| LABEL SECTION | ANNOTATION |
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| **FULL PRESCRIBING INFORMATION** | |
| **EXALGO is available only through the Exalgo Alliance™ Program** | Module 1.16 REMS |
| [*See Warnings and Precautions* (*5.13*)]. | |
| **WARNING:** | |
| **EXALGO contains the potent Schedule II opioid agonist, hydromorphone with an abuse liability similar to other opioid analgesics. EXALGO can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.** | Opioid class labeling |
| EXALGO tablets are an extended release formulation of hydromorphone indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered to be opioid tolerant are those who are taking at least 60 mg oral morphine/day, or at least 30 mg of oral oxycodone/day, or at least 12 mg hydromorphone/day, or an equianalgesic dose of another opioid, for a week or longer. | Module 2.5, Section 1<br>Opioid class labeling |
| EXALGO is contraindicated in the management of acute or postoperative pain and is not for use as a PRN analgesic. Fatal respiratory depression could occur in patients who are not opioid tolerant. | Module 2.5, Section 3<br>Opioid class labeling |
| **EXALGO tablets are to be swallowed whole** and are not to be broken, chewed, dissolved, crushed or *injected.* Taking broken, chewed, dissolved, **EXALGO** or its contents can lead to rapid release and absorption of a potentially fatal dose of hydromorphone. | |

| LABEL SECTION | ANNOTATION |
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| **1. INDICATIONS AND USAGE** | |
| EXALGO (hydromorphone HCl) Extended-Release Tablets is an extended-release oral formulation of hydromorphone hydrochloride intended for once daily administration indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. Patients considered to be opioid tolerant are those who are taking at least 60 mg oral morphine/day, or at least 30 mg of oral oxycodone/day, or at least 12 mg hydromorphone/day, or an equianalgesic dose of another opioid, for a week or longer. | Module 2.5, Section 1<br>Opioid class labeling |
| EXALGO must only be used in opioid tolerant patients because fatal respiratory depression could occur in patients who are not already receiving and tolerant to opioid therapy. | Opioid class labeling |
| EXALGO is contraindicated in the management of acute or postoperative pain and should not be used on an as needed basis (i.e., prn). EXALGO should not be used to manage (or treat) pain that is mild or not expected to persist for an extended period of time. | Module 2.5, Section 3 |
| Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction. | Opioid class labeling |
| **2. DOSAGE AND ADMINISTRATION** | |
| The dose range of EXALGO is 12 mg to 64 mg. The extended-release nature of the formulation allows EXALGO to be effectively administered every 24 hours with or without food. Discontinue all other extended-release opioids when beginning EXALGO therapy. | CSR 301, Section 10.5.2<br>Module 2.7.1, Section 2.5 |

| LABEL SECTION | ANNOTATION |
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| **2. 1 Initiation of Therapy**<br>It is critical to initiate the dosing regimen individually for each patient. Overestimating the EXALGO dose when converting patients from another opioid medication can result in fatal overdose with the first dose *[see Overdosage (10)]*.<br><br>In the selection of the initial dose of EXALGO, attention should be given to the following:<br>1. the daily dose, potency, and specific characteristics of the opioid the patient has been taking previously;<br>2. the reliability of the relative potency estimate used to calculate the equivalent hydromorphone dose needed;<br>3. the patient's degree of opioid tolerance;<br>4. the age, general condition, and medical status of the patient;<br>5. concurrent non-opioid analgesics and other medications, such as those with CNS activity *[see Drug Interactions (7]);*<br>6. the type and severity of the patient's pain;<br>7. the balance between pain control and adverse effects;<br>8. risk factors for abuse, addiction, or diversion, including a prior history of abuse, addiction, or diversion.<br>The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient. | 5.3.5.3 (ISE), Section 4 |
| **2.1.1 Conversion to EXALGO in Opioid Tolerant Patients**<br>**2.1.1.1 Conversion from oral hydromorphone to EXALGO**<br>Patients receiving oral hydromorphone may be converted to EXALGO by administering a starting dose equivalent to the patient's total daily oral hydromorphone dose. The dose of EXALGO can be titrated every 3 to 4 days until adequate pain relief and acceptable side effects have been achieved *[see Individualization of Dose (2.1.1.4)]* | Module 2.7.2, Section 2.2.4 |

| LABEL SECTION | ANNOTATION |
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**2.1.1.2 Conversion from other Oral Opioids to EXALGO**

For conversion from other opioids to EXALGO, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, EXALGO therapy should be started by administering 50% to 75% of the calculated total daily dose of EXALGO (see conversion ratio table below) once-daily every 24 hours. The initial dose of EXALGO can be titrated until adequate pain relief and acceptable side effects have been achieved. The following table provides approximate equivalent doses, which may be used as a guideline for conversion.

ANNOTATION: CSR NMT-1077-301, Section 9.5.6

- **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current oral opioid therapy to EXALGO.** No fixed conversion ratio is likely to be satisfactory in all patients, especially in patients receiving large opioid doses.
- There is substantial patient variation in the relative potency of different opioid drugs and formulations.
- The recommended doses are only a starting point, and close observation and titration is indicated until a satisfactory dose is obtained on the new therapy.

**Conversion Ratios to EXALGO***

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

ANNOTATION: Sarhill, 2001; Bruera, 1996; Curtis, 1999; Gabrail, 2004; Ripamonti, 1998

[a] Ratio for conversion of oral opioid dose to approximate hydromorphone equivalent dose.

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

| LABEL SECTION | ANNOTATION |
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| a. For patients on a regimen of mixed opioids, calculate the approximate oral hydromorphone dose for each opioid and sum the totals.<br>b. For patients on a regimen of fixed-ratio opioid/non-opioid analgesic medications, only the opioid component of these medications should be used in the conversion. The non-opioid component may be continued as a separate drug, or a different non-opioid analgesic may be selected.<br>2. In general, an appropriate starting dose of EXALGO is 50% to 75% of the calculated total daily dose every 24 hours.<br>3. Modify the starting dose if indicated, based primarily on considerations outlined in the 8 bulleted items listed above [see Dosage and Administration: Initiation of Therapy (2.1)].<br>4. The dose of EXALGO can be titrated every 3 to 4 days until adequate pain relief and acceptable side effects have been achieved [see Individualization of Dose (2.1.1.4)]<br><br>[b] **It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists.** The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.<br><br>* **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to EXALGO.** | |
| **2.1.1.3 Conversion from Transdermal Fentanyl to EXALGO**<br>Eighteen hours following the removal of the transdermal fentanyl patch, EXALGO treatment can be initiated. For each 25 µg/hr fentanyl transdermal dose the equianalgesic dose of EXALGO is 12 mg every 24 hours. An appropriate starting dose of EXALGO is 50% to 75% of the calculated total daily dose every 24 hours. | APS-2003 |
| **2.1.1.4 Individualization of Dosage**<br>Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. In clinical practice, titration of the total daily EXALGO dose should be based upon the severity of the patient's pain, the amount of supplemental opioid utilization, and the patient's ability to tolerate the opioid. Patients should be titrated to adequate analgesia with dose increases allowed every 3 to 4 days, in order to attain steady-state plasma concentrations of hydromorphone at each dose. As a guideline, dosage increases of 25%-50% of the current daily dose of EXALGO should be considered for each titration step. If more than two doses of rescue medication are needed within a 24 hour period for two consecutive days, the dose of EXALGO should usually be titrated upward. This formulation should be administered every 24 hours.<br><br>If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of an immediate-release opioid, or a non-opioid | Module 2.7.1, Section 2.1.5<br>CSR NMT 1077-301, Section 9.1.1.2 |

