

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MORPHABOND™ safely and effectively. See full prescribing information for MORPHABOND.

MORPHABOND™ (morphine sulfate) extended-release tablets, for oral use
CII

Initial U.S. Approval: 1941

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

See full prescribing information for complete boxed warning.

- MORPHABOND exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors and conditions. (5.1)
- Serious, life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow MORPHABOND tablets whole to avoid exposure to a potentially fatal dose of morphine. (5.2)
- Accidental ingestion of MORPHABOND, especially by children, can result in fatal overdose of morphine. (5.2)
- Prolonged use of MORPHABOND during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.3)

INDICATIONS AND USAGE

MORPHABOND 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. (1)

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 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. (1)
- MORPHABOND is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- MORPHABOND 100mg tablets, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, or an equianalgesic dose of another opioid. (2.1)

- For opioid-naïve and opioid non-tolerant patients, initiate with 15 mg tablets orally every 12 hours. (2.2)
- Do not abruptly discontinue MORPHABOND in a physically dependent patient. (2.4)
- Instruct patients to swallow MORPHABOND tablets intact. (2.1)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg, 30 mg, 60 mg, 100 mg (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to morphine (4)

WARNINGS AND PRECAUTIONS

- Risk of life-threatening respiratory depression in elderly, cachectic, and debilitated patients, and in patients with chronic pulmonary disease: Monitor closely. (5.5, 5.6)
- Severe hypotension: Monitor during dose initiation and titration. Avoid use of MORPHABOND in patients with circulatory shock. (5.7)
- Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness: Monitor for sedation and respiratory depression. Avoid use of MORPHABOND in patients with impaired consciousness or coma. (5.8)

ADVERSE REACTIONS

Most common adverse reactions: constipation, nausea, and sedation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Inspirin Delivery Technologies at 1-845-589-0277 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CNS depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4, 7)
- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with MORPHABOND because they may reduce analgesic effect of MORPHABOND or precipitate withdrawal symptoms. (5.11, 7)
- Monoamine oxidase inhibitors (MAOIs): Avoid MORPHABOND in patients taking MAOIs or within 14 days of stopping such treatment. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Nursing is not recommended. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

MORPHABOND™ 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, and monitor all patients regularly for the development of these behaviors or conditions [*see Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of MORPHABOND. Monitor for respiratory depression, especially during initiation of MORPHABOND or following a dose increase. Instruct patients to swallow MORPHABOND tablets whole; crushing, chewing, or dissolving MORPHABOND tablets can cause rapid release and absorption of a potentially fatal dose of morphine [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of MORPHABOND, especially by children, can result in a fatal overdose of morphine [*see Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHABOND 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 [*see Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

MORPHABOND 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 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 is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

MORPHABOND 100mg tablets, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mcg transdermal fentanyl per hour, 25 mg oral oxymorphone per day, 60 mg oral hydromorphone per day, or an equianalgesic dose of another opioid.

MORPHABOND tablets must be taken whole. Crushing, chewing, or dissolving MORPHABOND tablets will result in uncontrolled delivery of morphine and can lead to overdose or death [*see Warnings and Precautions (5.1)*].

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with MORPHABOND and adjust the dosage accordingly [*see Warnings and Precautions (5.2)*].

MORPHABOND is administered orally every 12 hours.

2.2 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse [*see Warnings and Precautions (5.1)*]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with MORPHABOND [*see Warnings and Precautions (5.2)*].

Use of MORPHABOND as the First Opioid Analgesic

Initiate treatment with MORPHABOND with 15 mg tablets orally every 12 hours.

Use of MORPHABOND in Patients who are not Opioid Tolerant (opioid-naïve patients)

The starting dosage for patients who are not opioid tolerant is MORPHABOND 15 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression [*see Warnings and Precautions (5.2)*].

Conversion from Other Oral Morphine to MORPHABOND

Patients receiving other oral morphine formulations may be converted to MORPHABOND by administering one-half of the patient's 24-hour requirement as MORPHABOND on an every-12-hour schedule.

