

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 HCl) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1984

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; and NEONATAL OPIOID WITHDRAWAL SYNDROME
See full prescribing information for complete boxed warning.

- EXALGO exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow EXALGO tablets whole to avoid exposure to a potentially fatal dose of hydromorphone. (5.2)
- Accidental ingestion of EXALGO, especially in children, can result in fatal overdose of hydromorphone. (5.2)
- Prolonged use of EXALGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).

INDICATIONS AND USAGE

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.

DOSAGE AND ADMINISTRATION

- For once daily administration (2.1)
- Instruct patients to swallow EXALGO tablets intact. (2.6)
- Do not abruptly discontinue EXALGO. (2.3, 5.12)
- To convert to EXALGO from another opioid, use available conversion factors to obtain estimated dose. (2.1)

- Dose may be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia. (2.2)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 8 mg, 12 mg, 16 mg, 32 mg (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients (4)
- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Narrowed or obstructed gastrointestinal tract (4)
- Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites (4, 5.10)

WARNINGS AND PRECAUTIONS

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4)
- Elderly, cachectic, debilitated patients and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effect: Monitor during dose initiation and titration (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of EXALGO in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention. (5.8)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact **Mallinckrodt at 1-800-778-7898** or **FDA at 1-800-FDA-1088** or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with EXALGO because they may reduce analgesic effect of EXALGO or precipitate withdrawal symptoms. (5.12, 7.2)
- Monoamine oxidase inhibitors (MAOIs): Avoid use of EXALGO in patients taking MAOIs or within 14 days of stopping such treatment. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: EXALGO is not recommended. Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: EXALGO is not recommended. Hydromorphone has been detected in human milk. Closely monitor infants of nursing women receiving EXALGO. (8.3)
- Hepatic or renal impairment: Administer a reduced dose of EXALGO in patients with moderate hepatic (8.6) and moderate renal impairment (8.7). Consider use of an alternate analgesic in patients with severe hepatic (8.6) and renal impairment. (8.7)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse

EXALGO exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing EXALGO, and monitor all patients regularly for the development of these behaviors or conditions [see *Warnings and Precautions (5.1)*].

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of EXALGO. Monitor for respiratory depression, especially during initiation of EXALGO or following a dose increase. Instruct patients to swallow EXALGO tablets whole; crushing, chewing, or dissolving EXALGO tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone [see *Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of EXALGO, especially by children, can result in a fatal overdose of hydromorphone [see *Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of EXALGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

EXALGO is 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 are inadequate.

Patients considered opioid tolerant are those who are receiving, 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.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

To avoid medication errors, prescribers and pharmacists must be aware that hydromorphone is available as both immediate-release 8 mg tablets and extended-release 8 mg tablets.

EXALGO should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Due to the risk of respiratory depression, EXALGO is only indicated for use in patients who are already opioid-tolerant. Discontinue or taper all other extended-release opioids when beginning EXALGO therapy. As EXALGO is only for use in opioid-tolerant patients, do not begin any patient on EXALGO as the first opioid.

Patients considered opioid-tolerant are those who are taking at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*]. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with EXALGO [see *Warnings and Precautions (5.2)*].

EXALGO tablets must be taken whole. Crushing, chewing, or dissolving EXALGO extended-release tablets will result in uncontrolled delivery of hydromorphone and can lead to overdose or death [see *Warnings and Precautions (5.2)*].

Conversion from Other Oral Hydromorphone Formulations to EXALGO

Patients receiving oral immediate-release hydromorphone may be converted to EXALGO by administering a starting dose equivalent to the patient's total daily oral hydromorphone dose, taken once daily.

Conversion from Other Oral Opioids to EXALGO

Discontinue all other around-the-clock opioid drugs when EXALGO therapy is initiated.

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is safer to underestimate a patient's 24-hour oral hydromorphone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydromorphone requirements, which could result in adverse reactions.

In an EXALGO clinical trial with an open-label titration period, patients were converted from their prior opioid to EXALGO using the **Table 1** as a guide for the initial EXALGO dose. The recommended starting dose of EXALGO is 50% of the calculated estimate of daily hydromorphone requirement. Calculate the estimated daily hydromorphone requirement using **Table 1**.

Consider the following when using the information in **Table 1**:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** EXALGO.
- The table **cannot** be used to convert **from** EXALGO to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

Table 1.
Conversion Factors to EXALGO

| Prior Oral Opioid | Approximate Oral Conversion Factor |
|--------------------------|-------------------------------------------|
| Hydromorphone | 1 |
| Codeine | 0.06 |
| Hydrocodone | 0.4 |
| Methadone | 0.6 |
| Morphine | 0.2 |
| Oxycodone | 0.4 |
| Oxymorphone | 0.6 |

To calculate the estimated EXALGO dose using **Table 1**:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral hydromorphone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydromorphone dose for each opioid and sum the totals to obtain the approximate total hydromorphone daily dose.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate EXALGO strength(s) available.