| LABEL SECTION | ANNOTATION |
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| analgesic may be administered. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control. | Opioid class labeling |
| During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family. Patients and caregivers/family members should be advised of the potential side effects. | Opioid class labeling |
| **2.1.1.5 Supplemental Analgesia**<br>The intent of the titration period is to establish a patient-specific once-daily dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. During the initial titration of EXALGO, patients should consider using supplemental analgesic treatment such as behavioral therapy, non-opioid analgesics or short-acting opioid analgesics as needed until analgesic efficacy with EXALGO is obtained. Due to the extended-release pharmacokinetic profile of the product, specific attention should be given to the first dose, as patients may not experience significant analgesic effects for the first 6 hours. In addition to once-daily EXALGO therapy, supplemental rescue medication in the form of immediate-release preparations should be made available to all patients with chronic pain for "rescue" from breakthrough pain or to prevent pain that occurs predictably during certain patient activities (incident pain). Individual supplemental rescue medication doses of immediate-release opioids should generally not exceed 5-15% of the 24 hour EXALGO dose. | CSR 1077-301, Section 9.5.9.1<br>Module 2.7.2, Section 2.2.1.1.3<br>APS-2003 |

| LABEL SECTION | ANNOTATION |
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| **2.2 Maintenance of Therapy**<br>Once patients become stable on once-daily EXALGO therapy, the dose may be continued for as long as pain relief is necessary. If patients need to titrate while on maintenance therapy, the same method outlined in Individualization of Dose should be followed to re-establish pain control.<br><br>During chronic therapy with EXALGO, the continued need for around-the-clock opioid therapy should be assessed periodically. Patients should continue to be assessed for their clinical risks for opioid abuse, addiction, or diversion particularly with high-dose formulations. | Opioid class labeling |
| **2.3 Discontinuation of EXALGO**<br>When the patient no longer requires therapy with EXALGO, doses should be tapered gradually, by 25-50% every 2 or 3 days down to a dose of 8 mg before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the physically dependent patient. | CSR NMT 1077-301, Section 9.5.5 |
| **2.4 Renal and Hepatic Impairment**<br>Patients with moderate hepatic and renal impairment should be started on a reduced dose and closely monitored during dose titration. In patients with severe renal impairment a longer dosing interval should also be considered and these patients should in addition be monitored during maintenance therapy for development of opioid-related adverse reactions. | Module 2.7.2, Section 2.4.2 |
| **3. DOSAGE FORMS AND STRENGTHS**<br>EXALGO Tablets are available in 8 mg, 12 mg, 16 mg or 32 mg dosage strengths. The 8 mg tablets are round, biconvex, red tablets imprinted with "HM 8" on one side. The 12 mg tablets are round, biconvex, dark yellow tablets imprinted with "HM 12" on one side. The 16 mg tablets are round, biconvex, yellow tablets imprinted with "HM 16" on one side. The 32 mg tablets are round, biconvex, white tablets imprinted with "HM 32" on one side. | Module 3.2.P.5.1 |

| LABEL SECTION | ANNOTATION |
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| **4. CONTRAINDICATIONS** | |
| EXALGO **must not** be used in opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant. | Opioid class labeling |
| EXALGO is contraindicated in the management of acute or postoperative pain. EXALGO **must not** be used on an as needed basis (i.e., prn). | Module 2.5, Section 3 |
| EXALGO **must not** be used to manage (or treat) pain that is mild or not expected to persist for an extended period of time. | |
| EXALGO is contraindicated in any situation where opioids are contraindicated such as: in patients with respiratory depression, especially in the absence of resuscitative equipment or in unmonitored settings; in patients with acute or severe bronchial asthma or hypercarbia; in patients who have or are suspected of having a paralytic ileus. | Opioid class labeling |
| EXALGO is contraindicated in patients who have had surgical procedures and/or underlying disease that would result in narrowing of the gastrointestinal tract, or have "blind loops" of the gastrointestinal tract or gastrointestinal obstruction. | Module 5.3.5.3 (ISS), Section 2.6.9.1 |
| EXALGO is contraindicated in patients with known hypersensitivity to any of its components including the active agent, hydromorphone hydrochloride. | Opioid class labeling |
| **5. WARNINGS AND PRECAUTIONS** | |
| *See Boxed Warning* – WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE | |
| **5.1 General** | |
| EXALGO tablets are to be swallowed whole, and are not to be broken, chewed, crushed, or dissolved. Taking broken, chewed, crushed, dissolved EXALGO or its contents leads to the rapid release and absorption of a potentially fatal dose of hydromorphone. If attempts are made to extract the drug from the hard outer shell for purposes of | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| parenteral abuse, the injection of tablet excipients could be toxic and may result in lethal complications.<br><br>EXALGO should only be used in patients who are already receiving opioid therapy, and who have demonstrated opioid tolerance. Use in non-opioid tolerant patients may lead to fatal respiratory depression.<br><br>Opioid analgesics should be used with caution especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension. | Module 2.6.6.8.6.4<br><br>Opioid class labeling<br><br>Opioid class labeling |
| **5. 2 Respiratory Depression**<br>Respiratory depression is the chief hazard of EXALGO.<br><br>Respiratory depression is a particular problem: in non-opioid tolerant patients; in elderly or debilitated patients as well as those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation; when opioids are given in conjunction with other agents that depress respiration.<br><br>Respiratory depression from opioids is manifested by a reduced urge to breath and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drug with sedative properties and opioids especially dangerous. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.<br><br>EXALGO should be used with extreme caution in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea, myxedema, kyphoscoliosis or CNS depression. In these patients, even moderate therapeutic doses of hydromorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and hydromorphone should be employed only under careful medical supervision at the lowest effective dose. | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| **5.3 Misuse, Abuse, and Diversion of Opioids**<br>EXALGO contains hydromorphone, an opioid agonist similar to morphine, and is a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.<br><br>Like other opioid agonists, legal or illicit, hydromorphone can be abused. This should be considered when prescribing or dispensing EXALGO tablets in situations where the healthcare professional is concerned about an increased risk of misuse, abuse, or diversion.<br><br>Breaking, crushing, chewing, or dissolving the contents of a EXALGO tablet can result in the uncontrolled delivery of the opioid and poses a significant risk of overdose and death *[see Drug Abuse and Addiction (9.2)]*.<br><br>Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.<br><br>Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product. | Opioid class labeling |
| **5.4 Interactions with Alcohol and other CNS Depressants**<br>The concurrent use of EXALGO with other central nervous system (CNS) depressants, including but not limited to other opioids, illicit drugs, sedatives, hypnotics, general anesthetics, phenothiazines, muscle relaxants, other tranquilizers, and alcohol, increases the risk of respiratory depression, hypotension, and profound sedation, potentially resulting in coma or death. Use with caution and in reduced dosages in patients taking these agents. *[see Clinical Pharmacology: Alcohol Effect (12.3.4)]*.<br><br>Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| symptoms. | |
| **5.5 Head Injury and Increased Intracranial Pressure**<br>In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. | Opioid class labeling |
| **5.6 Hypotensive Effect**<br>EXALGO, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines, general anesthetics, or other agents that compromise vasomotor tone.<br><br>EXALGO, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure. | Opioid class labeling |
| **5.7 Gastrointestinal Transit Time and Obstruction**<br>Clinical conditions or medicinal products that cause a sudden and significant shortening of gastrointestinal transit time may result in decreased hydromorphone absorption with EXALGO and may potentially lead to withdrawal symptoms in patients with a physical dependence on opioids.<br><br>Because the EXALGO tablet does not appreciably change in shape in the GI tract, EXALGO should not be administered to 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 rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable extended-release formulations. Due to the extended-release design of the tablet, EXALGO must only be used in patients who are able to swallow the tablet whole. | Module 2.7.4, Section 6.3<br><br>Module 5.3.5.3 (ISS), Section 2.6.9.1 |