Conversion from Other Opioids to MORPHABOND

Discontinue all other around-the-clock opioid drugs when MORPHABOND therapy is initiated

There are no established conversion ratios for conversion from other opioids to MORPHABOND defined by clinical trials. Initiate dosing using MORPHABOND 15 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral morphine dosage and provide rescue medication (e.g., immediate-release morphine) than to overestimate the 24-hour oral morphine dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to MORPHABOND

When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to MORPHABOND, consider the following general points:

Parenteral to oral morphine ratio: Between 2 to 6 mg of oral morphine may be required to provide analgesia equivalent to 1 mg of parenteral morphine. Typically, a dose of morphine that is approximately three times the previous daily parenteral morphine requirement is sufficient.

Other parenteral or oral non-morphine opioids to oral morphine sulfate: Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. Published relative potency data are available, but such ratios are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.

Conversion from Methadone to MORPHABOND

Close monitoring is of particular importance when converting 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 can accumulate in the plasma.

2.3 Titration and Maintenance of Therapy

Individually titrate MORPHABOND to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MORPHABOND to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as

monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of MORPHABOND, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the MORPHABOND dose. Because steady-state plasma concentrations are approximated in 1 day, MORPHABOND dosage adjustments may be done every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, the subsequent dosages may be reduced. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of MORPHABOND

When the patient no longer requires therapy with MORPHABOND tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue MORPHABOND.

3 DOSAGE FORMS AND STRENGTHS

- 15 mg extended-release tablets (round, blue-colored, coated tablets ink-printed with “IDT/M15” on one side; and plain on the other)
- 30 mg extended-release tablets (round, purple-colored, coated tablets ink-printed with “IDT/M30” on one side; and plain on the other)
- 60 mg extended-release tablets (round, orange-colored, coated tablets ink-printed with “IDT/M60” on one side; and plain on the other)
- 100 mg extended-release tablets* (round, gray-colored, coated tablets ink-printed with “IDT/M100” on one side; and plain on the other)

*100 mg tablets are for use in opioid-tolerant patients only

4 CONTRAINDICATIONS

MORPHABOND is contraindicated in patients with:

- Significant respiratory depression [*see Warnings and Precautions (5.2)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.6)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus. [*see Warnings and Precautions (5.9)*]
- Hypersensitivity (e.g., anaphylaxis) to morphine [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

MORPHABOND contains morphine, a Schedule II controlled substance. As an opioid, MORPHABOND exposes its users to the risks of addiction, abuse, and misuse. As extended-release products such as MORPHABOND 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 [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHABOND 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, and monitor all patients receiving MORPHABOND 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 (e.g., major depression). 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, but use in such patients necessitates intensive counseling about the risks of proper use of MORPHABOND along with intensive monitoring for signs of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHABOND. Addiction can occur at recommended dosages and if the drug is misused or abused.

Abuse or misuse of MORPHABOND by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death [*see Overdosage (10)*].

Opioid agonists such as MORPHABOND are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing MORPHABOND. 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 [*see Patient Counseling Information (17)*]. 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.

5.2 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. Respiratory depression from opioid use, 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 [*see Overdosage (10)*]. 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, 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.

To reduce the risk of respiratory depression, proper dosing and titration of MORPHABOND are essential [*see Dosage and Administration (2)*]. Overestimating the MORPHABOND dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of MORPHABOND, especially by children, can result in respiratory depression and death due to an overdose of morphine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHABOND during pregnancy can result in withdrawal signs 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. 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.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn [*see Use in Specific Populations (8)*].

5.4 Risks due to Interactions with Central Nervous System Depressants

Hypotension, profound sedation, respiratory depression, coma, and death may result if MORPHABOND is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, tranquilizers, general anesthetics, phenothiazines, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of MORPHABOND in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol and/or illicit drugs that cause CNS depression. If the decision to begin MORPHABOND is made, start with a lower dosage of MORPHABOND, monitor patients for signs of sedation, respiratory depression, and hypotension, and consider using a lower dosage of the concomitant CNS depressant [*see Drug Interactions (7)*].