Example conversion from a single opioid to EXALGO:

Step 1: Sum the total daily dose of the opioid

- 30 mg of oxycodone 2 times daily = 60 mg total daily dose of oxycodone

Step 2: Calculate the approximate equivalent dose of oral hydromorphone based on the total daily dose of the current opioid using **Table 1**

- 60 mg total daily dose of oxycodone x Conversion Factor of 0.4 = 24 mg of oral hydromorphone daily

Step 3: Calculate the approximate starting dose of EXALGO to be given every 24 hours, which is 50% of the calculated oral hydromorphone dose. Round down, if necessary, to the appropriate EXALGO tablet strengths available.

- 50% of 24 mg results in an initial dose of 12 mg of EXALGO once daily
- Adjust individually for each patient

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to EXALGO.

Conversion from Transdermal Fentanyl to EXALGO

Eighteen hours following the removal of the transdermal fentanyl patch, EXALGO treatment can be initiated. To calculate the 24-hour EXALGO dose, use a conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of EXALGO. Then reduce the EXALGO dose by 50%.

For example:

Step 1: Identify the dose of transdermal fentanyl.

- 75 mg of transdermal fentanyl

Step 2: Use the conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of EXALGO.

- 75 mg of transdermal fentanyl : 36 mg total daily dose of EXALGO

Step 3: Calculate the approximate starting dose of EXALGO to be given every 24 hours, which is 50% of the converted dose. Round down, if necessary, to the appropriate EXALGO tablet strengths available.

- 50% of 36 mg results in an initial dose of 18 mg, which would be rounded down to 16 mg of EXALGO once daily
- Adjust individually for each patient

Conversion from Methadone to EXALGO

Close monitoring is of particular importance 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 can accumulate in the plasma.

2.2 Titration and Maintenance of Therapy

Individually titrate EXALGO to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving EXALGO to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

Plasma levels of EXALGO are sustained for 18 to 24 hours. Dosage adjustments of EXALGO may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.

Patients who experience breakthrough pain may require a dose increase of EXALGO, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the EXALGO dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Discontinuation of EXALGO

When a patient no longer requires therapy with EXALGO, taper doses gradually, by 25% to 50% every 2 or 3 days down to a dose of 8 mg before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the opioid-tolerant patient.

To dispose of unused EXALGO flush all remaining tablets down the toilet or remit to authorities at a certified drug take-back program.

2.4 Hepatic Impairment

Start patients with moderate hepatic impairment on 25% of the EXALGO dose that would be prescribed for patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with EXALGO and during dose titration. Use of alternate analgesics is recommended for patients with severe hepatic impairment [see *Use in Specific Populations* (8.6)].

2.5 Renal Impairment

Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the EXALGO dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with EXALGO and during dose titration. As EXALGO is only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment [see *Use in Specific Populations (8.7)*].

2.6 Administration of EXALGO

Instruct patients to swallow EXALGO tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of hydromorphone [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

EXALGO extended-release tablets are available in 8 mg, 12 mg, 16 mg or 32 mg dosage strengths. The 8 mg tablets are round, biconvex, red tablets imprinted with "EXH 8" on one side. The 12 mg tablets are round, biconvex, dark yellow tablets imprinted with "EXH 12" on one side. The 16 mg tablets are round, biconvex, yellow tablets imprinted with "EXH 16" on one side. The 32 mg tablets are round, biconvex, white tablets imprinted with "EXH 32" on one side.

4 CONTRAINDICATIONS

EXALGO is contraindicated in:

- Opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant.
- Patients with significant respiratory depression
- Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Patients with known or suspected paralytic ileus
- Patients who have had surgical procedures and/or underlying disease resulting in narrowing of the gastrointestinal tract, or have "blind loops" of the gastrointestinal tract or gastrointestinal obstruction.
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite-containing medications [see *Warnings and Precautions (5.10)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

EXALGO contains hydromorphone, a Schedule II controlled substance. As an opioid, EXALGO exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence (9)*]. As modified-release products such as EXALGO deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydromorphone present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed EXALGO and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing EXALGO, and monitor all patients receiving EXALGO for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of EXALGO for the proper management of pain in any given patient.

Patients at increased risk may be prescribed modified-release opioid formulations such as EXALGO, but use in such patients necessitates intensive counseling about the risks and proper use of EXALGO along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of EXALGO by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of hydromorphone and can result in overdose and death [see *Overdosage (10)*].

Opioid agonists such as EXALGO are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing EXALGO. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of EXALGO, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with EXALGO and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of EXALGO are essential [see *Dosage and Administration (2)*]. Overestimating the EXALGO dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of EXALGO, especially by children, can result in respiratory depression and death due to an overdose of hydromorphone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of EXALGO during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if EXALGO is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of EXALGO in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS

depression. If the decision to begin EXALGO is made, start with one third to one half the calculated starting dose, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [see *Drug Interactions* (7.1)].

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating EXALGO and when EXALGO is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.2)].

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with EXALGO, as in these patients, even usual therapeutic doses of EXALGO may decrease respiratory drive to the point of apnea [see *Warnings and Precautions* (5.2)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Hypotensive Effect

EXALGO may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see *Drug Interactions* (7.1)]. Monitor these patients for signs of hypotension after initiating or titrating the dose of EXALGO.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking EXALGO who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with EXALGO. EXALGO may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of EXALGO in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

EXALGO is contraindicated in patients with paralytic ileus. Avoid the use of EXALGO in patients with other GI obstruction.

