Press Release

Daiichi Sankyo, Inc. and Inspirion Delivery Sciences LLC Announce Plans for Commercialization of RoxyBond™ (oxycodone hydrochloride) Tablets CII in the U.S.

RoxyBond is the first and only FDA-approved immediate-release opioid medication with abuse-deterrent claims in its approved labeling

Parsippany, NJ and Morristown, NJ (May 30, 2017) – Daiichi Sankyo, Inc. and Inspirion Delivery Sciences LLC (Inspirion) announced today that Daiichi Sankyo will lead the U.S. commercialization of FDA-approved RoxyBond™ (oxycodone hydrochloride) immediate-release tablets, for oral use, CII with Inspirion providing additional salesforce as part of Inspirion's co-promotion rights under the License Agreement. RoxyBond is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. RoxyBond is the first and only immediate-release opioid analgesic with approved labeling describing its abuse-deterrent properties, consistent with the FDA's 2015 Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. RoxyBond is approved in three dosage strengths: 5, 15, and 30 mg.

"Data show that most people who abuse prescription opioids start with immediate-release formulations. Upon launch of RoxyBond, we'll be able to offer healthcare providers a valuable option that helps deter the potential for misuse and abuse while providing their patients relief from pain," said Ken Keller, President, Administrative and Commercial, Daiichi Sankyo, Inc. "This combination of abuse-deterrent properties and clinical value for medically appropriate patients makes RoxyBond a good strategic fit for our growing pain franchise."

RoxyBond is an abuse-deterrent formulation of immediate-release oxycodone that uses physical and chemical barriers, without incorporating aversive agents or opioid antagonists. RoxyBond, which features SentryBond™, a unique patent-protected abuse-deterrent technology, is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse, even if subjected to physical manipulation and/or chemical extraction.

Data from in vitro and clinical studies suggest that RoxyBond has physicochemical properties that are expected to make abuse via injection difficult and reduce abuse by the intranasal route of

administration. However, abuse by the intranasal, oral and intravenous routes is still possible.

Daiichi Sankyo secured the rights to commercialize RoxyBond following FDA approval as part of a License Agreement the company entered into with Inspirion in 2016 for MorphaBond™ ER (morphine sulfate) extended-release tablets, for oral use, CII and a separate investigational Inspirion compound in the U.S., such compound being RoxyBond. Under the terms of the agreement, Inspirion will receive an additional license fee payment and is also eligible for potential sales based milestones as well as royalties on net sales.

“We are excited to bring RoxyBond to market as the first immediate-release abuse-deterrent opioid, in addition to MorphaBond ER -- both products feature our SentryBond technology,” said Inspirion’s CEO, Stefan Aigner, MD, CFA. “We look forward to launching RoxyBond with Daiichi Sankyo, a strong partner with an established market presence and commitment to responsible marketing of prescription medications.”

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, use of RoxyBond should be reserved for patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products) have not been tolerated or are not expected to be tolerated, and have not provided adequate analgesia or are not expected to provide adequate analgesia.

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

Please see important safety information, including boxed warning and indication below.

About SentryBond™

The SentryBond technology platform combines inactive excipients with active pharmaceutical ingredients (API) in a tablet that is specifically designed to frustrate abuse for various methods of manipulation and routes of administration. SentryBond is designed to slow the intended immediate-release properties of RoxyBond when manipulated then insufflated compared to taking RoxyBond orally intact. SentryBond is designed to maintain the extended release properties of MorphaBond ER, even if manipulated and/or chemically extracted. SentryBond Technology imparts its abuse-deterrent characteristics via physical and chemical methods, without the use of antagonist or aversive agents. SentryBond technology is covered by an issued U.S. patent, with additional U.S. and global patent applications pending.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with a Competitive Advantage in Oncology," Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com.

About Inspirion Delivery Sciences

Inspirion Delivery Sciences LLC is a privately held specialty pharmaceutical company that is dedicated to advancing solutions in the field of prescription drug abuse deterrence through continued innovation. Recognizing the serious unmet public health need to combat the escalating crisis of prescription opioid abuse and misuse, Inspirion began pioneering the development of novel abuse-deterrent technologies. For more information, visit the Company's website at www.inspirionds.com.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ROXYBOND

INDICATION

ROXYBOND™ (oxycodone hydrochloride) tablets, for oral use, CII is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve ROXYBOND for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or non-opioid combination products) have not been tolerated, are not expected to be tolerated, have not provided adequate analgesia, or are not expected to provide adequate analgesia.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of ROXYBOND. Monitor for respiratory depression, especially during initiation of ROXYBOND or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of ROXYBOND, especially by children, can result in a fatal overdose of oxycodone.

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

Cytochrome P450 3A4 Interaction
The concomitant use of ROXYBOND with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving ROXYBOND and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

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

CONTRAINDICATIONS

ROXYBOND is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and known hypersensitivity (e.g., anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

ROXYBOND contains oxycodone, a Schedule II controlled substance, and thus exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ROXYBOND. Addiction can occur at recommended dosages, when taken as directed, and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ROXYBOND, and monitor all patients receiving ROXYBOND for the development of these behaviors and conditions. Risks

are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness. The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ROXYBOND, but use in such patients necessitates intensive counseling about the risks and proper use of ROXYBOND along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ROXYBOND. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drugs. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ROXYBOND, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of ROXYBOND.