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| **5.8 Sulfites**<br>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. | Opioid class labeling |
| **5.9 MAO Inhibitors**<br>EXALGO is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. | Opioid class labeling |
| **5.10 Special Risk Groups**<br>EXALGO should be used with caution in elderly (≥ 65 years) and debilitated patients and in patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease. *[see Use in Specific Populations (8)]*<br>EXALGO should be used with caution in the following conditions: alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression; delirium tremens; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; moderate to severe impairment of pulmonary or renal function; moderate impairment of hepatic function; and toxic psychosis.<br><br>Hydromorphone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings. | Opioid class labeling |
| **5.11 Use in Pancreatic/Biliary Tract Disease**<br>The administration of opioids may obscure the diagnosis or clinical course of acute abdominal conditions. Therefore it is important to make sure that the patient is not suffering from intestinal occlusion, especially of the ileus, before initiation of treatment. Hydromorphone also can cause an increase in biliary tract pressure as a result of spasm in the sphincter of Oddi. Caution should therefore be exercised in the administration of EXALGO to patients with inflammatory or obstructive bowel disorders, acute pancreatitis secondary to biliary tract disease and in patients | Opioid class labeling |

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| about to undergo biliary surgery. | |
| **5.12 Physical Dependence**<br>In general, EXALGO should not be abruptly discontinued. However, EXALGO, like other opioids, can be safely discontinued without the development of withdrawal symptoms by slowly tapering the daily dose *[see Drug Abuse and Dependence: Dependence (9.3)]*. | Opioid class labeling<br>CSR NMT 1077-301, Section 9.5.5 |

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| **5.13 Exalgo Alliance Program**<br><br>EXALGO is available only through the Exalgo Alliance™ Program. The purpose of this program is to evaluate and mitigate the risks of overdose, abuse and diversion. The program is designed to ensure that only appropriate patients receive EXALGO. The program is designed to ensure that prescribers, pharmacists, and patients understand the risk-benefit profile and appropriate use and handling of EXALGO.<br><br>Under the Exalgo Alliance Program, only wholesalers, prescribers, pharmacies, and patients enrolled in the program are able to distribute, prescribe, dispense, or receive EXALGO. Please contact the Exalgo Alliance Program Contact Center at 1-XXX-XXX-XXXX or via the website at ExalgoAlliance.com for detailed information.<br><br>**Prescriber Information**<br><br>To enroll in the Exalgo Alliance program, prescribers must be educated to understand (1) the risks of opioids and responsible opioid prescribing and use; (2) EXALGO risks; (3) responsible EXALGO prescribing and dispensing; (4) safe EXALGO use and handling.<br><br>**Prescribers are required to:**<br><br>• Ensure each patient is opioid-tolerant and understands EXALGO risks and safe use and handling<br>• Ensure the patient has reviewed the Medication Guide<br>• Enroll the patient into the Exalgo Alliance Program<br><br>**Patient Information**<br><br>Patients should be fully counseled by their physician and pharmacist on and understand the risk-benefit profile and EXALGO safe use and handling before an initial prescription is written.<br><br>**Patients who are prescribed EXALGO must be instructed to:**<br><br>• Read the Medication Guide<br>• Not use EXALGO for short-term pain relief from injuries or surgery<br>• Keep EXALGO in a safe place away from children and from anyone whom has not been prescribed | Module 1.16 REMS |

| LABEL SECTION | ANNOTATION |
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| EXALGO<br>• Always protect EXALGO from theft or misuse at home or at work<br>**Pharmacy Information**<br>To enroll in the Exalgo Alliance program, pharmacists must be educated to understand (1) the risks of opioids and responsible opioid prescribing and use; (2) EXALGO risks; (3) responsible EXALGO prescribing and dispensing; (4) safe EXALGO use and handling.<br>**Pharmacists are required to:**<br>• Verify that each patient presenting a prescription is eligible to receive EXALGO<br>• Provide counseling to patients on EXALGO safe use and handling prior to dispensing any EXALGO prescription<br>• Provide the Medication Guide and instruct the patient to read it | |

| LABEL SECTION | ANNOTATION |
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| **6. ADVERSE REACTIONS** | |
| **6.1 Clinical Studies Experience** | |
| EXALGO was administered to a total of 2,385 patients in 14 controlled and uncontrolled clinical studies. Of these, 420 patients were exposed to EXALGO for greater than 6 months and 141 exposed for greater than one year. | Module 2.7.4, Table 4 |
| The adverse reactions seen with EXALGO were typical opioid side effects. Expect opioid side effects and manage them accordingly. | Module 5.3.5.3, Section 1.1.3 |
| The overall incidence of adverse reactions in elderly patients 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. | Module 5.3.5.3, Section 8.1.1.1<br>Module 5.3.5.3, Section 8.1.3.1 |
| 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 practice. | |
| 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 1. | CSR NMT 1077-301 Synopsis |
| **Table 1: 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** | CSR NMT 1077-301, Section 12.1.1.2 and Section 12.1.2.2 |
| Preferred Term / Open-Label Titration Phase EXALGO / Double-Blind Treatment Phase EXALGO / Double-Blind Treatment Phase Placebo | |

| LABEL SECTION | | | | ANNOTATION |
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| | (N = 447) | (N = 134) | (N = 134) | |
| Constipation | 69 (15.4) | 10 (7.5) | 5 (3.7) | |
| Nausea | 53 (11.9) | 12 (9.0) | 10 (7.5) | |
| Somnolence | 39 (8.7) | 1 (0.7) | 0 (0.0) | |
| Headache | 35 (7.8) | 7 (5.2) | 10 (7.5) | |
| Vomiting | 29 (6.5) | 8 (6.0) | 6 (4.5) | |
| Drug withdrawal syndrome | 22 (4.9) | 13 (9.7) | 16 (11.9) | |
| Pruritus | 21 (4.7) | 1 (0.7) | 0 (0.0) | |
| Dizziness | 17 (3.8) | 3 (2.2) | 2 (1.5) | |
| Asthenia [a] | 16 (3.6) | 2 (1.5) | 6 (4.5) | |
| Insomnia | 13 (2.9) | 7 (5.2) | 5 (3.7) | |
| Diarrhea | 13 (2.9) | 5 (3.7) | 9 (6.7) | |
| Back pain | 13 (2.9) | 6 (4.5) | 8 (6.0) | |
| Dry Mouth | 13 (2.9) | 2 (1.5) | 0 (0.0) | |
| Edema Peripheral | 13 (2.9) | 3 (2.2) | 1 (0.7) | |
| Hyperhidrosis | 13 (2.9) | 2 (1.5) | 2 (1.5) | |
| Anorexia [b] | 10 (2.2) | 2 (1.5) | 0 (0.0) | |
| Arthralgia | 9 (2.0) | 8 (6.0) | 3 (2.2) | |
| Anxiety | 9 (2.0) | 0 (0.0) | 4 (3.0) | |
| Abdominal pain [c] | 9 (2.0) | 4 (3.0) | 3 (2.2) | |
| Muscle spasms | 5 (1.1) | 3 (2.2) | 1 (0.7) | |
| Weight decreased | 3 (0.7) | 4 (3.0) | 3 (2.2) | |