Because the EXALGO tablet is nondeformable and does not appreciably change in shape in the GI tract, EXALGO is contraindicated in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, 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 pseudoobstruction, or Meckel's diverticulum). There have been reports of obstructive symptoms in patients with known strictures or risk of strictures, such as previous GI surgery, in association with the ingestion of drugs in nondeformable extended-release formulations.

It is possible that EXALGO tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

The hydromorphone in EXALGO may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.10 Sulfites

EXALGO contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.11 Use in Patients with Convulsive or Seizure Disorders

The hydromorphone in EXALGO may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during EXALGO therapy.

5.12 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including EXALGO. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [see *Drug Interactions (7.2)*].

When discontinuing EXALGO, gradually taper the dose [see *Dosage and Administration (2.3)*]. Do not abruptly discontinue EXALGO.

5.13 Driving and Operating Machinery

EXALGO may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of EXALGO and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse [see *Warnings and Precautions (5.1)*]
- Life Threatening Respiratory Depression [see *Warnings and Precautions (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.3)*]
- Interactions with Other CNS Depressants [see *Warnings and Precautions (5.4)*]
- Hypotensive Effect [see *Warnings and Precautions (5.7)*]
- Gastrointestinal Effects [see *Warnings and Precautions (5.9)*]
- Seizures [see *Warnings and Precautions (5.11)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

EXALGO was administered to a total of 2,524 patients in 15 controlled and uncontrolled clinical studies. Of these, 423 patients were exposed to EXALGO for greater than 6 months and 141 exposed for greater than one year.

The most common adverse reactions leading to study discontinuation were nausea, vomiting, constipation, somnolence, and dizziness. The most common treatment-related serious adverse reactions from controlled and uncontrolled chronic pain studies were drug withdrawal syndrome, overdose, confusional state, and constipation.

The overall incidence of adverse reactions in patients greater than 65 years of age was higher, with a greater than 5% difference in rates for constipation and nausea when compared with younger patients. The overall incidence of adverse reactions in female patients was higher, with a greater than 5% difference in rates for nausea, vomiting, constipation and somnolence when compared with male patients.

A 12-week double-blind, placebo-controlled, randomized withdrawal study was conducted in opioid tolerant patients with moderate to severe low back pain [see *Clinical Studies (14)*]. A total of 447 patients were enrolled into the open-label titration phase with 268 patients randomized into the double-blind treatment phase. The adverse reactions that were reported in at least 2% of the patients are contained in **Table 2**.

Table 2.
Number (%) of Patients with Adverse Reactions Reported in ≥ 2% of Patients
with Moderate to Severe Low Back Pain During the Open-Label Titration Phase or Double-Blind
Treatment Phase by Preferred Term

| Preferred Term | Open-Label | Double-Blind Treatment Phase | |
|-----------------------------|-----------------|------------------------------|-----------------|
| | Titration Phase | EXALGO (N=134) | Placebo (N=134) |
| | EXALGO (N=447) | EXALGO (N=134) | Placebo (N=134) |
| Constipation | 69 (15) | 10 (7) | 5 (4) |
| Nausea | 53 (12) | 12 (9) | 10 (7) |
| Somnolence | 39 (9) | 1 (1) | 0 (0) |
| Headache | 35 (8) | 7 (5) | 10 (7) |
| Vomiting | 29 (6) | 8 (6) | 6 (4) |
| Pruritus | 21 (5) | 1 (1) | 0 (0) |
| Dizziness | 17 (4) | 3 (2) | 2 (1) |
| Insomnia | 13 (3) | 7 (5) | 5 (4) |
| Dry Mouth | 13 (3) | 2 (1) | 0 (0) |
| Edema Peripheral | 13 (3) | 3 (2) | 1 (1) |
| Hyperhidrosis | 13 (3) | 2 (1) | 2 (1) |
| Anorexia/Decreased Appetite | 10 (2) | 2 (1) | 0 (0) |
| Arthralgia | 9 (2) | 8 (6) | 3 (2) |
| Abdominal Pain | 9 (2) | 4 (3) | 3 (2) |
| Muscle Spasms | 5 (1) | 3 (2) | 1 (1) |
| Weight Decreased | 3 (1) | 4 (3) | 3 (2) |

The adverse reactions that were reported in at least 2% of the total treated patients (N=2,474) in the 14 chronic clinical trials are contained in **Table 3**.

Table 3.
Number (%) of Patients with Adverse Reactions Reported in \geq 2% of Patients with Chronic Pain Receiving EXALGO in 14 Clinical Studies by Preferred Term

| Preferred Term | All Patients (N=2,474) |
|-----------------------------|------------------------|
| Constipation | 765 (31) |
| Nausea | 684 (28) |
| Vomiting | 337 (14) |
| Somnolence | 367 (15) |
| Headache | 308 (12) |
| Asthenia/Fatigue | 272 (11) |
| Dizziness | 262 (11) |
| Diarrhea | 201 (8) |
| Pruritus | 193 (8) |
| Insomnia | 161 (7) |
| Hyperhidrosis | 143 (6) |
| Edema Peripheral | 135 (5) |
| Anorexia/Decreased Appetite | 139 (6) |
| Dry Mouth | 121 (5) |
| Abdominal Pain | 115 (5) |
| Anxiety | 95 (4) |
| Back Pain | 95 (4) |
| Dyspepsia* | 88 (4) |
| Depression | 81 (3) |
| Dyspnea | 76 (3) |
| Muscle Spasms | 74 (3) |
| Arthralgia | 72 (3) |
| Rash | 64 (3) |
| Pain in Extremity | 63 (3) |
| Pain | 58 (2) |
| Drug Withdrawal Syndrome | 55 (2) |
| Pyrexia | 52 (2) |
| Fall | 51 (2) |
| Chest pain | 51 (2) |

