

Study Characterizes Extractability Properties of Once-Daily Extended-Release Hydromorphone

Covidien

Properties of OROS^(R) technology also shown to provide predictable, consistent blood plasma levels of hydromorphone at steady-state, reducing peaks and troughs

AUSTIN, Texas, May 19, 2011 (BUSINESS WIRE) --

Covidien (NYSE: COV), a leading global provider of healthcare products, announced the results of two studies that compare the physical and pharmacological properties of once-daily hydromorphone extended-release (ER) tablets to immediate-release (IR) hydromorphone and other ER opioids. The studies will be presented at the American Pain Society's Annual Scientific Meeting being held here May 19-21.

In the United States, once-daily hydromorphone ER is approved by the U.S. Food and Drug Administration (FDA) under the brand name EXALGO^(R) (hydromorphone HCl) Extended-Release Tablets (CII). It is indicated for opioid-tolerant patients with moderate-to-severe pain requiring continuous, around-the-clock analgesia for an extended period of time. It is not intended to be used for as-needed pain relief and is not indicated for the management of acute or postoperative pain. EXALGO is designed using the OROS^(R) drug delivery system, which releases hydromorphone at a controlled rate.

The intentional manipulation of long-acting opioids by chewing or crushing to achieve a rapid onset of effect, or high, is a growing problem in the United States. In an in vitro study, once-daily hydromorphone ER tablets (32 mg) were evaluated versus other ER opioids for certain physical properties related to manipulation, including hardness, tablet milling and dissolution/extraction. Results of hardness testing demonstrated that once-daily hydromorphone ER withstood significantly more force before cracking than the active comparator (>80-125 lb_f vs. <20 lb_f, respectively). Milling the tablets yielded approximately 30 percent of active ingredient from once-daily hydromorphone ER in the smallest particle-size fraction versus approximately 65 percent from the active comparator. The 32 mg formulation is not FDA approved.

A component that physicians consider when monitoring patients for the risks of abuse during pain management is "drug likability." A rapid peak in euphoric or pleasurable effect a patient may experience soon after the administration of some drugs is a significant factor in determining "drug likability." Separately, in a previously reported open-label, repeat-dose study of 22 patients, once-daily hydromorphone ER was shown to provide predictable, consistent 24-hour blood plasma levels of hydromorphone at steady state (four days after administration is started), reducing peaks and troughs compared to those levels seen with IR hydromorphone. At steady state, the mean peak-to-trough fluctuation in plasma

levels was 60.5 percent \pm 41.1 percent with once-daily hydromorphone ER versus 172 percent \pm 57.6 percent with hydromorphone IR. Further, the current analysis demonstrated that once-daily hydromorphone mean concentrations remained above 50 percent of the maximum plasma concentration (C_{max}) substantially longer than hydromorphone IR (20.5 hours vs. 7.5 hours).

"As a supplier of opioid pain medications in the United States, Covidien's Mallinckrodt business is dedicated to safe and appropriate use of these important pain treatments," said Herbert Neuman, M.D., Vice President, Medical Affairs and Chief Medical Officer, Pharmaceuticals, Covidien. "Although once-daily hydromorphone ER can still be misused or abused, these studies indicate that the pharmacological and physical properties of this formulation are performing as designed to make it less susceptible to blood plasma level peaks and troughs and potentially difficult to manipulate."

Key clinical poster presentations at the meeting include:

- Characterization of the Pharmacokinetic Profile of Single-Dose Once-Daily Hydromorphone ER (OROS Hydromorphone ER) Versus IR Hydromorphone Administered Over 24 Hours in Healthy Subjects
- Tamper-Resistant Properties of Once-Daily Hydromorphone ER (OROS Hydromorphone ER)
- Characterization of the Steady-State Pharmacokinetic Profile of Once-Daily Hydromorphone ER (OROS Hydromorphone ER) Versus IR Hydromorphone in Healthy Subjects
- Sustained Safety and Efficacy of Once-Daily Hydromorphone ER (OROS Hydromorphone ER) Compared With Twice-Daily Oxycodone CR Over 52 Weeks in Patients With Moderate to Severe Chronic Noncancer Pain
- A Repeat-Dose, Steady-State Pharmacokinetic Evaluation of Once-Daily Hydromorphone ER (OROS Hydromorphone ER) in Patients With Chronic Cancer or Noncancer Pain

IMPORTANT RISK INFORMATION FOR EXALGO

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

Potential for Abuse

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

diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Proper Patient Selection

EXALGO is an extended-release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid, for a week or longer.

EXALGO is for use in opioid tolerant patients only.

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

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

Limitations of Use

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

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

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

- EXALGO is also contraindicated in patients who:
 - have significant impaired respiratory function including those with acute or severe bronchial asthma or hypercarbia
 - have or are suspected to have paralytic ileus
 - have narrowed or obstructed gastrointestinal (GI) tract including those from previous surgery or "blind loops" in the GI tract
 - have known hypersensitivity to any components including hydromorphone hydrochloride and sulfites
- Avoid concurrent use of EXALGO and alcohol. Concurrent use of EXALGO with central nervous system depressants, including alcohol, increases risk of respiratory depression, hypotension, and profound sedation, potentially

resulting in coma or death. EXALGO may impair the ability to drive a car or operate machinery.

- EXALGO is not intended for use in patients who have received monoamine oxidase inhibitors within 14 days of starting EXALGO.
- Use with caution and in reduced doses in older or debilitated patients, as well as patients with renal or hepatic insufficiency, Addison's disease, delirium tremens, myxedema or hypothyroidism, prostatic hypertrophy or urethral stricture, toxic psychosis. May aggravate convulsions in patients with convulsive disorders; may induce or aggravate seizures in some clinical settings. Consider use of an alternate analgesic in patients with severe renal impairment.
- Use EXALGO with extreme caution in patients susceptible to the intracranial effects of CO₂ retention.
- Respiratory depression, which occurs more frequently in elderly or debilitated patients, is the chief hazard with EXALGO.
- EXALGO should not be abruptly discontinued. Administer no more frequently than every 24 hours. Titrate doses no more often than every 3-4 days to achieve steady state plasma levels.
- Do not abruptly discontinue EXALGO.
- Serious adverse events could also include hypotensive effects, GI effects, cardiac arrest from overdose and precipitation of withdrawal. Most common adverse events (>10%) are: constipation (31%), nausea (28%), vomiting, somnolence, headache and dizziness.

See Full Prescribing Information for additional Important Risk Information.

http://www.exalgo.com/media/pdf/EXALGO_FullPrescribingInformation.pdf [1]

EXALGO is a registered trademark of Mallinckrodt Inc.

OROS is a registered trademark of ALZA Corporation.

ABOUT COVIDIEN

Covidien is a leading global healthcare products company that creates innovative medical solutions for better patient outcomes and delivers value through clinical leadership and excellence. Covidien manufactures, distributes and services a diverse range of industry-leading product lines in three segments: Medical Devices, Pharmaceuticals and Medical Supplies. With 2010 revenue of \$10.4 billion, Covidien has 41,000 employees worldwide in more than 65 countries, and its products are sold in over 140 countries. Please visit www.covidien.com [2] to learn more about our business.

[SOURCE](#) [3]

Source URL (retrieved on 03/10/2014 - 12:33am):

<http://www.mdtmag.com/news/2011/05/study-characterizes-extractability-properties-once-daily-extended-release-hydromorphone>

Links:

[1] http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.exalgo.com%2Fmedia%2Fpdf%2FEXALGO_FullPrescribingInformation.pdf&esheet=6730294&lan=en-US&anchor=http%3A%2F%2Fwww.exalgo.com%2Fmedia%2Fpdf%2FEXALGO_FullPrescribingInformation.pdf&index=1&md5=346573e822e6acc67e7d0d6c7dc174ae

[2] <http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.covidien.com&esheet=6730294&lan=en-US&anchor=www.covidien.com&index=2&md5=1e3ef87327a91eae40bad3a28200e8f8>

[3] <http://investor.covidien.com/phoenix.zhtml?c=207592&p=RssLanding&cat=news&id=1565500>