain additional prescriptions.

Drug Seeking Behavior: Tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s).

Misuse: Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.

Physical Dependence: A state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time. Tolerance could occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

References:

1. EXALGO Full Prescribing Information. EXALGO [package insert] Hazelwood, MO: Mallinckrodt Inc.; 2010. **2.** American Academy of Pain Medicine, the Pain Society and the American Society of Addiction Medicine. Definitions related to the use of opioids for the treatment of pain. WMJ. 2001; 100(5):28-9 **3.** Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005; 6:432-42 **4.** Savage SR. Assessment for addiction in pain-treatment settings. Clin J Pain 2002; 18(4 Suppl.): S28-38 **5.** Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med. 2005 Mar-Apr; 6(2): 107-12 **6.** Fleming MF; Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007 Jul; 8(7): 573-82 **7.** World Health Organization Cancer Pain Relief: Guide to Opioid Availability. http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=2247<http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=2247>; 1996 **8.** Model Policy for the Use of Controlled Substances for the Treatment of Pain. http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf<http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf>; 2004. Federation of State Medical Boards. **9.** Fishman, Scott M. *Responsible Opioid Prescribing: A Physician's Guide*. Washington DC: Waterford Life Sciences; 2007. **10.** Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009 Feb; 10(2): 113-30

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SHARON H HERTZ
03/24/2010
Signing for Larissa Lapteva, M.D.