* Reflux esophagitis, gastroesophageal reflux disease and Barrett's esophagus were grouped and reported with dyspepsia

The following Adverse Reactions occurred in patients with an overall frequency of < 2% and are listed in descending order within each System Organ Class:

Cardiac disorders: palpitations, tachycardia, bradycardia, extrasystoles

Ear and labyrinth disorders: vertigo, tinnitus

Endocrine disorders: hypogonadism

Eye disorders: vision blurred, diplopia, dry eye, miosis

Gastrointestinal disorders: flatulence, dysphagia, hematochezia, abdominal distension, hemorrhoids, abnormal feces, intestinal obstruction, eructation, diverticulum, gastrointestinal motility disorder, large intestine perforation, anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defecation

General disorders and administration site conditions: chills, malaise, feeling abnormal, feeling of body temperature change, feeling jittery, hangover, gait disturbance, feeling drunk, body temperature decreased

Infections and infestations: gastroenteritis, diverticulitis

Injury, poisoning and procedural complications: contusion, overdose

Investigations: weight decreased, hepatic enzyme increased, blood potassium decreased, blood amylase increased, blood testosterone decreased

Metabolism and nutrition disorders: dehydration, fluid retention, increased appetite, hyperuricemia

Musculoskeletal and connective tissue disorders: myalgia

Nervous system disorders: tremor, sedation, hypoesthesia, paresthesia, disturbance in attention, memory impairment, dysarthria, syncope, balance disorder, dysgeusia, depressed level of consciousness, coordination abnormal, hyperesthesia, myoclonus, dyskinesia, crying, hyperreflexia, encephalopathy, cognitive disorder, convulsion, psychomotor hyperactivity

Psychiatric disorders: confusional state, nervousness, restlessness, abnormal dreams, mood altered, hallucination, panic attack, euphoric mood, paranoia, dysphoria, listless, suicide ideation, libido decreased, aggression

Renal and urinary disorders: dysuria, urinary retention, urinary frequency, urinary hesitation, micturition disorder

Reproductive system and breast disorders: erectile dysfunction, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: rhinorrhea, respiratory distress, hypoxia, bronchospasm, sneezing, hyperventilation, respiratory depression

Skin and subcutaneous tissue disorders: erythema

Vascular disorders: flushing, hypertension, hypotension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EXALGO:

Immune system disorders: hypersensitivity

Skin and subcutaneous tissue disorders: angioedema, urticaria

7 DRUG INTERACTIONS

7.1 CNS Depressants

The concomitant use of EXALGO with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and EXALGO for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.4)*].

7.2 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of EXALGO or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving EXALGO.

7.3 Monoamine Oxidase Inhibitors (MAOI)

The effects of opioid analgesics may be potentiated by MAOIs. EXALGO is not recommended for use in patients who have received MAOIs within 14 days. If concurrent therapy with an MAOI and EXALGO is unavoidable, monitor patients for increased respiratory and central nervous system depression.

7.4 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with EXALGO may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when EXALGO is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see *Warnings and Precautions (5.3)*].

Teratogenic Effects – Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. EXALGO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.2)*].

Hydromorphone was not teratogenic in pregnant rats given oral doses up to 6.25 mg/kg/day or in pregnant rabbits administered oral doses up to 25 mg/kg/day during the period of organogenesis (~1.2 times the human exposure following 32 mg/day).

Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenicity likely the result of maternal toxicity associated with sedation and hypoxia. In Syrian hamsters given single subcutaneous doses from 14 to 258 mg/kg during organogenesis (gestation days 8 to 10), doses \geq 19 mg/kg hydromorphone produced skull malformations (exencephaly and cranioschisis). Continuous infusion of hydromorphone (5 mg/kg, s.c.) via implanted osmotic mini pumps during organogenesis (gestation days 7 to 10) produced soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (supraoccipital, checkerboard and split sternbrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were at doses approximately three-fold higher and < one-fold lower, respectively, than a 32 mg human daily oral dose on a body surface area basis.

Nonteratogenic Effects

In the pre- and post-natal effects study in rats, neonatal viability was reduced at 6.25 mg/kg/day (~1.2 times the human exposure following 32 mg/day).

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. EXALGO is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

8.3 Nursing Mothers

Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Nursing should not be undertaken while a patient is receiving EXALGO since hydromorphone is excreted in the milk.

8.4 Pediatric Use

The safety and effectiveness of EXALGO in patients 17 years of age and younger have not been established.

8.5 Geriatric Use

Elderly patients have been shown to be more sensitive to the adverse effects of opioids compared to the younger population. Therefore, closely monitor elderly patients for respiratory and central nervous system depression when prescribing EXALGO, particularly during initiation and titration.