[a] Fatigue was grouped and reported with asthenia
[b] Decreased appetite was grouped and reported with anorexia
[c] Abdominal pain upper was grouped and reported with abdominal pain

| LABEL SECTION | ANNOTATION |
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| The adverse reactions that were reported in at least 2% of the total treated patients (n=2,335) and the subset of opioid tolerant patients (n=1,251) in the 13 chronic clinical trials are contained in Table 2: | |
| **Table 2: Number (%) of Patients with Adverse Reactions Reported in ≥2% of Patients with Chronic Pain Receiving EXALGO in 13 Clinical Studies by Preferred Term** | ISS Table 2.4.2.6 and Table 2.4.11.5 |

| Preferred Term | All Patients [a] (N = 2,335) | Opioid Tolerant Patients (N = 1,251) |
|---|---|---|
| Constipation | 702 (30.1) | 280 (22.4) |
| Nausea | 642 (27.5) | 290 (23.2) |
| Vomiting | 322 (13.8) | 180 (14.4) |
| Somnolence | 322 (13.8) | 162 (12.9) |
| Headache | 300 (12.8) | 160 (12.8) |
| Asthenia [b] | 263 (11.3) | 145 (11.6) |
| Dizziness | 247 (10.6) | 109 (8.7) |
| Diarrhea | 194 (8.3) | 90 (7.2) |
| Pruritus | 183 (7.8) | 81 (6.5) |
| Insomnia | 158 (6.8) | 104 (8.3) |
| Hyperhidrosis | 136 (5.8) | 81 (6.5) |
| Edema Peripheral | 132 (5.7) | 92 (7.4) |
| Anorexia [c] | 131 (5.6) | 71 (5.7) |
| Dry Mouth | 110 (4.7) | 58 (4.6) |
| Abdominal Pain [d] | 109 (4.7) | 67 (5.4) |
| Anxiety | 95 (4.1) | 63 (5.0) |
| Back Pain | 94 (4.0) | 70 (5.6) |
| Dyspepsia [e] | 82 (3.5) | 48 (3.8) |
| Depression | 79 (3.4) | 51 (4.1) |

| LABEL SECTION | | | ANNOTATION |
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| Dyspnea [f] | 76 (3.3) | 49 (3.9) | |
| Muscle Spasms | 73 (3.1) | 50 (4.0) | |
| Arthralgia | 71 (3.0) | 42 (3.4) | |
| Rash | 64 (2.7) | 40 (3.2) | |
| Pain in extremity | 62 (2.7) | 44 (3.5) | |
| Pain | 57 (2.4) | 40 (3.2) | |
| Drug withdrawal syndrome | 55 (2.4) | 46 (3.7) | |
| Pyrexia | 51 (2.2) | 34 (2.7) | |
| Fall | 49 (2.1) | 30 (2.4) | |
| Chest discomfort [g] | 49 (2.1) | 37 (3.0) | |
| [a] Includes opioid naïve, opioid treated but not tolerant and opioid tolerant patients.<br>[b] Fatigue was grouped and reported with asthenia<br>[c] Decreased appetite was grouped and reported with anorexia<br>[d] Abdominal pain upper was grouped and reported with abdominal pain<br>[e] Reflux esophagitis, gastroesophageal reflux disease and Barrett's esophagus were grouped and reported with dyspepsia<br>[f] Dyspnea exacerbated and dyspnea exertional were grouped and reported with dyspnea<br>[g] Chest pain and non-cardiac chest pain were grouped and reported with chest discomfort | | | |
| The following Adverse Reactions occurred in patients with an overall frequency of <2% are listed in descending order within each System Organ Class:<br><br>***Cardiac disorders:*** palpitations, tachycardia, bradycardia, extrasystoles<br><br>***Ear and labyrinth disorders:*** vertigo, tinnitus<br><br>***Endocrine disorders:*** hypogonadism<br><br>***Eye disorders:*** vision blurred, diplopia, dry eye, miosis<br><br>***Gastrointestinal disorders:*** flatulence, dysphagia, hematochezia, abdominal distension, hemorrhoids, abnormal | | | 2.7.4, Section 2.1.9.3<br>ISS Table 2.4.1.2<br>CSR DO-130 Table 12 (for oxygen saturation decreased) |

| LABEL SECTION | ANNOTATION |
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| feces, intestinal obstruction, eructation, diverticulum, gastrointestinal motility disorder, large intestine perforation, anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defecation<br><br>***General disorders and administration site conditions:*** chills, malaise, feeling abnormal, feeling hot and cold, feeling jittery, hangover, difficulty in walking, feeling drunk, hypothermia<br><br>***Infections and infestations:*** gastroenteritis, diverticulitis<br><br>***Injury, poisoning and procedural complications:*** contusion, overdose<br><br>***Investigations:*** weight decreased, hepatic enzyme increased, blood potassium decreased, blood amylase increased, blood testosterone decreased, oxygen saturation decreased<br><br>***Metabolism and nutrition disorders:*** dehydration, fluid retention, increased appetite, hyperuricemia<br><br>***Musculoskeletal and connective tissue disorders:*** myalgia<br><br>***Nervous system disorders:*** tremor, sedation, hypoesthesia, paraesthesia, disturbance in attention, memory impairment, dysarthria, syncope, balance disorder, dysgeusia, depressed level of consciousness, coordination abnormal, hyperesthesia, myoclonus, dyskinesia, hyperreflexia, encephalopathy, cognitive disorder, convulsion, psychomotor hyperactivity<br><br>***Psychiatric disorders:*** confusional state, nervousness, restlessness, abnormal dreams, mood altered, hallucination, panic attack, euphoric mood, paranoia, dysphoria, listless, crying, suicide ideation, libido decreased, aggression<br><br>***Renal and urinary disorders:*** dysuria, urinary retention, pollakiuria, urinary hesitation, micturition disorder<br><br>***Reproductive system and breast disorders:*** erectile dysfunction, sexual dysfunction<br><br>***Respiratory, thoracic and mediastinal disorders:*** rhinorrhoea, respiratory distress, hypoxia, bronchospasm, sneezing, hyperventilation, respiratory depression | |

| LABEL SECTION | ANNOTATION |
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| ***Skin and subcutaneous tissue disorders:*** erythema<br><br>***Vascular disorders:*** flushing, hypertension, hypotension | |
| **6.2 Post Marketing Experience**<br>No potential new safety signal has been identified during post-approval use of EXALGO based on routine and product-specific surveillance activities to identify Adverse Reactions. 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. | 2.7.4, Section 6 |
| **7. DRUG INTERACTIONS** | |
| In vitro data suggest that hydromorphone in clinically relevant concentrations has minimal potential to moderate the activity of human hepatic CYP450 activities. Metabolism of hydromorphone is predominantly through conjugation with glucuronic acid as a first pass effect, with no identified active metabolites and with little potential for drug-drug interactions at the level of metabolizing enzymes. The low level of protein binding of hydromorphone to human plasma proteins (27%) makes it unlikely to result in protein-displacement drug-drug interactions. | Module 2.6.4.5.2<br>Module 2.6.4.5<br>Module 2.6.4.4.2 |
| Monoamine oxidase inhibitors (MAOIs) may cause CNS excitation or depression, hypotension or hypertension if co-administered with opioids. EXALGO is not intended for patients taking MAOIs or within 14 days of stopping such treatment. | Opioid class labeling |
| The concomitant use of hydromorphone with morphine agonist/antagonists (buprenorphone, nalbuphine, pentazocine) could lead to a reduction of the analgesic effect by competitive blocking of receptors, thus leading to risk of withdrawal symptoms. Therefore, this combination is not recommended. | Opioid class labeling |
| The concomitant use of central nervous system depressants such as hypnotics, sedatives, general anesthetics, antipsychotics and alcohol may cause additive depressant effects and respiratory depression. Additionally, hypotension and profound sedation or coma could occur. When this combination is indicated, the dose of one or both agents should be reduced. | Opioid class labeling |
| The concomitant use of alcohol should be avoided. *[see Clinical Pharmacology: Alcohol Effect (12.3.4)].* | Module 2.5, Section 3 |

