The Role of Abuse-Deterrent Formulations in Opioid Abuse

As the most accessible health care providers and medication experts, pharmacists are uniquely positioned to provide education and counseling to patients regarding the potential for misuse and abuse with opioid therapy. According to data from the 2016 National Survey on Drug Use and Health (NSDUH), 11.5 million Americans 12 years and older reported that they misused prescription pain relievers, defined as using an opioid medication without a valid prescription, for a different purpose than prescribed, or in greater quantities than prescribed (ie, more frequently, at higher doses, or for longer periods of time). Nearly 53% of Americans aged 12 years and older who misused prescription opioids obtained them from a friend or relative. According to data from the 2015 NSDUH, 87% of those who obtained prescription opioids for free from friends or relatives reported that the friend or relative received the opioids from a physician.

Because opioid abuse is a complex societal problem with no single solution, pharmacists have an important role in understanding the patterns of misuse of prescription opioids and increasing awareness of formulations in development aimed to deter misuse and abuse. Importantly, this knowledge can be used to better educate patients, as well as assist health care teams in decision making for improvements in prescribing practices.

Understanding Methods of Opioid Misuse and Abuse

In addition to taking a large number of opioid tablets orally, abuse may occur by manipulating or tampering with an immediate-release (IR) or extended-release (ER) prescription opioid for alternative nonoral routes of administration. The Researchers and Participants Interacting Directly (RAPID) Program consists of a subset of nationally representative treatment-seeking opioid users from the ongoing nationwide Survey of Key Informants' Patient (SKIP) Program, which collects and analyzes postmarketing data on the abuse and diversion of prescription opioid analgesics and heroin. In an analysis of data collected from RAPID program participants with a lifetime history of prescription opioid abuse, approximately 70% of respondents initiated with or progressed to nonoral routes of administration. Morphine sulfate is the most prescribed ER opioid, accounting for 44% of all prescriptions in 2018, and it is widely abused. In a survey including both ER and IR morphine formulations, 62% of morphine sulfate abuse involved tampering. Tampering with ER opioid medications may be intended to override the ER mechanism to allow faster onset of action and delivery of the maximum opioid concentration via nonoral routes of administration (eg, injection or inhalation), resulting in increased psychoactive effects, also known as dose dumping. Injection is the most common route of ER morphine abuse. Based on data collected from US patients in substance abuse treatment in 2009, ER morphine abuse via injection was reported by 48% of patients.

Supporting Safe Opioid Prescription Use in the Pharmacy

Risk-assessment tools may help stratify risk of opioid misuse among patients with pain, but there are no validated tools to assess a patient’s environment and risk of prescription opioid diversion. National and state initiatives have been implemented to assist in the prevention of opioid misuse and diversion. State-run Prescription Drug Monitoring Programs support the pharmacist in evaluating the patient’s history of controlled substance prescriptions, identify patients at risk of opioid misuse, and ensure the appropriate use of opioids to deter potential abuse and diversion. When verifying an opioid prescription, pharmacists also evaluate the prescription for any physical signs that it has been modified or forged and assess patient behaviors to prevent diversion, misuse, and abuse.

On September 18, 2018, the FDA mandated that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for all opioid analgesics intended for outpatient use. The Opioid Analgesic REMS program is designed to ensure that the benefits of opioid analgesics outweigh the risk of addiction, abuse, misuse, deaths, and overdose. REMS can include tools to ensure safe use, restricted distribution, patient registries, and other patient monitoring. Although the

Indication and Important Safety Information

Indication
MORPHABOND™ ER (morphine sulfate) extended-release tablets, for oral use, CII is an opioid agonist 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 (eg, 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.
REMS program requires that training be made available for health care providers, including doctors and pharmacists, involved in the management of patients with pain. Training is not mandatory for health care providers to prescribe or dispense opioid analgesics. To obtain further information on the Opioid Analgesic REMS and for a list of accredited REMS continuing education, call 1-800-503-0784, or go to www.opioidanalgesicrems.com.