8.6 Hepatic Impairment

In a study that used a single 4 mg oral dose of immediate-release hydromorphone tablets, four-fold increases in plasma levels of hydromorphone (C_{max} and $AUC_{0-\infty}$) were observed in patients with moderate hepatic impairment (Child-Pugh Group B). Start patients with moderate hepatic impairment on 25% of the EXALGO dose that would be used in patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with EXALGO and during dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied. As further increases in C_{max} and $AUC_{0-\infty}$ of hydromorphone in this group are expected, use of alternate analgesics is recommended [see *Dosage and Administration* (2.4)].

8.7 Renal Impairment

Administration of a single 4 mg dose of immediate-release hydromorphone tablets resulted in two-fold and four-fold increases in plasma levels of hydromorphone (C_{max} and AUC_{0-48h}) in moderate ($CL_{cr} = 40$ to 60 mL/min) and severe ($CL_{cr} < 30$ mL/min) impairment, respectively. In addition, in patients with severe renal impairment hydromorphone appeared to be more slowly eliminated with longer terminal elimination half-life (40 hours) compared to subjects with normal renal function (15 hours). Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the EXALGO dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with EXALGO and during dose titration. As EXALGO is only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment [see *Dosage and Administration* (2.5)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EXALGO contains hydromorphone, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. EXALGO can be abused and is subject to misuse, abuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*].

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common to addicts and drug abusers. Drug-seeking 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). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

EXALGO, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of EXALGO

EXALGO is intended for oral use only. Abuse of EXALGO poses a risk of overdose and death. This risk is increased with concurrent abuse of EXALGO with alcohol and other substances.

Taking cut, broken, chewed, crushed, or dissolved EXALGO poses a hazard of overdose and death.

With intravenous abuse, the tablet excipients, especially polyethylene oxide, can be expected to result in necrosis and inflammation of cardiac tissues. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

EXALGO should not be abruptly discontinued [see *Dosage and Administration (2.3)*]. If EXALGO is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [see *Warnings and Precautions (5.3)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes pulmonary edema, bradycardia, hypotension and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, such as naloxone and naltrexone, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. Such agents should be administered cautiously to patients who are known, or suspected to be, physically dependent on EXALGO. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

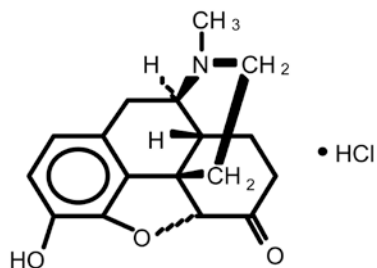
Because the duration of reversal would be expected to be less than the duration of action of hydromorphone in EXALGO, carefully monitor the patient until spontaneous respiration is reliably re-established. EXALGO will continue to release hydromorphone adding to the hydromorphone load for up to 24 hours after administration, necessitating prolonged monitoring for at least 24 to 48 hours beyond the overdose. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

EXALGO extended-release tablets are for oral use and contain hydromorphone hydrochloride, a mu-opioid agonist.

Hydromorphone hydrochloride USP is 4,5 α -epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. Hydromorphone hydrochloride is a white or almost white crystalline powder that is freely soluble in water, very slightly soluble in ethanol (96%), and practically insoluble in methylene chloride. Its empirical formula is C₁₇H₁₉NO₃•HCl. The compound has the following structural formula:



EXALGO also contains the following inactive ingredients: butylated hydroxytoluene, cellulose acetate, iron oxide black, ferric oxide red (8 mg only), ferric oxide yellow (12 mg, 16 mg, and 32 mg only), hypromellose, lactose anhydrous, lactose monohydrate, magnesium stearate, polyethylene glycol, polyethylene oxide, povidone, sodium chloride, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine. Hydromorphone is principally an agonist of mu-receptors, showing a weak affinity for κ -receptors. Comparing relative binding affinity for mu- and κ -opioid receptors, hydromorphone binds more specifically to mu-receptors than structurally related morphine. As an opioid agonist, the principle therapeutic action of hydromorphone is analgesia. 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). Interaction with the mu-opioid receptor subtype is believed to be responsible for most of hydromorphone's clinical effects. There is no intrinsic limit to the analgesic effect of hydromorphone. Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, sedation, nausea, and vomiting, which can result from high doses.

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when EXALGO is used in conjunction with alcohol, other opioids, legal or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System

Hydromorphone produces dose-related respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Hydromorphone depresses the cough reflex by direct effect on the cough center in the medulla.

Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic. Marked mydriasis, rather than miosis, may be seen due to severe hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by hydromorphone. Hydromorphone causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm. The end result is constipation. Hydromorphone also can cause an increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects on the Cardiovascular System

Hydromorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by hydromorphone and can contribute to opioid-induced hypotension. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

12.3 Pharmacokinetics

Absorption

EXALGO is an extended-release formulation of hydromorphone that produces a gradual increase in hydromorphone concentrations. Following a single-dose administration of EXALGO, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose. The median T_{max} values ranged from 12 to 16 hours. The mean half-life was approximately 11 hours, ranging from 8 to 15 hours in most individual subjects. Linear pharmacokinetics has been demonstrated for EXALGO over the dose range 8 to 64 mg, with a dose-proportional increase in C_{max} and overall exposure ($AUC_{0-\infty}$) (see **Table 4**). Steady-state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached after 3 to 4 days of once-daily dosing of EXALGO. At steady state, EXALGO given once daily maintained hydromorphone plasma concentrations within the same concentration range as the immediate-release tablet given 4 times daily at the same total daily dose and diminished the fluctuations between peak and trough concentrations seen with the immediate-release tablet (see **Figure 1**). The bioavailability of EXALGO once daily and immediate-release hydromorphone four times daily in adults is comparable, as presented in **Table 4**.

