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; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 patient's risk before prescribing, and monitor regularly for these behaviors and 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 by 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).**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.4, 7).**

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Warnings and Precautions (5)	12/2016

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 per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per 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

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain.
- For once daily administration IN OPIOID-TOLERANT PATIENTS (2.1).
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patients response, prior analgesic experience, and risk factors for addiction, abuse and misuse (2.3).
- Instruct patients to swallow EXALGO tablets intact, and not to cut, break, chew, crush, or dissolve the tablets (risk of potentially fatal overdose) (2.1, 5.1).
- Dose may be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia (2.3).
- Do not abruptly discontinue EXALGO in a physically-dependent patient (2.4, 5.11).
- Moderate Hepatic Impairment: Initiate treatment with 25% of the dose that would be prescribed for patients with normal hepatic function. Monitor closely for respiratory and central nervous system depression (2.5).
- Moderate and Severe Renal Impairment: Initiate treatment in patients with moderate renal impairment with 50% and patients with severe renal impairment with 25% of the EXALGO dose that would be prescribed for patients with normal renal function. Monitor closely for respiratory and central nervous system depression (2.6).

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 in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Narrowed or obstructed gastrointestinal tract (4)
- Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites (4, 5.12)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly Cachectic Debilitated Patients: Monitor closely, particularly during initiation and titration (5.5).
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid (5.6).
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of EXALGO in patients with circulatory shock (5.7).
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of EXALGO in patients with impaired consciousness or coma (5.8).

ADVERSE REACTIONS

Most common adverse reactions (incidence >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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue EXALGO if serotonin syndrome is suspected (7).
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of hydromorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI (7).
- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with EXALGO because they may reduce analgesic effect of EXALGO or precipitate withdrawal symptoms (5.11, 7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Not recommended (8.2).
- Severe Hepatic Impairment: Use not recommended (8.6).
- Severe Renal Impairment: Consider an alternate analgesic (8.7).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Boxed Warning

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 and 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)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of EXALGO and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

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 per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per 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 Important Dosage and Administration Information

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

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- 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 and following dosage increases with EXALGO and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Instruct patients to swallow EXALGO tablets whole *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving EXALGO tablets will result in uncontrolled delivery of hydromorphone and can lead to overdose or death *[see Warnings and Precautions (5.1)].*

2.2 Initial Dosage

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.

There is substantial inter-patient variability in the relative potency of different opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of EXALGO. It is safer to underestimate a patient’s 24-hour oral hydromorphone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydromorphone dosage and manage an adverse reaction due to overdose.

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.

2.3 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.

2.4 Discontinuation of EXALGO

When a patient no longer requires therapy with EXALGO, taper doses gradually, by 25% to 50% every 2 to 3 days while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue EXALGO.

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

2.5 Dosage Modifications in Patients with Moderate 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)]*.

2.6 Dosage Modifications in Patients with Renal Impairment

Start patients with moderate renal impairment on 50% 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)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: available in 8 mg, 12 mg, 16 mg or 32 mg dosage strengths.

8 mg tablets: round, biconvex, red tablets imprinted with "EXH 8" on one side.
12 mg tablets: round, biconvex, dark yellow tablets imprinted with "EXH 12" on one side.
16 mg tablets: round, biconvex, yellow tablets imprinted with "EXH 16" on one side.
32 mg tablets: 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 *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.5)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warning and Precautions (5.9)].*
- 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 *[see Warnings and Precautions (5.9)]*.
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone *[see Warnings and Precautions (5.12)]*

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 and 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)]*.

Opioids 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 (CO_2) 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 dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with EXALGO and following dosage 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 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks from Concomitant use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of EXALGO with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when EXALGO is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.5 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of EXALGO in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: EXALGO treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of EXALGO *[see Warnings and Precautions (5.2)].*

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)].*

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, 5.4)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without

recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.7 Severe Hypotension

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)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of EXALGO. In patients with circulatory shock, EXALGO may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of EXALGO in patients with circulatory shock.

5.*8* Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), EXALGO may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with EXALGO.

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 Risks of Use in Patients with Gastrointestinal Conditions

EXALGO is contraindicated in patients with known or suspected gastrointestinal obstruction, including 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. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.10 Increased Risk of Seizures in Patients with Seizure Disorders

The hydromorphone in EXALGO may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during EXALGO therapy.

5.11 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving 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)]*.

When discontinuing EXALGO, gradually taper the dose *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue EXALGO *[see Drug Abuse and Dependence (9.3)]*.

5.12 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 *[see Adverse Reactions (6.2)]*.

5.13 Risks of 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 *[see Patient Counseling Information (17)]*.

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 Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.6)]*
- Severe Hypotension *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Adverse Reactions*[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Withdrawal *[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 Titration Phase	Double-Blind Treatment Phase	
	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 ≥ 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 hydromorphone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs *[see Drug Interactions (7)]*.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use *[see Warnings and Precautions (5.6)]*.