To reduce the risk of respiratory depression, proper dosing and titration of ROXYBOND are essential. Overestimating the ROXYBOND dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
Concomitant use of ROXYBOND with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of ROXYBOND is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in ROXYBOND-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using ROXYBOND with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ROXYBOND-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ROXYBOND until stable drugs effects are achieved. Concomitant use of ROXYBOND with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using ROXYBOND with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ROXYBOND with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar

pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when ROXYBOND is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate dangerous machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

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

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

Patients with Chronic Pulmonary Disease: ROXYBOND -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ROXYBOND.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating ROXYBOND and when ROXYBOND is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. ROXYBOND should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Severe Hypotension

ROXYBOND may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs. Monitor these patients for signs of hypotension after initiating or titrating the dosage of

ROXYBOND. In patients with circulatory shock, use of ROXYBOND may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ROXYBOND in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ROXYBOND may reduce the respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ROXYBOND. Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of ROXYBOND in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions
ROXYBOND is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. The oxycodone in ROXYBOND may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders
The oxycodone in ROXYBOND may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during ROXYBOND therapy.

Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including ROXYBOND. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing ROXYBOND, gradually taper the dosage. Do not abruptly discontinue ROXYBOND in these patients.

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

Adverse Reactions
The common adverse reactions seen on initiation of therapy with oxycodone hydrochloride tablets are dose related and are opioid-related adverse reactions. The most frequent of these included nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.

Drug Interactions
- Concomitant use of CYP3A4 inducers can decrease the plasma concentration of oxycodone, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
- Concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of respiratory depression, profound sedation, coma, and death.

- The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
- MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).
- Mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of ROXYBOND and/or may precipitate withdrawal symptoms.
- Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

These are not all the possible side effects of ROXYBOND. Please see **Full Prescribing Information**, including BOXED WARNINGS, and Medication Guide. Patients and health care providers may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR MORPHABOND ER

INDICATION

MORPHABOND™ ER (morphine sulfate) extended-release tablets, for oral use, CII is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve MORPHABOND ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
MORPHABOND ER is not indicated as an as-needed (prn) analgesic.

IMPORTANT SAFETY INFORMATION

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

Addiction, Abuse, and Misuse
MORPHABOND ER™ 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 MORPHABOND ER, 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 MORPHABOND ER. Monitor for respiratory depression, especially during initiation of MORPHABOND ER or following a dose increase. Instruct patients to swallow MORPHABOND ER tablets whole; crushing, chewing, or dissolving MORPHABOND ER tablets can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Ingestion

Accidental ingestion of even one dose of MORPHABOND ER, especially by children, can result in a fatal overdose of morphine.

Neonatal Opioid Withdrawal Syndrome

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

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

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

CONTRAINDICATIONS

MORPHABOND ER is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; concurrent use of monoamine oxidase inhibitors (MAOIs) or use MAOIs within the last 14 days; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (e.g., anaphylaxis) to morphine.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

MORPHABOND ER contains morphine, a Schedule II controlled substance, and thus exposes its users to the risks of addiction, abuse, and misuse. As extended-release products such as MORPHABOND ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of morphine present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHABOND ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing MORPHABOND ER, and monitor all patients receiving MORPHABOND ER for development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness. The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed extended-release opioid formulations such as MORPHABOND ER, but use in such patients necessitates intensive counseling about the risks of proper use of MORPHABOND ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of MORPHABOND ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death. Opioid agonists such as MORPHABOND ER are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing MORPHABOND

ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper storage and disposal of unused drug.

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of MORPHABOND ER, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases with MORPHABOND ER. To reduce the risk of respiratory depression, proper dosing and titration of MORPHABOND ER are essential. Overestimating the MORPHABOND ER dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

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

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

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

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

Life -Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of MORPHABOND ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: MORPHABOND ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory

reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of MORPHABOND ER.
Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating MORPHABOND ER and when MORPHABOND ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors
Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. MORPHABOND ER should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Severe Hypotension
MORPHABOND ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs. Monitor these patients for signs of hypotension after initiating or titrating the dosage of MORPHABOND ER. In patients with circulatory shock, MORPHABOND ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MORPHABOND ER in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), MORPHABOND ER may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with MORPHABOND ER. Avoid the use of MORPHABOND ER in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions
MORPHABOND ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. The morphine in MORPHABOND ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders
The morphine in MORPHABOND ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during MORPHABOND ER therapy.

Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including MORPHABOND ER. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing MORPHABOND ER, gradually taper the dosage. Do not abruptly discontinue MORPHABOND ER.

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

Adverse Reactions
In clinical trials, the most common adverse reactions with morphine sulfate extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.

Drug Interactions
- Concomitant use of benzodiazepines or other CNS depressants can increase the risk of respiratory depression, profound sedation, coma and death.
- The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
- Mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of MORPHABOND ER and/or may precipitate withdrawal symptoms.
- Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity.
- The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
- The concomitant use of PGP-inhibitors can increase the exposure to morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death.

These are not all the possible side effects of MORPHABOND ER. Please see Full Prescribing Information, including BOXED WARNINGS, and Medication Guide. Patients and health care providers may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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