Figure 1.
Mean Steady-State Plasma Concentration Profile

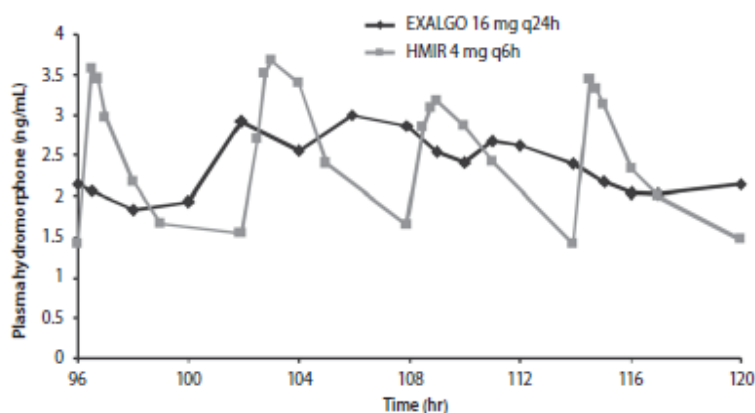


Table 4.
Mean (\pm SD) EXALGO Pharmacokinetic Parameters

| Regimen | Dosage | T _{max} * (hrs) | C _{max} (ng/mL) | AUC (ng-hr/mL) | T _{1/2} (hr) |
|--------------------------------|-------------|--------------------------|--------------------------|----------------|-----------------------|
| Single Dose (N = 31) | 8 mg | 12 (4-30) | 0.93 (1.01) | 18.1 (5.8) | 10.6 (4.3) |
| | 16 mg | 16 (6-30) | 1.69 (0.78) | 36.5 (11.3) | 10.3 (2.4) |
| | 32 mg | 16 (4-24) | 3.25 (1.37) | 72.2 (24.3) | 11.0 (3.2) |
| | 64 mg | 16 (6-30) | 6.61 (1.75) | 156.0 (30.6) | 10.9 (3.8) |
| Multiple Dose† (N = 29) | 16 mg q24h | 12 (6-24) | 3.54 (0.96) [‡] | 57.6 (16.3) | NA |
| | IR 4 mg q6h | 0.75 (0.5-2) | 5.28 (1.37) [§] | 54.8 (14.8) | NA |

NA = not applicable

* Median (range) reported for T_{max}

† Steady-state results on Day 5 (0-24 hours)

[‡] C_{min} 2.15 (0.87) ng/mL

[§] C_{min} 1.47 (0.42) ng/mL

Food Effect

The pharmacokinetics of EXALGO are not affected by food as indicated by bioequivalence when administered under fed and fasting conditions. Therefore, EXALGO may be administered without regard to meals. When a 16 mg dose of EXALGO was administered to healthy volunteers immediately following a high-fat meal, the median time to C_{max} (T_{max}) was minimally affected by the high-fat meal occurring at 16 hours compared to 18 hours while fasting.

Distribution

Following intravenous administration of hydromorphone to healthy volunteers, the mean volume of distribution was 2.9 (\pm 1.3) L/kg, suggesting extensive tissue distribution. The mean extent of binding of hydromorphone to human plasma proteins was determined to be 27% in an in vitro study.

Metabolism

After oral administration of an immediate-release formulation, hydromorphone undergoes extensive first-pass metabolism and is metabolized primarily in the liver by glucuronidation to hydromorphone-3-glucuronide, which follows a similar time course to hydromorphone in plasma. Exposure to the glucuronide metabolite is 35 to 40 times higher than exposure to the parent drug. In vitro data suggest that hydromorphone in clinically relevant concentrations has minimal potential to inhibit the activity of human hepatic CYP450 enzymes including CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A11.

Excretion

Approximately 75% of the administered dose is excreted in urine. Most of the administered hydromorphone dose is excreted as metabolites. Approximately 7% and 1% of the dose are excreted as unchanged hydromorphone in urine and feces, respectively.

Specific Populations

Geriatric Patients

Population PK analysis performed on plasma concentration data from 407 osteoarthritis (OA) patients using EXALGO showed an average 11% increase in hydromorphone AUC in the elderly group (65 to 75 years of age) when compared to the younger age group (less than or equal to 65 years of age).

Pediatric Patients

The pharmacokinetics of EXALGO were not evaluated in a pediatric population.

Gender

Females appeared to have approximately 10% higher mean systemic exposure in terms of C_{max} and AUC values.

Race

The effect of race on EXALGO pharmacokinetics has not been studied.