5.5 Risk of Life Threatening Respiratory Depression in Elderly, Cachectic, and 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 and when MORPHABOND is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.2)*].

5.6 Risk of Apnea in Patients with Chronic Pulmonary Disease

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

MORPHABOND-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 [*see Warnings and Precautions (5.2)*]. Therefore, closely monitor these patients especially when initiating and titrating MORPHABOND. Alternatively, consider the use of alternative non-opioid analgesics in these patients.

5.7 Severe Hypotension

MORPHABOND 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 (e.g., phenothiazines or general anesthetics) [*see Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of MORPHABOND. In patients with circulatory shock, MORPHABOND may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MORPHABOND in patients with circulatory shock.

5.8 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 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.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of MORPHABOND in patients with impaired consciousness or coma.

5.9 Risks of Use in Patients with Gastrointestinal Conditions

MORPHABOND is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. The morphine in MORPHABOND 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.

5.10 Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in MORPHABOND 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 therapy.

5.11 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. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing MORPHABOND, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue MORPHABOND [*see Drug Abuse and Dependence (9.3)*].

5.12 Risks of Driving and Operating Machinery

MORPHABOND 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 and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [*see Warnings and Precautions (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.3)*]
- Interactions with Other CNS Depressants [*see Warnings and Precautions (5.4)*]
- Severe Hypotension [*see Warnings and Precautions (5.7)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.9)*]
- Seizures [*see Warnings and Precautions (5.10)*]
- Withdrawal [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trial Experience

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.

MORPHABOND may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock [*see Overdosage (10)*].

Most Frequently Observed 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.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain.

Less Frequently Observed Reactions

Cardiovascular disorders: tachycardia, bradycardia, palpitations

Eye disorders: visual impairment, vision blurred, diplopia, miosis

Gastrointestinal disorders: dry mouth, diarrhea, abdominal pain, constipation, dyspepsia

General disorders and administration site conditions: chills, feeling abnormal, edema, edema peripheral, weakness

Hepatobiliary disorders: biliary colic

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: muscle rigidity, muscle twitching

Nervous system disorders: presyncope, syncope, headache, tremor, uncoordinated muscle movements, convulsion, intracranial pressure increased, taste alteration, paresthesia, nystagmus

Psychiatric disorders: agitation, mood altered, anxiety, depression, abnormal dreams, hallucination, disorientation, insomnia

Renal and urinary disorders: urinary retention, urinary hesitation, antidiuretic effect

Reproductive system and breast disorders: reduced libido and/or potency

Respiratory, thoracic and mediastinal disorders: laryngospasm

Skin and subcutaneous tissue disorders: pruritus, urticaria, rash

Vascular disorders: flushing, hypotension, hypertension

6.2 Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of morphine sulfate extended-release: amenorrhea, asthenia, bronchospasm, confusional state, drug hypersensitivity, fatigue, hyperalgesia, hypertonia, ileus, increased hepatic enzymes, intestinal obstruction, lethargy, malaise, pulmonary edema, thinking disturbances, somnolence, and vertigo.

Anaphylaxis has been reported with ingredients contained in morphine sulfate extended-release. Advise patients how to recognize such a reaction and when to seek medical attention.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with MORPHABOND.

Table 1: Clinically Significant Drug Interactions with MORPHABOND

Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	The concomitant use of CNS depressants can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reduce the dosage of the MORPHABOND and consider using a lower dosage of the CNS depressant. Monitor patients for signs of respiratory depression, sedation, and hypotension [see <i>Warnings and Precautions (5.4)</i>].
<i>Examples:</i>	Alcohol, sedatives, tranquilizers, general anesthetics, phenothiazines, anxiolytics, hypnotics, neuroleptics, other opioids.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of MORPHABOND and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MORPHABOND and/or the muscle relaxant as necessary.
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	The concomitant use of MAOIs can potentiate the effects of morphine and can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI.
Cimetidine	
<i>Clinical Impact:</i>	The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than

	otherwise expected and decrease the dosage of MORPHABOND and/or cimetidine as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when MORPHABOND is used concomitantly with anticholinergic drugs.
P-Glycoprotein (PGP) Inhibitors	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MORPHABOND and/or the PGP-inhibitor as necessary.
<i>Example:</i>	quinidine

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, including poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see Warnings and Precautions (5.3)].