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| **8. USE IN SPECIFIC POPULATIONS**<br><br>**8.1 Pregnancy (Pregnancy Category C)**<br>There are no adequate and well-controlled studies in pregnant women. No clinical data on exposed pregnancies are available. While studies in rats and rabbits revealed no teratogenic effects, reproductive toxicity has been observed. Hydromorphone has been shown to cross the placental barrier in experimental animals. The potential teratogenic risk for humans from use of hydromorphone and other opioids during pregnancy is unknown. EXALGO should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations: Labor and Delivery (8.2), Drug Abuse and Dependence: Abuse and Addiction (9.2), and Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)]* | Module 2.6.6.6, Module 2.6.4.4.3 and Module 2.7.4, Section 5.4 |
| **8.2 Labor and Delivery**<br>EXALGO is not recommended for use in women during and immediately prior to labor and delivery. Administration of hydromorphone to the mother shortly before delivery may result in some degree of respiratory depression in the neonate. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as nalaxone, should be available for reversal of opioid–induced respiratory depression in the neonate.<br><br>Neonates born to mothers who have been taking opioids chronically before delivery may exhibit withdrawal symptoms, including irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The onset, duration, and severity of the syndrome do not always correlate with the dose or duration of maternal opioid use. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or Phenobarbital.<br><br>EXALGO Tablets should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus *[See Drug Abuse and Dependence: Abuse and Addiction (9.2)].* | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| **8.3 Nursing Mothers**<br>Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breast-feeding 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. | Edwards 2003 |
| **8.4 Pediatric Use**<br>The safety and efficacy of EXALGO in pediatric patients below 18 years of age has not been studied. | Module 2.5, Section 6 |
| **8.5 Geriatric Use**<br>Elderly patients have been shown to be more sensitive to the adverse effects of EXALGO compared to the younger population. Therefore, extra caution should be shown, and the initial dose should be reduced. Concomitant use of other medications, especially tricyclic antidepressants, increases the risk of confusion and constipation. Diseases of the prostate gland and the urinary tract are often seen in the elderly. This contributes to the increased risk of urinary retention. The above considerations emphasize the importance of caution rather than imply a restriction on the use of opioids in the elderly. | Module 2.7.4, Section 5.1.1 |
| **8.6 Renal and Hepatic Impairment**<br>**8.6.1 Hepatic Impairment**<br>In studies that used single oral dosing with immediate-release hydromorphone tablets, hepatic impairment reduced the first-pass metabolism thereby increasing the bioavailability of hydromorphone such that four-fold increases in plasma levels of hydromorphone were seen in subjects with moderate hepatic dysfunction. Patients with moderate hepatic impairment should be started on a reduced dose and closely monitored during dose titration. | Module 2.7.2, Section 3.1.4.1 |

| LABEL SECTION | ANNOTATION |
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| **8.6.2 Renal Impairment**<br>Renal impairment affected the pharmacokinetics of hydromorphone and its metabolites hydromorphone 3-glucuronide and hydromorphone 3-sulphate following administration of an immediate-release tablet. The effects of renal impairment on hydromorphone pharmacokinetics were two-fold and four-fold increases in plasma levels of hydromorphone in moderate and severe impairment, respectively. There were also substantial changes in hydromorphone 3-glucuronide elimination kinetics for the severe impairment group, although hemodialysis was effective at reducing plasma levels of both hydromorphone and its metabolites. Patients with moderate renal impairment should be started on a reduced dose and closely monitored during dose titration. In patients with severe renal impairment a longer dosing interval should also be considered and these patients should in addition be monitored during maintenance therapy for development of opioid-related adverse reactions. | Module 2.7.2, Section 3.1.4.2 |
| **8.7 Gender**<br>Plasma concentrations and pharmacokinetic parameters following administration of EXALGO are comparable in male and female subjects. | Module 2.7.2, Section 3.1.4.4 |
| **9. DRUG ABUSE AND DEPENDENCE**<br>**9.1. Controlled substance**<br>Hydromorphone is a Schedule II controlled substance that can produce drug dependence of the morphine type. EXALGO can be abused and is subject to misuse, abuse, addiction, and criminal diversion *[see Warnings and Precautions: Misuse, Abuse and Diversion of Opioids (5.3)]*. | Opioid class labeling |
| **9.2. Abuse and Addiction**<br>EXALGO should be handled in a way to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [*see How Supplied/Storage and Handling (16.1)]*. | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, 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.<br><br>Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.<br><br>"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.<br><br>Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since EXALGO may be diverted for non-medical use, careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.<br><br>Abuse of EXALGO poses a risk of overdose and death. This risk is increased with concurrent abuse of EXALGO with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV<br><br>Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.<br><br>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. | |

| LABEL SECTION | ANNOTATION |
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| **9.3. Dependence**<br>Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance could occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.<br><br>Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.<br><br>Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations: Usage in Pregnancy (8.1) and Use in Specific Populations: Labor and Delivery (8.2)]*. | Opioid class labeling |
| **10. OVERDOSAGE**<br>Acute overdosage with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia, hypotension and death. The extended-release characteristics of EXALGO should also be taken into account when treating the overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects. Deaths due to overdose could occur with abuse and misuse of EXALGO.<br><br>Due to the delayed mean apparent peak plasma level of EXALGO occurring at 16 hours following administration as well as the mean apparent 14-18 hour elimination half-life of EXALGO, patients who receive an overdose will require an extended period of monitoring and treatment that may go beyond 24-48 hours.<br><br>In the treatment of hydromorphone overdosage, primary attention should be given to the re-establishment of a patent | Opioid class labeling<br><br>Module 2.5, Section 5.9.1<br><br>Module 2.7.2, Section 2.2.1.1.3 and 3.1.2 |

| LABEL SECTION | ANNOTATION |
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| airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac message or defibrillation. | Opioid class labeling |
| The pure opioid antagonists, such as naloxone and naltrexone, are specific antidotes to respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. In patients who are physically dependent on any opioid agonist including EXALGO, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use. | Opioid class labeling |

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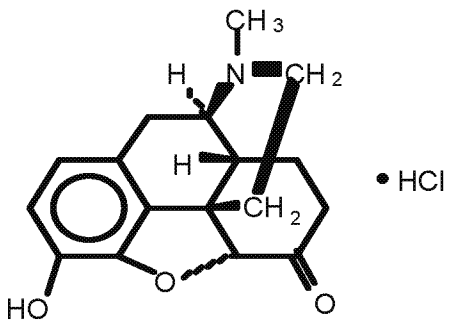
| **11. DESCRIPTION** | |
| EXALGO is an extended-release formulation of hydromorphone HCl, a potent opioid, intended for oral administration. Each extended-release tablet for once-a-day administration delivers 8, 12, 16, or 32 mg of hydromorphone HCl, USP. | Module 3.2.P.1 |
| Hydromorphone hydrochloride, USP is 4,5α-epoxy-3-hydroxy-17-methlymorphinan-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. The compound has the following structural formula: | Roy, 1988<br>HM-MSDS |
|  | |
| EXALGO also contains the following inert ingredients: butylated hydroxytoluene, cellulose acetate, iron oxide black, ferric oxide red (8 mg only), ferric oxide yellow (12, 16 mg and 32 mg only), hypromellose, lactose anhydrous, lactose monohydrate, magnesium stearate; polyethylene glycol, polyethylene oxide, povidone, sodium chloride, titanium dioxide and triacetin. | Module 3.2.P.2.1 |
| **11.1 System Components and Performance**<br>EXALGO is an orally administered extended release tablet, which uses osmotic energy to deliver hydromorphone hydrochloride at a controlled rate to relieve pain over a period of approximately 24 hours. The system resembles a conventional tablet in appearance. It is comprised of an active bilayer core surrounded by a semi-permeable, rate- | |