Hepatic Impairment

In a study that used a single 4 mg oral dose of immediate-release hydromorphone tablets, four-fold increases in plasma levels of hydromorphone (C_{max} and $AUC_{0-\infty}$) were observed in patients with moderate hepatic impairment (Child-Pugh Group B). Pharmacokinetics of hydromorphone in severe hepatic impairment patients has not been studied. Further increase in C_{max} and $AUC_{0-\infty}$ of hydromorphone in this group is expected. Start patients with moderate hepatic impairment on 25% of the usual dose of EXALGO and closely monitor for respiratory and central nervous system depression during dose titration. Consider alternate analgesic therapy for patients with severe hepatic impairment [see *Dosage and Administration (2.4) and Specific Populations (8.6)*].

Renal Impairment

Renal impairment affected the pharmacokinetics of hydromorphone and its metabolites following administration of a single 4 mg dose of immediate-release tablets. The effects of renal impairment on hydromorphone pharmacokinetics were two-fold and four-fold increases in plasma levels of hydromorphone (C_{max} and AUC_{0-48h}) in moderate ($CL_{cr} = 40$ to 60 mL/min) and severe ($CL_{cr} < 30$ mL/min) impairment, respectively. In addition, in patients with severe renal impairment hydromorphone appeared to be more slowly eliminated with longer terminal elimination half-life (40 hr) compared to subjects with normal renal function (15 hr). Start patients with moderate renal impairment on 50% of the usual EXALGO dose for patients with normal renal function and closely monitor for respiratory and central nervous system depression during dose titration. As EXALGO is only intended for once-daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment [see *Dosage and Administration (2.5) and Use in Specific Populations (8.7)*].

Drug Interaction/Alcohol Interaction

An in vivo study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 16 mg of EXALGO in healthy, fasted or fed volunteers. The results showed that the hydromorphone mean $AUC_{0-\infty}$ was 5% higher and 4% lower (not statistically significant) in the fasted and fed groups respectively after co-administration of 240 mL of 40% alcohol. The $AUC_{0-\infty}$ was similarly unaffected in subjects following the co-administration of EXALGO and alcohol (240 mL of 20% or 4% alcohol).

The change in geometric mean C_{max} with concomitant administration of alcohol and EXALGO ranged from an increase of 10% to 31% across all conditions studied. The change in mean C_{max} was greater in the fasted group of subjects. Following concomitant administration of 240 mL of 40% alcohol while

fasting, the mean C_{max} increased by 37% and up to 151% in an individual subject. Following the concomitant administration of 240 mL of 20% alcohol while fasting, the mean C_{max} increased by 35% and up to 139% in an individual subject. Following the concomitant administration of 240 mL of 4% alcohol while fasting, the mean C_{max} increased by 19% on average and as much as 73% for an individual subject. The range of median T_{max} for the fed and fasted treatments with 4%, 20% and 40% alcohol was 12 to 16 hours compared to 16 hours for the 0% alcohol treatments.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of hydromorphone hydrochloride were completed in both Han-Wistar rats and CrI:CD1[®](ICR) mice. Hydromorphone HCl was administered to Han-Wistar rats (2, 5, and 15 mg/kg/day for males, and 8, 25 and 75 mg/kg/day for females) for 2 years by oral gavage. In female rats, incidences of hibernoma (tumor of brown fat) were increased at 10.5 times the maximum recommended daily exposure based on AUC at the mid dose (2 tumor, 25 mg/kg/day) and 53.7 times the maximum recommended human daily exposure based on AUC at the maximum dose (4 tumors, 75 mg/kg/day). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in male rats. The systemic drug exposure (AUC, ng•h/mL) at the 15 mg/kg/day in male rats was 7.6 times greater than the human exposure at a single dose of 32 mg/day of EXALGO. There was no evidence of carcinogenic potential in CrI:CD1[®](ICR) mice administered hydromorphone HCl at doses up to 15 mg/kg/day for 2 years by oral gavage. The systemic drug exposure (AUC, ng•h/mL) at the 15 mg/kg/day in mice was 1.1 (in males) and 1.2 (in females) times greater than the human exposure at a single dose of 32 mg/day of EXALGO.

Mutagenesis

Hydromorphone was not mutagenic in the in vitro bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the in vitro human lymphocyte chromosome aberration assay or the in vivo mouse micronucleus assay.

Impairment of Fertility

Hydromorphone given orally to rats during the mating period caused a slight but statistically significant reduction in implantations at 6.25 mg/kg/day (~1.2 times the human exposure following to 32 mg/day).