Teratogenic Effects -Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. MORPHABOND should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study; however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Non-Teratogenic Effects

Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome [see *Warnings and Precautions (5.3)*], reversible reduction in brain volume, small size, decreased ventilatory response to CO₂ and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Published literature has reported that exposure to morphine during pregnancy in animals is associated with reduction in growth and a host of behavioral abnormalities in the offspring. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, IP) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. MORPHABOND is not recommended for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including MORPHABOND, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of

excess sedation and respiratory depression. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate.

8.3 Nursing Mothers

Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. The amount of morphine received by the infant varies depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism.

Withdrawal signs can occur in breast-feeding infants when maternal administration of morphine is stopped.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with MORPHABOND.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

The pharmacokinetics of MORPHABOND have not been studied in elderly patients. Clinical studies of morphine sulfate extended-release did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of MORPHABOND slowly in geriatric patients [*see Warnings and Precautions (5.5)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

MORPHABOND contains morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. MORPHABOND can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

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. Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug seeking" behavior is very common to persons with substance use disorders. 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 health care provider(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.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers 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.

MORPHABOND, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

Risks Specific to Abuse of MORPHABOND

MORPHABOND is for oral use only. Abuse of MORPHABOND poses a risk of overdose and death. This risk is increased with concurrent abuse of MORPHABOND with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved MORPHABOND enhances drug release and increases the risk of overdose and death.

Parenteral abuse of MORPHABOND can be expected to result in 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.

Abuse Deterrence Studies

MORPHABOND is formulated with inactive ingredients that make the tablet more difficult to adulterate for misuse and abuse while maintaining extended-release characteristics even if the

tablet is subjected to physical manipulation, and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of MORPHABOND, a series of in vitro laboratory manipulation, extraction, and syringeability, studies was conducted. An in vivo clinical abuse potential study was also conducted. The results of these studies are summarized below. Overall, the results indicate that MORPHABOND has properties that are expected to reduce abuse or misuse via injection or insufflation; however, abuse by these routes is still possible.

In Vitro Testing

MORPHABOND has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of extended-release opioids for administration by various routes, including oral consumption, intranasal insufflation, injection, and smoking.

Abusers may manipulate extended-release opioids in order to prepare the tablets for oral, intranasal, or intravenous administration. The laboratory test data demonstrated that, relative to morphine sulfate extended-release tablet, MORPHABOND has increased resistance to cutting, crushing, or breaking using a variety of tools. When subjected to a liquid environment the manipulated MORPHABOND formulation forms a viscous material that resists passage through a needle.

Clinical Studies

A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in 25 non-dependent recreational opioid users with a history of intranasal drug abuse was performed to determine the relative bioavailability and abuse potential of crushed intranasal MORPHABOND 60 mg tablets compared with crushed intranasal morphine sulfate extended-release tablet 60 mg tablets, and intact orally administered MORPHABOND 60 mg tablets. The intact oral tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route.