| LABEL SECTION | ANNOTATION |
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| controlling membrane. The bilayer core is composed of an active drug layer containing hydromorphone HC1 and excipients and a push layer containing osmotically active components. An orifice is laser-drilled on the drug layer dome of the tablet. The tablet is clear and color over-coated and imprinted for product and dose differentiation.<br><br>The EXALGO tablet is designed to offer control of drug release over extended periods of time through the establishment and maintenance of an osmotic activity gradient across the semi-permeable membrane. The flux of water across the rate-controlling membrane is dictated by the osmotic activity gradient across the membrane and the permeability of the rate-controlling membrane. The flux of water into the core in turn controls the rate of drug delivered from the tablet and also provides drug release independent of environmental pH, agitation, and other conditions encountered in the gastrointestinal tract. In an aqueous environment, such as the gastrointestinal tract, the clear and color overcoats of the tablet dissipate and water permeates through the rate-controlling membrane into the tablet core as a result of the osmotic activity gradient established across the membrane. The water hydrates the bilayer core, causing the osmotic push layer to expand and thus, pushing the hydrated drug layer out through the orifice. The biologically inert core of the tablet remains intact during GI transit and is eliminated in the feces as an insoluble shell. It is possible that EXALGO extended release tablets may be visible on abdominal x-rays under certain circumstances especially when digital enhancing techniques are used.<br><br>The tablets are to be swallowed whole and are not to be broken, chewed, dissolved or crushed. Breaking, chewing, dissolving or crushing EXALGO tablets will destroy the osmotic pump and if orally administered will lead to a rapid release and absorption of a potentially fatal dose of hydromorphone. | Module 3.2.P.1<br><br>Module 2.5, Section 3 |

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| **12. CLINICAL PHARMACOLOGY**<br><br>**12.1. Mechanism of action**<br>Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine. Hydromorphone is principally an agonist of μ-receptors, showing a weak affinity for κ-receptors. Comparing relative binding affinity for μ- and κ-opioid receptors, hydromorphone binds more specifically to μ-receptors than structurally related morphine. As an opioid agonist, the principal therapeutic action of hydromorphone is analgesia. The precise mechanism of action of opioid analgesics is not known but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS). Interaction with the μ- opioid receptor subtype is believed to be responsible for most of hydromorphone's clinical effects. There is no intrinsic limit to the analgesic effect of hydromorphone; unlike with mixed agonist/antagonists or non-opioid analgesics, and like morphine, adequate doses will relieve even the most severe pain. Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, sedation, nausea, and vomiting, which can result from high doses. | Module 2.4.2<br>Module 2.6.2.2 |
| **12.2 Pharmacodynamics**<br>As with all opioid analgesics, hydromorphone exerts its principal pharmacological effects on the CNS and smooth muscle, including the gastrointestinal tract. These effects are expressed and modulated by binding to specific opioid receptors. Hydromorphone is principally an agonist of μ-receptors, showing a weak affinity for κ-receptors. Analgesia occurs as a consequence of the binding of hydromorphone to the μ-receptors of the CNS. Although estimates vary (from 2 to 10 times), oral hydromorphone appears to be approximately 5 times as potent (by weight) as morphine. Respiratory depression occurs principally by direct action on the cerebral respiratory control centers. Opioids may cause nausea and vomiting due to direct stimulation of the chemoreceptor for emesis in the posterior area of the medulla. | Reisine and Pasternak 1996 |
| **12.2.1. Central Nervous System**<br>Opioids produce dose-related respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in | Opioid class labeling |

| LABEL SECTION | ANNOTATION |
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| carbon dioxide tension and to electrical stimulation.<br><br>Opioids depress the cough reflex by direct effect on the cough center in the medulla. Antitussive effects could occur with doses lower than those usually required for analgesia.<br><br>Opioids cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic. Marked mydriasis, rather than miosis, may be seen due to severe hypoxia in overdose situations. | |
| **12.2.2. Gastrointestinal Tract and Other Smooth Muscle**<br>Opioids decrease gastric, biliary and pancreatic secretions, and cause a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Opioids also can cause an increase in bilary tract pressure as a result of spasm of the Sphincter of Oddi. | Opioid class labeling |
| **12.2.3. Cardiovascular System**<br>Opioids may produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine may occur with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating. | Opioid class labeling |
| **12.2.4. Endocrine System**<br>Opioid agonists have been shown to have a variety of effects on the secretion of hormones. 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 in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids. | Opioid class labeling |
| **12.2.5. Concentration-Adverse Reaction Relationships**<br>Hydromorphone is associated with typical opioid-related adverse reactions. There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. | Module 2.7.2, Section 2.5 |

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| As with all opioids, the dose must be individualized *[see Dosage and Administration (2.1.1.4)]*. The effective analgesic dose for some patients will be too high to be tolerated by other patients. | |
| **12.3. Pharmacokinetics**<br><br>**12.3.1 Pharmacokinetics and Metabolism**<br>EXALGO is an extended–release formulation of hydromorphone that produces a gradual increase in hydromorphone concentrations reaching approximately 50% of peak concentrations (Cmax) by 6 hours after a single dose. Hydromorphone concentrations are sustained for 18 to 24 hours. In a single dose study, 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). Mean pharmacokinetic parameters of hydromorphone after administration of single and multiple doses of EXALGO and immediate release hydromorphone are presented in Table 3. | Module 2.7.2, Section 2.2.3.2 and 2.2.4.1 |

**Table 3: Mean (±SD) EXALGO Pharmacokinetic Parameters**

| Regimen | Dosage | Tmax (hrs) | Cmax (ng/mL) | AUC (ng · hr/mL) | $T_{½}$ (hr) |
|---|---|---|---|---|---|
| Single Dose | 8 mg | 16.0 (7.2) | 0.93 (1.01) | 18.1 (5.8) | 10.6 (4.3) |
| | 16 mg | 16.8 (5.4) | 1.69 (0.78) | 36.5 (11.3) | 10.3 (2.4) |
| | 32 mg | 15.7 (5.4) | 3.25 (1.37) | 72.2 (24.3) | 11.0 (3.2) |
| | 64 mg | 17.4 (5.7) | 6.61 (1.75) | 156.0 (30.6) | 10.9 (3.8) |
| Multiple Dose[a] | 16 mg q24h | 12.3 (5.4) | 3.54 (0.96)[b] | 57.6 (16.3) | NA |
| | IR 4 mg q6h | 8.4 (4.6) | 5.28 (1.37)[c] | 54.8 (14.8) | NA |

NA = not applicable
a. Steady-state results on Day 5 (0-24 hours)
b. Cmin 2.15 (0.87) ng/ml
c. Cmin 1.47 (0.42) ng/ml

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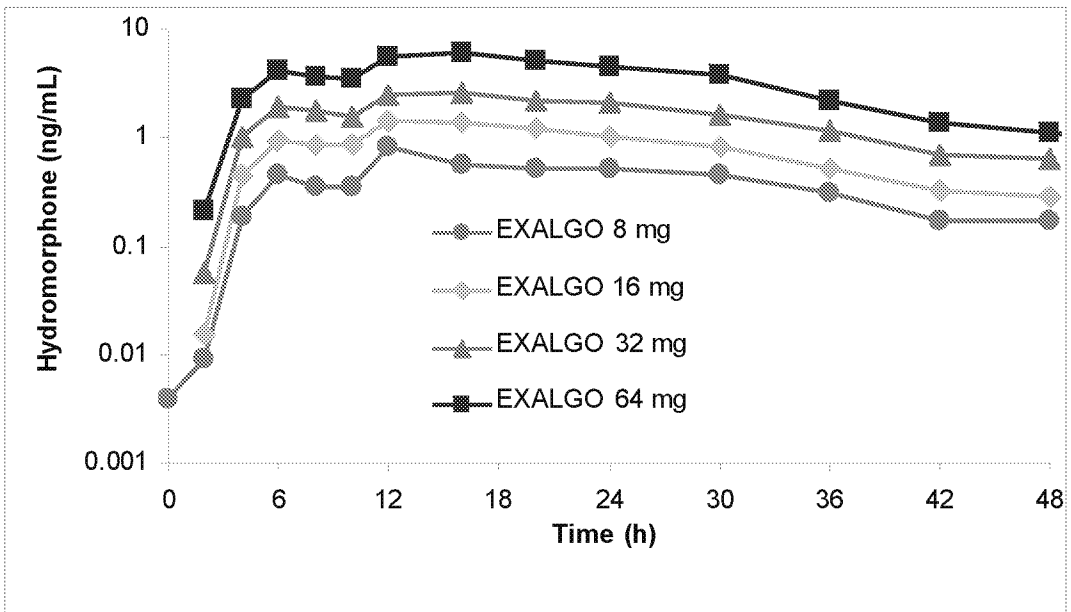
| **12.3.2. Absorption**<br>Following a single oral dose of EXALGO, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose; the mean $T_{max}$ values were approximately 13 to 17 hours. This demonstrates that hydromorphone is released in a controlled manner consistent with once-daily dosing. The mean absolute bioavailability of hydromorphone after a single dose of 8, 16, or 32 mg of EXALGO ranged from 22% to 24% (Figure 1).<br><br>**Figure 1:**<br>  <br> | Module 2.7.1, Section 2.1.1 and 2.4.2 |