14 CLINICAL STUDIES

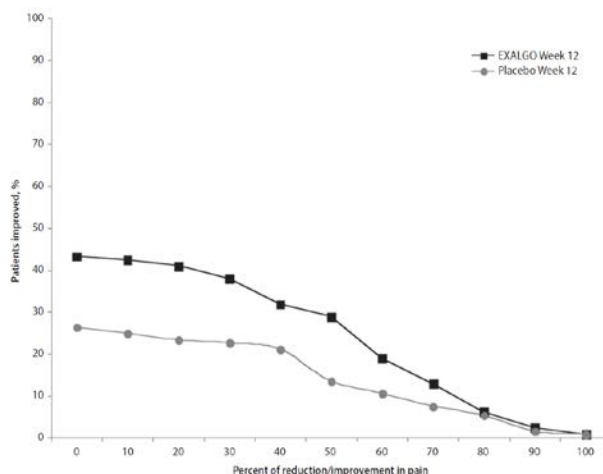
EXALGO was investigated in a double-blind, placebo-controlled, randomized withdrawal study in opioid tolerant patients with moderate-to-severe low back pain. Patients were considered opioid tolerant if they were currently on opioid therapy that was ≥ 60 mg/day of oral morphine equivalent for at least 2 months prior to screening. Patients entered an open-label conversion and titration phase with EXALGO, were converted to a starting dose that was approximately 75% of their total daily morphine equivalent dose, and were dosed once daily until adequate pain control was achieved while exhibiting tolerable side effects. Supplemental immediate-release hydromorphone tablets were allowed throughout the study. Patients who achieved a stable dose entered a 12-week, double-blind, placebo-controlled, randomized treatment phase. Mean daily dose at randomization was 37.8 mg/day (range of 12 mg/day to 64 mg/day). Fifty-eight (58) percent of patients were successfully titrated to a stable dose of EXALGO during the open-label conversion and titration phase.

During the double-blind treatment phase, patients randomized to EXALGO continued with the stable dose achieved in the conversion and titration phase of the study. Patients randomized to placebo received, in a blinded manner, EXALGO and matching placebo in doses tapering from the stable dose achieved in conversion and titration. During the taper down period, patients were allowed immediate-release hydromorphone tablets as supplemental analgesia to minimize opioid withdrawal symptoms in placebo patients. After the taper period, the number of immediate-release hydromorphone tablets was limited to

two tablets per day. Forty-nine (49) percent of patients treated with EXALGO and 33% of patients treated with placebo completed the 12-week treatment period.

EXALGO provided superior analgesia compared to placebo. There was a significant difference between the mean changes from Baseline to Week 12 or Final Visit in average weekly pain intensity Numeric Rating Scale (NRS) scores obtained from patient diaries between the two groups. The proportion of patients with various degrees of improvement from screening to Week 12 or Final Visit is shown in **Figure 2**. For this analysis, patients who discontinued treatment for any reason prior to Week 12 were assigned a value of zero improvement.

Figure 2.
Percent Reduction in Average Pain Intensity from Screening to Week 12 or Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

EXALGO Extended-Release Tablet Strengths

| Strength | Color | Tablet Description | Bottle Count | NDC |
|----------|-------------|----------------------------------------|--------------|--------------|
| 8 mg | Red | Round, biconvex, printed with "EXH 8" | 100 | 23635-408-01 |
| 12 mg | Dark yellow | Round, biconvex, printed with "EXH 12" | 100 | 23635-412-01 |
| 16 mg | Yellow | Round, biconvex, printed with "EXH 16" | 100 | 23635-416-01 |
| 32 mg | White | Round, biconvex, printed with "EXH 32" | 100 | 23635-432-01 |

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Addiction, Abuse, and Misuse

Inform patients that the use of EXALGO, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share EXALGO with others and to take steps to protect EXALGO from theft or misuse.

Life-threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting EXALGO or when the dose is increased, and that it can occur even at recommended doses [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store EXALGO securely and to dispose of unused EXALGO by flushing the tablets down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of EXALGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions (5.3)*].

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if EXALGO is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take EXALGO, including the following:

- Swallowing EXALGO whole
- Not crushing, chewing, splitting or dissolving the tablets
- Using EXALGO exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing EXALGO without first discussing the need for a tapering regimen with the prescriber

Gastrointestinal Blockage

Advise patients that people with certain stomach or intestinal problems such as narrowing of the intestines or previous surgery may be at higher risk of developing a blockage. Symptoms include abdominal distension, abdominal pain, severe constipation, or vomiting. Instruct patients to contact their healthcare provider immediately if they develop these symptoms.

Hypotension

Inform patients that EXALGO may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that EXALGO may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in EXALGO. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that EXALGO can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Disposal

Advise patients to flush the unused tablets down the toilet when EXALGO is no longer needed.

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Hazelwood, MO 63042 USA

www.Exalgo.com or call 1-800-778-7898



Medication Guide

EXALGO® (eks-al-goh) (hydromorphone hydrochloride) extended-release tablets, CII

EXALGO is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, in people who are already regularly using opioid pain medicine, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about EXALGO:

- **Get emergency help right away if you take too much EXALGO (overdose).** When you first start taking EXALGO, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
- Never give anyone else your EXALGO. They could die from taking it. Store EXALGO away from children and in a safe place to prevent stealing or abuse. Selling or giving away EXALGO is against the law.

Do not take EXALGO if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking EXALGO, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- allergy to sulfites
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of EXALGO during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** EXALGO passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking EXALGO with certain other medicines can cause serious side effects.

When taking EXALGO:

- Do not change your dose. Take EXALGO exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow EXALGO whole. Do not cut, break, chew, crush, dissolve, snort, or inject EXALGO because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking EXALGO without talking to your healthcare provider.**
- EXALGO is contained in a hard tablet shell that you may see in your bowel movement; this is normal.
- After you stop taking EXALGO, flush any unused tablets down the toilet.

While taking EXALGO, DO NOT:

- Drive or operate heavy machinery, until you know how EXALGO affects you. EXALGO can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with EXALGO may cause you to overdose and die.

The possible side effects of EXALGO are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of EXALGO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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