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in EXALGO *[see Contraindications (4) and Warnings and Precautions (5.12)].*

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with EXALGO.

Table 4: Clinically Significant Drug Interactions with EXALGO

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, , antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue EXALGO if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	

Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.4)].*
Intervention:	The use of EXALGO is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of EXALGO and/or precipitate withdrawal symptoms *[see Warnings and Precautions (5.11)]*.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Hydromorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression *[see Warnings and Precautions (5.4)].*
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of EXALGO and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when EXALGO is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no adequate and well-controlled studies in pregnant women. Based on animal data, advise pregnant women of the potential risk to a fetus.

In animal reproduction studies, reduced postnatal survival of pups, developmental delays, and altered behavioral responses were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses 2.1 times the human daily dose of 32 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 4.8 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 2.3 times the HDD to pregnant mice. No malformations were noted at 2.1 or 17 times the HDD in pregnant rats or rabbits, respectively [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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. 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. EXALGO is not recommended for use in pregnant women during or immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including EXALGO can prolong labor through actions which 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 dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data
Animal Data

Pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 1.75, 3.5, or 7 mg/kg/day (0.5, 1.1, or 2.1 times the HDD of 32 mg/day based on body surface area, respectively). Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in the two highest dose groups). There was no evidence of malformations or embryotoxicity reported.

Pregnant rabbits were treated with hydromorphone hydrochloride from Gestation Day 6 to 20 via oral gavage doses of 10, 25, or 50 mg/kg/day (4.3, 8.5, or 17 times the HDD of 32 mg/day based on body surface area, respectively). Maternal toxicity was noted in the highest dose group (reduced food consumption and body weights). There was no evidence of malformations or embryotoxicity reported.

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of hydromorphone hydrochloride (19 to 258 mg/kg) on Gestation Day 8 to pregnant hamsters (4.8 to 65.4 times the HDD of 32 mg/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity. No neural tube defects were noted at 14 mg/kg (3.5 times the human daily dose of 32 mg/day). In a published study, CF-1 mice were treated subcutaneously with continuous infusion of 7.5, 15, or 30 mg/kg/day hydromorphone hydrochloride (1.1, 2.3, or 4.6 times the human daily dose of 32 mg based on body surface area) via implanted osmotic pumps during organogenesis (Gestation Days 7 to 10). Soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (split supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites) were observed at doses 2.3 times the human dose of 32 mg/day based on body surface area. The findings cannot be clearly attributed to maternal toxicity.

Pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 6 to Lactation Day 21 via oral gavage doses of 1.75, 3.5, or 7 mg/kg/day (0.5, 1.1, or 2.1 times the HDD of 32 mg/day based on body surface area, respectively). Reduced pup weights were noted at 1.1 and 2.1 times the human daily dose of 32 mg/day and increased pup deaths, delayed ear opening, reduced auditory startle reflex, and reduced open-field activity were also noted at 2.1 times the HDD. Maternal toxicity was noted in all

treatment groups (reduced food consumption and body weights in all groups) and decreased maternal care in the high dose group.

8.2 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with EXALGO. 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.

Clinical Considerations

Monitor infants exposed to EXALGO through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.1)]*.

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 (aged 65 years or older) may have increased sensitivity to hydromorphone. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of EXALGO slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.2)]*.

Hydromorphone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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 (2.5)]*.

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 (CLcr = 40 to 60 mL/min) and severe (CLcr < 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. 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 (2.6)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EXALGO contains hydromorphone, a Schedule II controlled substance.

9.2 Abuse

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

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

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.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: 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 in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider. “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. Healthcare provider 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 state and federal 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 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 central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved EXALGO enhances drug release and increases the risk of overdose and death.

With intravenous abuse, the inactive ingredients in EXALGO, especially polyethylene oxide, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

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 (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., 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 signs *[see Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

Clinical Presentation
Acute overdosage with EXALGO can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with 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, naloxone and nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydromorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose.

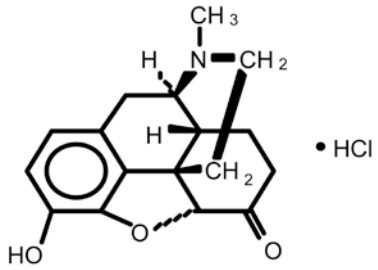
Because the duration of reversal is expected to be less than the duration of action of hydromorphone in EXALGO, carefully monitor the patient until spontaneous respiration is reliably reestablished. EXALGO will continue to release hydromorphone and add to the hydromorphone load for up to 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experiences 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 initiated 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, an opioid agonist.