| LABEL SECTION | ANNOTATION |
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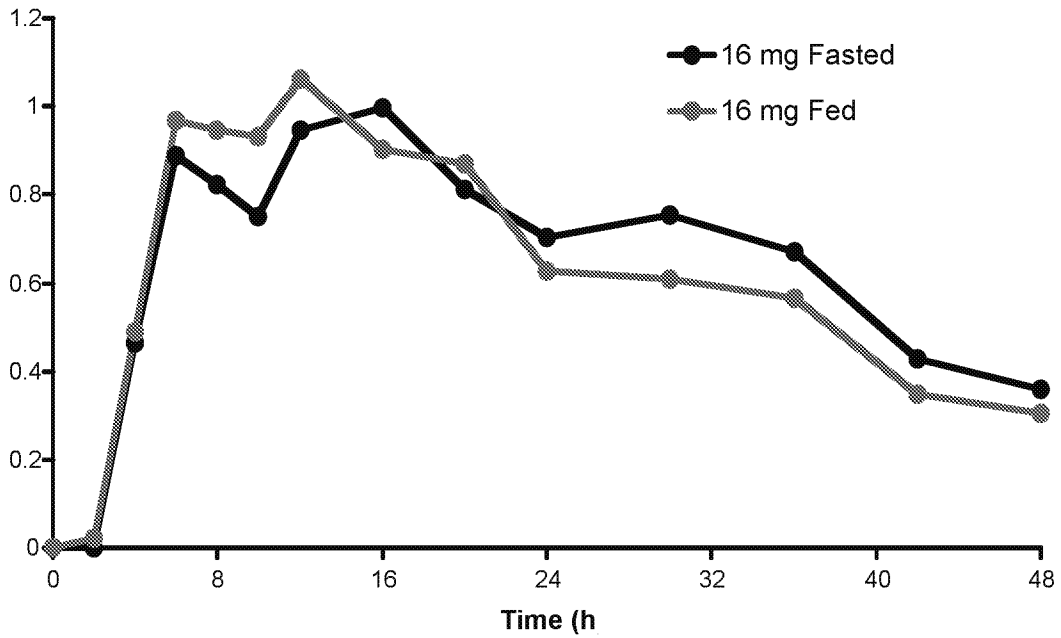
| **12.3.3. Food Effect**<br>The pharmacokinetics of EXALGO are not affected by food as indicated by bioequivalence when administered under fed and fasting conditions. Therefore, EXALGO may be administered without regard to meals. When a 16 mg dose of EXALGO was administered to healthy volunteers immediately following a high-fat meal, Cmax was 6% lower and AUC was 1% lower than following a dose administered while fasting. The time to Cmax (Tmax) was minimally affected by the high-fat meal occurring at 16 hours compared to 18 hours while fasting. (Figure 2)<br><br>**Figure 2**<br>  <br> | Module 2.7.1, Section 2.1.4 |

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| **12.3.4. Alcohol Effect**<br>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 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 was similarly unaffected in subjects following the co-administration of EXALGO and alcohol (240 mL of 20% or 4% alcohol).<br><br>The change in geometric mean Cmax with concomitant administration of alcohol and EXALGO ranged from an increase of 10% to 31% across all conditions studied. The change in mean Cmax was greater in the fasted group of subjects. Following concomitant administration of 240 mL of 40% alcohol while fasting the mean Cmax increased by 37%, and up to 250% in an individual subject. Following the concomitant administration of 240mL of 20% alcohol while fasting the mean Cmax increased by 35% and up to 240% in an individual subject. Following the concomitant administration of 240 mL of 4 % alcohol while fasting the mean Cmax increased by 19% on average and as much as 170% for an individual subject. | Module 2.7.2, Section 2.4.6 |
| **12.3.5. Distribution**<br>Following intravenous administration of hydromorphone to healthy volunteers, the mean volume of distribution was 216 liters, 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. | Module 2.7.2, Section 2.2.1.1.1<br><br>Module 2.7.2, Section 3.1.4.5 |
| **12.3.6. Metabolism and Excretion**<br>After oral administration of an immediate release formulation, hydromorphone undergoes extensive first-pass metabolism and is metabolized primarily in the liver by glucuronidation to the inactive metabolite hydromorphone-3-glucuronide, which follows a similar time course to hydromorphone in plasma. Exposure to the glucuronide metabolite is 35-40 times higher than exposure to the parent drug. Unlike morphine, no active 6-glucuronide metabolite is produced. Most of the administered hydromorphone dose is excreted as metabolites, with urine as the major route of excretion, accounting for 75% of the administered dose. Approximately 7% and 1% of the dose are excreted as unchanged hydromorphone in urine and feces, respectively. | Module 2.7.2, Section 2.1.1 |

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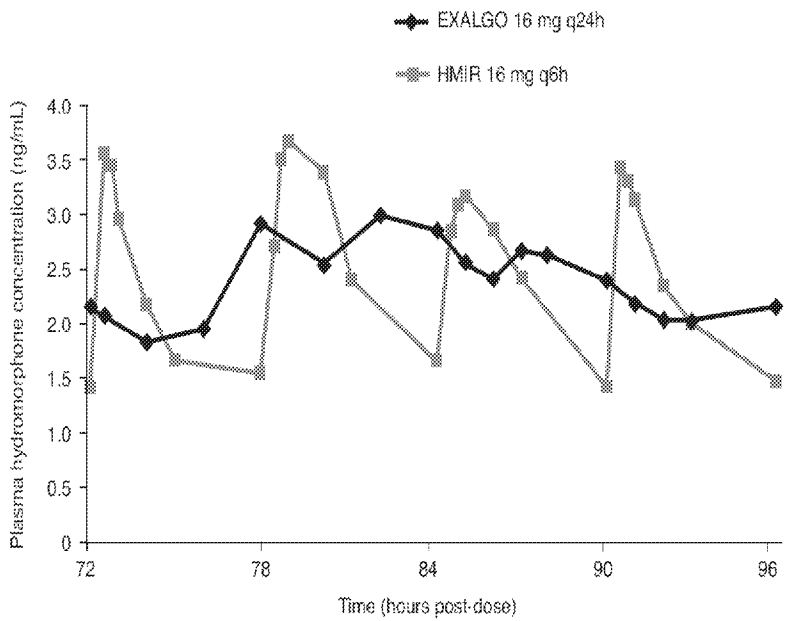
| **12.3.7. Hydromorphone Profile in Plasma**<br>Steady-state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached after 3 to 4 days of once-daily dosing of EXALGO. At steady state, EXALGO given once daily maintained hydromorphone plasma concentrations within the same concentration range as the immediate-release tablet given 4 times daily at the same total daily dose, and diminished the periodic fluctuations between peak and trough concentrations seen with the immediate-release tablet (see Figure 3). The relative bioavailability of EXALGO once daily and hydromorphone four times daily in adults is comparable (see Table 3).<br>**Figure 3**<br>  <br> | Module 2.7.2, Section 2.2.4 |