ROLE AND FUNCTION OF ABUSE-DETERRENT FORMULATIONS

In addition to best practices in the pharmacy to prevent misuse, abuse, and diversion, pharmacists have an opportunity to collaborate with prescribers, and better understand patient needs with opioid therapy, and actively participate in the selection of specific opioid formulations. For patients with risk factors for misuse, or in cases in which there is suspected misuse of opioid medications or unintentional diversion, a pharmacist may recommend an abuse-deterrent formulation (ADF) to minimize the risk of abuse.

Opioid ADFs are being developed to maintain effective pain relief while reducing the potential for abuse through manipulation of the drug delivery formulation. This is counted as a high public health priority by the FDA. Currently, 6 opioid products have FDA-approved ADF labeling in ER or IR formulations in the United States. ADFs are specifically formulated to target expected routes of abuse. They are designed to make manipulation of an oral dosage form more difficult or to make a manipulated opioid product less appealing for nonoral routes of abuse, such as crushing for intranasal administration or dissolving for injection. There is currently limited real-world evidence showing the effects of ADFs on opioid abuse. ADFs are expected to play an important role in deterring abuse; however, they may still be abused.

Pharmacist awareness of available ADFs of opioid medications is essential to their role in mitigating opioid abuse with selection of the appropriate management and patient counseling.

INNOVATIONS IN ABUSE-DETERRENT FORMULATIONS:

MORPHABOND™ ER

MORPHABOND™ ER (morphine sulfate) extended-release tablet is a single-agent, abuse-deterrent morphine with familiar efficacy, safety, and dosing comparable to MS Contin®, the reference drug on which FDA approval was based. MORPHABOND ER demonstrated bioequivalence to MS Contin® with a 1-to-1 dosing conversion. There are 4 available dosage strengths (15, 30, 60, and 100 mg) of MORPHABOND ER; notably, 100-mg doses should be reserved for opioid-tolerant patients.

Abuse-Deterrent Technology

MORPHABOND ER with SentryBond™ Technology is formulated with physical and chemical properties to reduce abuse. The active ingredient, contained within a polymer matrix of inactive ingredients, is difficult to visibly distinguish or physically separate from the polymer matrix. MORPHABOND ER with SentryBond Technology allows for:

- Increased resistance to cutting, crushing, and/or breaking relative to MS Contin®
- Resistance to extraction using select household and laboratory solvents under various conditions including selected pretreatment
- Formation of a viscous material if physically manipulated and placed in liquid

IMPORTANT SAFETY INFORMATION

BOXED WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); 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 and conditions.

Opioid Analgesic REMS

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to:

- Complete a REMS-compliant education program,
- Counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- Consider other tools to improve patient, household, and community safety

For additional BOXED WARNINGS, please see next page.
MORPHABOND ER is formulated to prevent dose dumping by maintaining similar morphine concentrations even when manipulated. MORPHABOND ER has properties that are expected to reduce abuse or misuse by intranasal and intravenous (IV) routes; however, abuse by intranasal, IV, and oral routes is still possible.13

**CLINICAL ABUSE-DETERRENT STUDIES**

The intranasal abuse potential and relative bioavailability of MORPHABOND ER was evaluated in a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study in nondependent recreational opioid users with a history of intranasal drug abuse (N = 25). In this study, which was designed in accordance with FDA guidance, patients were randomly assigned to receive crushed intranasal MORPHABOND ER (60 mg), crushed intranasal MS Contin® (60 mg), intact oral MORPHABOND ER (60 mg), or placebo.13,21