Hydromorphone hydrochloride USP is 4,5α-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 $C_{17}H_{19}NO_3$•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 a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of hydromorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

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 both increases in carbon dioxide tension and to electrical stimulation.

Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis, rather than miosis, may be seen due to severe hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
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 is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

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, sweating and/or orthostatic hypotension.

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.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)].*

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.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydromorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.3)]*.

Concentration–Adverse Reaction Relationships
There is a relationship between increasing hydromorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and

respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

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

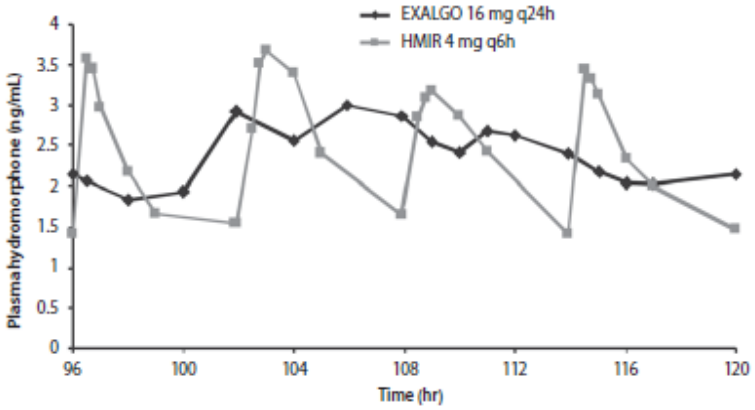


Table 5.
Mean (±SD) EXALGO Pharmacokinetic Parameters

Regimen	Dosage	T_{max}* (hrs)	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (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 (±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.

Elimination

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
Age: 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).

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

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 (2.5) 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 (CLcr = 40 to 60 mL/min) and severe (CLcr < 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 (2.6) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

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 Crl: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 Crl: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
Reduced implantation sites and viable fetuses were noted at 2.1 times the human daily dose of 32 mg/day in a study in which female rats were treated orally with 1.75, 3.5, or 7 mg/kg/day hydromorphone hydrochloride (0.7, 1.4, or 2.8 times a human daily dose of 24 mg/day (HDD) based on body surface area) beginning 14 days prior to mating through Gestation Day 7 and male rats were treated with the same hydromorphone hydrochloride doses beginning 28 days prior to and throughout mating.

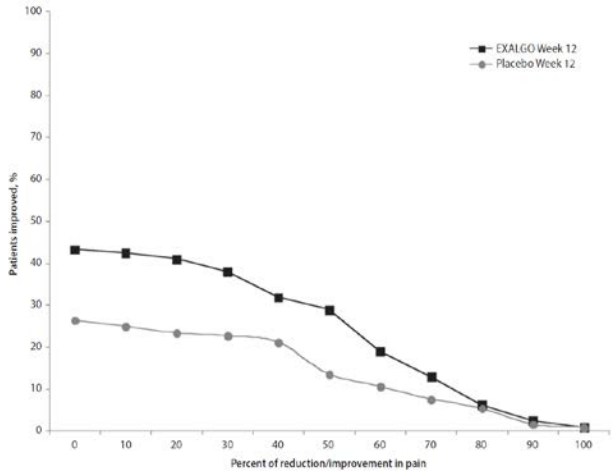
14 CLINICAL STUDIES

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

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 by 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.

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if EXALGO is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.4), Drug Interactions (7)].*

Serotonin Syndrome
Inform patients that EXALGO could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions 7]*.

MAOI Interaction
Inform patients to avoid taking EXALGO while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking EXALGO *[see Drug Interactions 7]*.

Adrenal Insufficiency
Inform patients that EXALGO could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.6)]*.

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

- EXALGO is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved EXALGO tablets can result in a fatal overdose *[see Dosage and Administration (2.1)].*
- Using EXALGO exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Do not discontinue EXALGO without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.4)]*.

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).

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 *[see Contraindications (4), Warnings and Precautions (5.12), and Adverse Reactions (6.2)].*

Pregnancy

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), Use in Specific Populations (8.1)].*

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that EXALGO can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)].*

Lactation
Advise patients that breastfeeding is not recommended during treatment with EXALGO *[see Use in Specific Populations (8.2)]*

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[Use in Specific Populations (8.3)].*

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 *[see Warnings and Precautions (5.13)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)].*

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

Distributed by:
Mallinckrodt Brand Pharmaceuticals, Inc.
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, 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.
- Taking EXALGO with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- 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.** Not recommended during treatment with EXALGO. It 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. Use the lowest dose possible for the shortest time needed.
- 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, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

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**

Distributed by: Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO 63042 USA, www.Exalgo.com or call 1-800-778-7898

Mallinckrodt™

This Medication Guide has been approved by the U.S. Food and Drug Administration. **Revised:** December 2016