| LABEL SECTION | ANNOTATION |
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| **13 NONCLINICAL TOXICOLOGY** | |
| **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** | |
| Long-term studies to evaluate the carcinogenic potential of hydromorphone in animals have not been completed. | Report MPF/DT 0041E |
| There was no evidence for mutagenicity or clastogenicity in the standard battery of genotoxicity studies. | Report MPF/DT 9854E |
| Hydromorphone was not mutagenic in the in vitro reverse mutation assay (Ames test) at concentrations up to 5,000 mcg/plate with or without metabolic activation, or the in vitro human lymphocyte chromosome aberration assay, tested up to 3200 mcg/mL with and without metabolic activation. Hydromorphone tested negative for clastogenic potential in the in vivo mouse micronucleus assay, with doses ranging from 10 to 100 mg/kg. | Report MPF/DT 9855E<br>Report MPF/DT 9858E |
| Nonclinical data from oral administration of hydromorphone reveal no special hazard for humans based on conventional studies of genotoxicity and fertility. In rats, a slight but statistically significant reduction in implantations was observed at 6.25 mg/kg/day, a dose level that produced maternal toxicity during the mating period. Plasma exposure (AUC) to hydromorphone at this dose level was 135 ng·hr/mL, providing a safety factor of about 1.5 over the human exposure (AUC) based on the median daily dose. Neonatal viability and survival were reduced in rats pre-weaning, at the maternal oral daily dose of 6.25 mg/kg. The latter appears to be a class effect of opioid analgesics. | Report MPF/DT 9859E |

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| **13.2 Animal Pharmacology and Toxicology**<br>Nonclinical data from oral administration of hydromorphone reveal no special hazards for humans based on conventional studies of safety pharmacology and repeated-dose toxicity. The major effects were opioid-related pharmacological activities on the central nervous system and gastrointestinal tract, including dose-related increase in sedation, hyperactivity, sudden death, weight loss and decrease in food consumption.<br><br>Animal studies have shown that some of the non-active components of EXALGO can cause serious damage to organs such as the heart, kidneys, and blood cells and even death, when injected intravenously. | Module 2.6.2.4<br>Module 2.6.6.1<br>Report TR-05-5643-007<br>Report TR-05-5643-014 |
| **14. CLINICAL STUDIES**<br><br>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 no intolerable side effects. Supplemental immediate release hydromorphone tablets were allowed during the conversion and titration phase. 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 (median 32.0 mg/day, range of 12 mg/day – 64 mg/day. Fifty eight percent of patients were successfully titrated to a stable dose of EXALGO during the open-label conversion and titration phase.<br><br>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. | CSR NMT 1077-301<br><br>CSR NMT-1077, Section 10.4<br>CSR NMT-1077, Section 11.2<br><br>CSR NMT-1077 Synopsis |

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| EXALGO provided superior analgesia compared to placebo. There was a statistically significant difference between the mean changes from Baseline to Week 12 or Final Visit in average weekly pain intensity NRS scores obtained from patient diary between the two groups ($p<0.0001$ in ITT). A significantly smaller change on average pain intensity scores from Baseline to Week 12 or Final Visit was seen in the EXALGO group (median change 0.2 unit) as compared to placebo group (median change 1.6 unit). The analgesic effect of EXALGO was maintained throughout the double-blind treatment period in 77.3% of patients who completed the study. A statistically significant ($p=0.006$) higher proportion of EXALGO patients (60.6%) had at least a 30% reduction in pain score from Screening to Week 12 or Final Visit compared to 42.9% in placebo patients. The proportion of patients with various degrees of improvement from screening to Week 12 or Final Visit is shown in Figure 4. | CSR NMT-1077, Section 11.1 |

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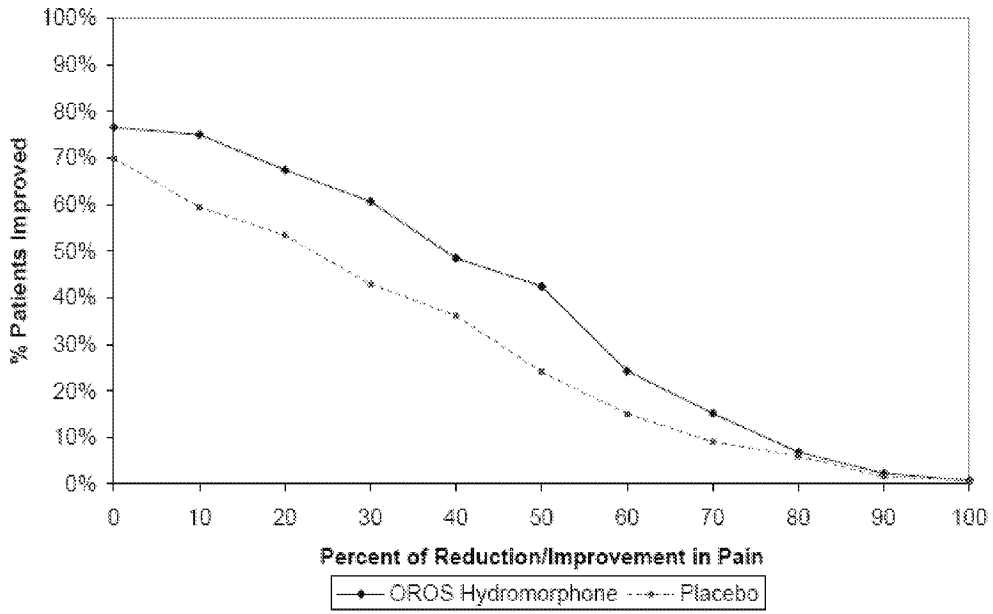
| **Figure 4: Patients achieving various levels of pain relief**  | |

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## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1. Storage and Handling

EXALGO Tablets are solid dosage forms that contain hydromorphone which is a controlled substance. Like fentanyl, methadone, morphine, oxycodone, and oxymorphone, hydromorphone is controlled under Schedule II of the federal Controlled Substances Act. EXALGO Tablets may be targeted for theft and diversion by criminals. *[see Warnings and Precautions (5)]* Healthcare professionals can telephone Neuromed Pharmaceutical's Medical Services Department (1-xxx-xxx-xxxx) for information on this product.

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

</td><td>Controlled Substances Act<br><br>Module 2.3.P.8.1.4</td></tr>
<tr><td>

### 16.2. Disposal of EXALGO

**Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed.** Information is available in the Medication Guide. **To dispose of unused EXALGO flush all remaining tablets down the toilet.**

</td><td>Opioid class labeling</td></tr>
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### 16.3. How Supplied

**EXALGO Tablet Strengths**

| Strength | Color | Bottle count | NDC |
|---|---|---|---|
| 8 mg | Red | 100 count bottle | NDC XXXX-XXXX-XX |
| 12 mg | Dark yellow | 100 count bottle | NDC XXXX-XXXX-XX |
| 16 mg | Yellow | 100 count bottle | NDC XXXX-XXXX-XX |
| 32 mg | White | 100 count bottle | NDC XXXX-XXXX-XX |

Manufactured for:

Neuromed Pharmaceuticals, Ltd.
Vancouver, B.C. Canada V6T 1Z3700

By:

ALZA Corporation
700 Eubanks Drive
Vacaville, CA 95688

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</td><td>Module 3.2.P.5.1<br><br>Module 2.3.P.7</td></tr>
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