**Intranasal Pharmacokinetics**

Even when manipulated, similar relative bioavailability was observed with intact oral and crushed intranasal administration. Administration of crushed intranasal and intact oral MORPHABOND ER resulted in lower mean maximum plasma morphine concentrations (26.2 and 18.6 ng/mL, respectively) compared with crushed intranasal MS Contin® (49.5 ng/mL). Within the first 30 minutes, exposure to morphine was lower for crushed intranasal and intact oral administration of MORPHABOND ER compared with crushed intranasal MS Contin®. The median time to maximum concentration for morphine was 46% longer for both crushed intranasal and intact oral MORPHABOND ER (1.6 hours for both routes) than for crushed intranasal MS Contin® (1.1 hours). The similar mean plasma concentrations demonstrated by intact oral and crushed intranasal MORPHABOND ER supports the ability of the abuse-deterrent technology to retain ER properties and prevent dose dumping despite manipulation ([FIGURE]).13,22

**Reduction of Drug Liking and Take Drug Again in Recreational Opioid Users**

Results from the clinical abuse potential study also support key primary and secondary end points for drug liking and take drug again, highlighting the role MORPHABOND ER can play in deterring opioid misuse. In the study, 76% (n = 19) of patients experienced at least some reduction in drug liking with crushed intranasal MORPHABOND ER compared with crushed intranasal administration of MS Contin® (71.7 vs 84.7 mm; P < .0001), with a 40% reduction in mean maximum effect. Furthermore, whether taken intact orally or crushed intranasally, there was no significant difference in drug liking for MORPHABOND ER (67.3 vs 71.7 mm; P = .1675).13,21

Study results also showed that crushed intranasal MORPHABOND ER significantly reduced mean take drug again scores compared with crushed intranasal MS Contin® (66.4 vs 76.4 mm; P = .034). In contrast, there was no significant difference in take drug again scores when crushed intranasal MORPHABOND ER was compared with intact oral MORPHABOND ER (66.4 vs 64.0 mm; P = .6306).13,21 Based on the results of abuse-deterrence studies, MORPHABOND ER was approved by the FDA with abuse-deterrence labeling.13,15 However, it is important for pharmacists to be aware that the abuse of MORPHABOND ER is still possible by intranasal, IV, and oral routes of administration.13

**IMPORTANT SAFETY INFORMATION**

| BOXED WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS (continued) |

**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.
THE ROLE OF THE PHARMACIST

Pharmacists assess the appropriateness of opioid prescriptions and provide access to opioids for patients who have a legitimate need, while working to prevent misuse, abuse, and diversion. As an integral part of the health care team, pharmacists may have the opportunity to actively collaborate with prescribers to increase awareness of best practices in mitigating opioid abuse and share knowledge of the opioid products available, such as ADFs. Pharmacists can emphasize the importance of including "dispense as written" on an ADF prescription to ensure the patient receives access to the appropriate opioid formulation. Pharmacists can also help patients address any financial barriers to prescribed opioid medications.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS (continued)

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 of MAOIs within the last 14 days; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (eg, 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. Because 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. Addiction can occur at recommended doses and if the drug is misused or abused.
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Addiction, Abuse, and Misuse (continued)**

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 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 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. Opioids 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. 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.

**Opioid Analgesic REMS**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the FDA has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all of the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of 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 fatal overdose with the first dose.

**Neonatal Opioid Withdrawal Syndrome**

Prolonged use of MORPHABOND ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

**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 risks of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with concomitant use of other CNS depressant drugs with opioid analgesics.
IMPACTFUL SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (continued)
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 (eg, phenothiazines or general anesthetics). 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 (eg, 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.

Opioids may also obscure the clinical course in a patient with a head injury. 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.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide.
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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 (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who are receiving 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, 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
• 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 (eg, respiratory depression, coma)
• 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 efficiency 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 P-gp-inhibitors can increase the exposure to morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death

REFERENCES
MORPHABOND ER and the MORPHABOND ER logo are trademarks of INSPIRION DELIVERY SCIENCES LLC.
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Please see additional Important Safety Information throughout, and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide.