From: Sales Representative
To: Target Customer
Subject: Live Speaker Program Invitation

Dear [insert name],

Attached please find an invitation to an upcoming XARTEMIS™ XR (oxycodone HCl and acetaminophen) Extended-Release Tablets, CII live speaker program. I hope you'll be able to join me, as well as your colleagues, for this informational opportunity.

If you would prefer not to receive Mallinckrodt speaker program invitations by e-mail from me in the future, please don't hesitate to advise me.

Please see below for Important Risk Information, including boxed warning, and accompanying Full Prescribing Information.

Sincerely,
[Sales Representative name]
[Include your contact information, but do not use any other signature message]

Attachments: Invitation
Package Insert

XARTEMIS™ XR (oxycodone HCl and acetaminophen) Extended-Release Tablets, for oral use, CII

INDICATIONS AND USAGE

XARTEMIS™ XR (oxycodone HCl and acetaminophen) Extended-Release Tablets (CII) is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate.

IMPORTANT RISK INFORMATION

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

Addiction, Abuse, and Misuse
XARTEMIS XR 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 XARTEMIS XR, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMIS XR. Monitor for respiratory depression, especially during initiation of XARTEMIS XR or following a dose increase. Instruct patients to swallow XARTEMIS XR tablets whole; crushing, chewing, or dissolving XARTEMIS XR can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure
Accidental ingestion of XARTEMIS XR, especially in children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized 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.

Hepatotoxicity
XARTEMIS XR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limit, and often involve more than one acetaminophen-containing product.

CONTRAINDICATIONS

- XARTEMIS XR is contraindicated in patients with:
  - known hypersensitivity to oxycodone, acetaminophen, or any other component of this product.
  - significant respiratory depression.
  - acute or severe bronchial asthma or hypercarbia.
  - known or suspected paralytic ileus.

WARNINGS AND PRECAUTIONS

- XARTEMIS XR contains oxycodone, a Schedule II controlled substance. As an opioid, XARTEMIS XR exposes users to the risks of addiction, abuse, and misuse. Abuse or misuse of XARTEMIS XR by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the oxycodone and can result in overdose and death. With intravenous abuse, the inactive ingredients in XARTEMIS XR can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.
- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of XARTEMIS XR, the risk is greatest during the initiation of therapy or following a dose increase. Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. In patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression, XARTEMIS XR may decrease respiratory drive to the point of apnea.
- Hypotension, profound sedation, coma, respiratory depression, and death may result if XARTEMIS XR is used concomitantly with alcohol or other central nervous system (CNS) depressants.
- The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.
- Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal.
- The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure.
- Oxycodone may cause severe hypotension particularly in individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs which compromise vasomotor tone such as phenothiazines.
- Due to the potential for acetaminophen hepatotoxicity at doses higher than 4000 milligrams/day, XARTEMIS XR should not be used concomitantly with other acetaminophen-containing products.
- Hypersensitivity and anaphylaxis associated with use of acetaminophen have been reported. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting.
- Due to characteristics of the formulation that cause the tablets to swell and become sticky when wet, consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen. Instruct patients not to pre-soak, lick or otherwise wet XARTEMIS XR tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in mouth.
- Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Oxycodone may cause spasm of the Sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.
- Since the CYP3A4 isoenzyme plays a major role in the metabolism of XARTEMIS XR, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.
- XARTEMIS XR may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

ADVERSE REACTIONS

- Serious adverse events may include respiratory depression and hepatotoxicity.
- Common adverse events include nausea, dizziness, headache, vomiting, constipation and somnolence.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Prolonged use of XARTEMIS XR during pregnancy can result in withdrawal signs in the neonate, which can be life threatening.

- Breast feeding: Oxycodone is present in human milk and may result in accumulation and toxicities such as sedation and respiratory depression in some infants. Acetaminophen is present in human milk in small quantities.
- Pediatrics: Safety and effectiveness in pediatric patients under the age of 18 years have not been established.