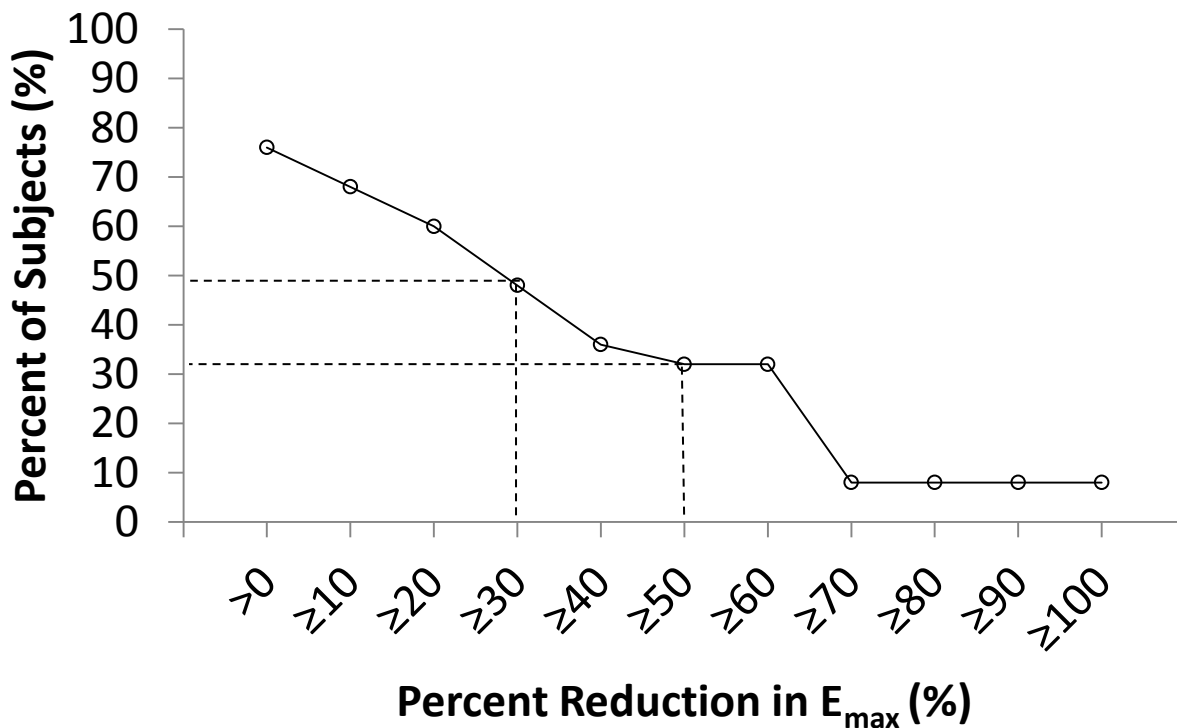
Drug liking was measured on a 100 mm bipolar visual analog scale (VAS) where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ('definitely would not take drug again') and 100 represents the strongest positive response ('definitely would take drug again').

Intranasal administration of crushed MORPHABOND was associated with statistically significantly lower drug liking (E_{\max}) scores ($P < 0.0001$), and significantly lower willingness to take the drug again (E_{\max}) scores ($P = 0.034$), compared to crushed extended-release morphine (Table 2). Drug liking and take drug again scores for crushed intranasal MORPHABOND were not significantly different from those of MORPHABOND taken orally intact. These data are consistent with the similar relative bioavailability after crushed intranasal and intact oral administration of MORPHABOND that support retention of its extended release properties when manipulated compared to morphine sulfate extended-release tablets [see *Clinical Pharmacology (12.3)*].

Table 2. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Administration of MORPHABOND, morphine sulfate extended-release tablet, and Placebo in Recreational Opioid Users (n=25)					
		Crushed Intranasal MORPHABOND 60 mg	Crushed Intranasal morphine sulfate extended-release tablet 60 mg	Placebo	Crushed Intranasal morphine sulfate extended-release tablet vs. Crushed Intranasal MORPHABOND Difference of LS Means (95% CI)
Drug Liking (E_{max})	Mean (SEM)	71.7 (2.87)	85.3 (2.42)	54.3 (1.63)	13.65 (7.80, 19.51)
	Median (Range)	72 (50-100)	85 (56-100)	51 (50-80)	
Take Drug Again (E_{max})	Mean (SEM)	66.4 (3.76)	76.4 (4.17)	49.1 (2.21)	9.96 (0.77, 19.14)
	Median (Range)	64.0 (38-100)	75.0 (17-100)	50.0 (0-64)	

Figure 1 demonstrates a comparison of peak drug liking scores for crushed MORPHABOND compared to crushed extended-release morphine in subjects who received both treatments intranasally. Seventy-six percent of subjects (n = 19) experienced some reduction in E_{max} of Drug Liking VAS with crushed MORPHABOND compared with crushed extended-release morphine, 48%; (n = 12) experienced at least a 30% reduction in E_{max} and 32% (n = 8) experienced at least a 50% reduction in E_{max} of drug liking.

Figure 1. Percent Reduction Profiles for E_{max} of Drug Liking for MORPHABOND vs. Morphine Sulfate ER Tablets (n=25), Following Intranasal Administration



Summary

The in vitro data demonstrate that MORPHABOND has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by intranasal, intravenous, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of MORPHABOND on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist

analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

MORPHABOND should not be abruptly discontinued [*see Dosage and Administration (2.4)*]. If MORPHABOND is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with MORPHABOND can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *see Clinical Pharmacology (12.2)*.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Because the duration of reversal would be expected to be less than the duration of action of morphine in MORPHABOND, carefully monitor the patient until spontaneous respiration is reliably re-established. MORPHABOND will continue to release morphine and add to the morphine load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the

physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

MORPHABOND (morphine sulfate) extended-release tablets are for oral use and contain morphine sulfate, an opioid agonist.

Each tablet contains the following inactive ingredients common to all strengths: hypromellose, xanthan gum, microcrystalline cellulose, sodium alginate, alginic acid, mannitol, colloidal silicon dioxide, magnesium stearate, ethyl acrylate and methyl methacrylate copolymer dispersion, lactose monohydrate, polysorbate 80, titanium dioxide, polyethylene glycol, shellac in ethanol, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol, and ammonium hydroxide.

The tablet strengths describe the amount of morphine per tablet as the pentahydrated sulfate salt (morphine sulfate).

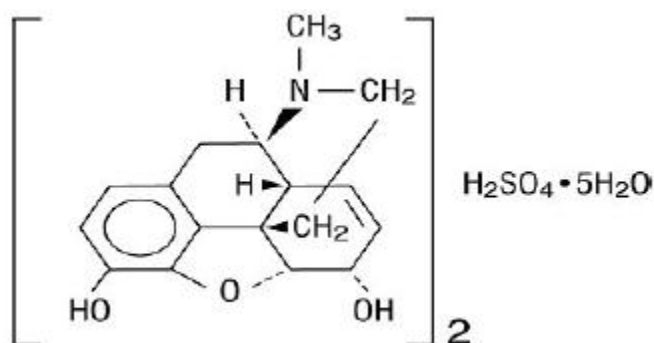
The 15 mg tablets also contain: FD&C Blue No. 1, FD&C Red No. 40 and FD&C Yellow No. 6

The 30 mg tablets also contain: FD&C Blue No. 2 and FD&C Red No. 40

The 60 mg tablets also contain: FD&C Yellow No. 6 and FD&C Red No. 40

The 100 mg tablets also contain: FD&C Blue No. 2, FD&C Yellow No. 6 and FD&C Red No. 40

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Its structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include analgesia, dysphoria, euphoria, somnolence, respiratory

depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

12.2 Pharmacodynamics

Plasma Level-Analgesia Relationships

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when MORPHABOND is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation. Specific CNS opiate receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm. The end result is constipation.

Morphine can cause a marked reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because morphine may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

12.3 Pharmacokinetics

MORPHABOND is an extended-release tablet containing morphine sulfate. Morphine is released from MORPHABOND somewhat more slowly than from immediate-release oral preparations. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is MORPHABOND or an immediate-release formulation. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Absorption

The oral bioavailability of morphine is approximately 20 to 40%. When MORPHABOND is given on a fixed dosing regimen, steady-state is achieved in about a day.

Food Effect

The effect of food upon the systemic bioavailability of MORPHABOND has not been systematically evaluated for all strengths. Administration of a single dose of MORPHABOND with a standardized high-fat meal resulted in a 33% increase in morphine peak plasma concentration and no change in AUC compared to fasted state.

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses placental membranes and has been found in breast milk. The volume of distribution (Vd) for morphine is approximately 3 to 4 liters per kilogram and morphine is 30 to 35% reversibly bound to plasma proteins.

Metabolism

The major pathways of morphine metabolism include glucuronidation to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%) and sulfation in the liver to produce morphine-3-etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.

Excretion

The elimination of morphine occurs primarily as renal excretion of M3G and its effective half-life after intravenous administration is normally 2 to 4 hours. Approximately 10% of the dose is excreted unchanged in urine. In some studies involving longer periods of plasma sampling, a longer terminal half-life of about 15 hours was reported. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling.

Special Populations

Geriatric Patients

The pharmacokinetics of MORPHABOND have not been studied in elderly patients.

Pediatric Patients

The pharmacokinetics of MORPHABOND have not been studied in pediatric patients below the age of 18.

Gender

A gender analysis of pharmacokinetic data from healthy subjects taking morphine sulfate extended-release indicated that morphine concentrations were similar in males and females.

Race

Chinese subjects given intravenous morphine had a higher clearance when compared to Caucasian subjects (1852 +/- 116 ml/min compared to 1495 +/-80 ml/min).

Hepatic Impairment

Morphine pharmacokinetics are altered in individuals with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these subjects, indicating diminished metabolic activity. Adequate

studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. The AUC is increased and clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Mutagenesis: No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, in vitro studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Impairment of Fertility: No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e., testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

16 HOW SUPPLIED/STORAGE AND HANDLING

MORPHABOND™ (morphine sulfate) extended-release tablets 15 mg are round, blue-colored, coated tablets ink-printed with IDT/M15 on one side; and plain on the other. They are supplied as follows:

NDC 69296-004-01: opaque plastic bottles containing 100 tablets

MORPHABOND™ (morphine sulfate) extended-release tablets 30 mg are round, purple-colored, coated tablets ink-printed with IDT/M30 on one side; and plain on the other. They are supplied as follows:

NDC 69296-003-01: opaque plastic bottles containing 100 tablets

MORPHABOND™ (morphine sulfate) extended-release tablets 60 mg are round, orange-colored, coated tablets ink-printed with IDT/M60 on one side; and plain on the other. They are supplied as follows:

NDC 69296-002-01: opaque plastic bottles containing 100 tablets

MORPHABOND™ (morphine sulfate) extended-release tablets 100 mg are round, gray-colored, coated tablets ink-printed with IDT/M100 on one side; and plain on the other. They are supplied as follows:

NDC 69296-001-01: opaque plastic bottles containing 100 tablets

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container.

CAUTION

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of MORPHABOND, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share MORPHABOND with others and to take steps to protect MORPHABOND from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting MORPHABOND or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store

MORPHABOND securely and to dispose of unused MORPHABOND by flushing the tablets down the toilet.

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur MORPHABOND is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider [see *Warnings and Precautions (5.4)*].

Important Administration Instructions [see *Dosage and Administration (2.1, 2.4)*, *Warnings and Precautions (5.2)*]

Instruct patients how to properly take MORPHABOND, including the following:

- Swallowing MORPHABOND tablets whole
- Not crushing, chewing, or dissolving the tablets
- Using MORPHABOND exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing MORPHABOND without first discussing the need for a tapering regimen with the prescriber

Hypotension

Inform patients that MORPHABOND may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions (5.7)*].

Driving or Operating Heavy Machinery

Inform patients that MORPHABOND may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions (5.12)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in MORPHABOND. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that prolonged use of MORPHABOND during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.3), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that MORPHABOND can (or may) cause fetal harm and to inform the prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Disposal of Unused MORPHABOND

Advise patients to flush the unused tablets down the toilet when MORPHABOND is no longer needed.

Healthcare professionals can telephone Inspirion Delivery Technologies (1-845-589-0277) for information on this product.

Inspirion Delivery Technologies LLC
Valley Cottage, NY 10989-2027

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