HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARYMO® ER safely and effectively. See full prescribing information for ARYMO ER.

ARYMO ER (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; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
See full prescribing information for complete boxed warning.

- **ARYMO ER 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 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 ARYMO ER tablets whole to avoid exposure to a potentially fatal dose of morphine. (5.2)**
- **Accidental ingestion of ARYMO ER, especially in children, can result in fatal overdose of morphine. (5.2)**
- **Prolonged use of ARYMO ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required 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)**
- **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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**

INDICATIONS AND USAGE

ARYMO ER 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 ARYMO ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- ARYMO ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- A single dose of ARYMO ER 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 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 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 15 mg tablets orally every 8 or 12 hours. (2.2)
- Do not abruptly discontinue ARYMO ER in a physically dependent patient. (2.4)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. (2.1, 5.9)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within 14 days (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, particularly during initiation and titration. (5.5, 5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of ARYMO ER in patients with circulatory shock. (5.8)
- 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 ARYMO ER in patients with impaired consciousness or coma. (5.9)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.10)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Egalet US Inc. at 1-800-518-1084 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue ARYMO ER if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with ARYMO ER because they may reduce analgesic effect of ARYMO ER or precipitate withdrawal symptoms. (5.11, 7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

ARYMO® 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 ARYMO ER, 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 ARYMO ER. Monitor for respiratory depression, especially during initiation of ARYMO ER or following a dose increase. Instruct patients to swallow ARYMO ER tablets whole; crushing, chewing, or dissolving ARYMO ER 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 ARYMO ER, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

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

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 *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of ARYMO 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.**

1 INDICATIONS AND USAGE

ARYMO ER 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 *[see Warnings and Precautions (5.1)]*, reserve ARYMO ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- ARYMO ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

A single dose of ARYMO ER 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 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, 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 and following dosage increases with ARYMO ER and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Instruct patients to take ARYMO ER tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Instruct patients not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Warnings and Precautions (5.10)]*. Cutting, breaking, crushing, chewing, or dissolving ARYMO ER tablets will result in uncontrolled delivery of morphine that could lead to overdose and death *[see Warnings and Precautions (5.1)]*.

ARYMO ER is administered orally every 8 or 12 hours.

2.2 Initial Dosing

Use of ARYMO ER as the First Opioid Analgesic (opioid-naïve patients)

Initiate treatment with ARYMO ER with 15 mg tablets orally every 8 or 12 hours.

Use of ARYMO ER in Patients who are not Opioid Tolerant (opioid-non-tolerant patients)

The starting dose for patients who are not opioid tolerant is ARYMO ER 15 mg orally every 8 or 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 ARYMO ER

Patients receiving other oral morphine formulations may be converted to ARYMO ER by administering one-half of the patient's 24-hour requirement as ARYMO ER on an every-12-hour schedule or by administering one-third of the patient's daily requirement as ARYMO ER on an every-8-hour schedule.

Conversion from Other Opioids to ARYMO ER

Discontinue all other around-the-clock opioid drugs when ARYMO ER therapy is initiated.

There are no established conversion ratios for conversion from other opioids to ARYMO ER defined by clinical trials. Initiate dosing using ARYMO ER 15 mg orally every 8 to 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 inter-patient variability in the potency of opioid drugs and opioid formulations.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to ARYMO ER.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to ARYMO ER

When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to ARYMO ER, 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 ARYMO ER

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 ARYMO ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ARYMO ER 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 *[see Warnings and Precautions (5.1)]*. 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 ARYMO ER, 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 ARYMO ER dose. Because steady-state plasma concentrations are approximated in 1 day, ARYMO ER dosage adjustments may be done every 1 to 2 days.

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

2.4 Discontinuation of ARYMO ER

When the patient no longer requires therapy with ARYMO ER tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue ARYMO ER.

3 DOSAGE FORMS AND STRENGTHS

- ARYMO ER (morphine sulfate) extended-release tablets 15 mg (blue film coated, capsule shaped tablets debossed with “EGLT 15”)
- ARYMO ER (morphine sulfate) extended-release tablets 30 mg (light purple film coated, capsule shaped tablets debossed with “EGLT 30”)
- ARYMO ER (morphine sulfate) extended-release tablets 60 mg (light orange film coated, capsule shaped tablets debossed with “EGLT 60”)

4 CONTRAINDICATIONS

ARYMO ER 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 (5.5)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days *[see Warnings and Precautions (5.6)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity (e.g., anaphylaxis) to morphine *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

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

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ARYMO ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ARYMO ER, and monitor all patients receiving ARYMO ER for development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (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 opioids such as ARYMO ER, but use in such patients necessitates intensive counseling about the risks of proper use of ARYMO ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Attempts at misuse or abuse of ARYMO ER by crushing, snorting, or injecting the dissolved product may compromise some of the extended-release properties resulting in delivery of morphine that could lead to overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ARYMO 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 *[see Patient Counseling Information (17)]*. Contact the 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 opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) 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 ARYMO ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases with ARYMO ER.

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

Accidental ingestion of even one dose of ARYMO ER, 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 ARYMO 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 *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

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 ARYMO 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 *[see Drug Interactions (7), Patient Counseling Information (17)]*.

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

The use of ARYMO 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: ARYMO 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 ARYMO ER *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating ARYMO ER and when ARYMO ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.4)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Interaction with Monoamine Oxidase Inhibitors

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

5.7 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.

5.8 Severe Hypotension

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

5.9 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ARYMO ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ARYMO ER.

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

5.10 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

Moistened ARYMO ER tablets may become sticky leading to difficulty in swallowing the tablets. Patients could experience choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick, or otherwise wet ARYMO ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

Tablet stickiness and swelling may also predispose patients to intestinal obstruction and exacerbation of diverticulitis. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.11 Risks of Use in Patients with Gastrointestinal Conditions

ARYMO ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The morphine in ARYMO 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.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in ARYMO 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 ARYMO ER therapy.

5.13 Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., 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 ARYMO ER. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

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

5.14 Risks of Driving and Operating Machinery

ARYMO 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 ARYMO ER and know how they will react to the medication *[see Patient Counseling Information (17)]*.

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 Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Withdrawal *[see Warnings and Precautions (5.13)]*

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.

ARYMO ER 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 formulations 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 formulations. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: 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.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ARYMO ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with ARYMO ER.

Table 1: Clinically Significant Drug Interactions with ARYMO ER

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.2)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ARYMO ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity *[see Warnings and Precautions (5.6)]*.
Intervention:	Do not use ARYMO ER in patients taking MAOIs or within 14 days of stopping such treatment.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of ARYMO ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.

Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dose of ARYMO ER and/or the muscle relaxant as necessary.
Cimetidine	
Clinical Impact:	The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dose of ARYMO ER and/or cimetidine as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dose of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when ARYMO ER is used concurrently with anticholinergic drugs.
P-Glycoprotein (P-gp) Inhibitors	
Clinical Impact:	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.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dose of ARYMO ER and/or the P-gp inhibitor as necessary.
Example:	Quinidine

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data with ARYMO ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.

Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects *[see Human Data]*. In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse. Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3-4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD *[see Animal Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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. 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 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. ARYMO ER is not recommended for use in women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including ARYMO ER, 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.

Data

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any

time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35-322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100-500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10-50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the

offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), 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 at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice were treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

8.2 Lactation

Risk Summary

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with extended-release morphine, including ARYMO ER. 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 ARYMO ER.

Clinical Considerations

Monitor infants exposed to ARYMO ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive

potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

In published animal studies, morphine administration adversely affected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats *[see Nonclinical Toxicology (13.1)]*.

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 ARYMO ER have not been studied in elderly patients. Clinical studies of morphine sulfate extended-release formulations 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, dose 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 ARYMO ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.5)]*.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of ARYMO ER and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of ARYMO ER and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ARYMO ER contains morphine, a Schedule II controlled substance.

9.2 Abuse

ARYMO ER contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. ARYMO ER 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 misuse and abuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction because 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 includes: 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 in 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 loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other healthcare 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. Healthcare 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.

ARYMO ER, 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 ARYMO ER

ARYMO ER is for oral use only. Abuse of ARYMO ER poses a risk of overdose and death. This risk is increased with concurrent abuse of ARYMO ER with alcohol and other central nervous system depressants. Attempting to cut, break, chew, crush, or dissolve ARYMO ER tablets may compromise some of the extended-release properties, resulting in delivery of morphine that could lead to overdose and death.

Parenteral abuse of ARYMO ER 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

ARYMO ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.

To evaluate the ability of ARYMO ER to reduce the potential for misuse and abuse, a series of abuse-deterrent in vitro laboratory physical manipulation, chemical extraction, and syringeability studies were conducted. One oral human abuse potential study and one intranasal human abuse potential study were conducted. In each study both pharmacokinetic and pharmacodynamic (subjective measures) data were collected. These data are described below for both studies.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the extended-release properties. The results of this testing demonstrated that ARYMO ER tablets, in comparison to morphine sulfate extended-release tablets, have increased resistance to cutting, crushing, grinding or breaking using a variety of tools. When subjected to a liquid environment, the manipulated ARYMO ER tablets form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Oral Human Abuse Potential Study

Pharmacokinetic Results

The pharmacokinetic profile of manipulated ARYMO ER was characterized following oral administration. The study was conducted in a randomized cross-over design. The pharmacokinetic profile of manipulated and intact ARYMO ER compared to crushed morphine sulfate extended-release was evaluated in 38 subjects after oral administration. The results are summarized in Table 2 and demonstrate that oral ingestion of manipulated ARYMO ER resulted in a higher C_{max}, but similar AUC, when compared to intact ARYMO ER. In addition, manipulated ARYMO ER had a lower C_{max} and longer T_{max} than crushed morphine sulfate extended-release tablets.

Table 2: Results from Oral Pharmacokinetic Study

PK Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 39)
	Manipulated (n = 38)	Intact (n = 38)	
C_{max} (ng/mL)			
Mean (SD)	28.7 (9.1)	17.8 (6.6)	42.3 (14.3)
Median (Range)	29.2 (12.5, 47.8)	16.7 (8.5, 32.3)	42.2 (14.2, 79.0)
T_{max} (h)			
Median (Range)	2.1 (0.9, 4.2)	4.1 (1.6, 6.1)	0.9 (0.6, 4.1)
$AUC_{0-\infty}$ (h*ng/mL)			
Mean (SD)	159.3 (36.8)	168.0 (53.6)	182.1 (49.9)
Median (Range)	157.1 (94.5, 215.3)	159.4 (80.9, 274.8)	185.5 (61.8, 284.1)

C_{max} = maximum observed plasma concentration; T_{max} = time to achieve the maximum observed plasma concentration; $AUC_{0-\infty}$ = area under the curve, zero to infinity

Pharmacodynamic Results

An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users; 38 subjects completed the study. Treatment arms included manipulated ARYMO ER 60 mg tablets (taken with juice), intact ARYMO ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate extended-release tablets (mixed in juice), and placebo.

Drug liking was measured on a 100 mm bipolar visual analog scale (VAS) where 50 represents a neutral response of "neither like nor dislike", 0 represents "strong disliking", and 100 represents "strong 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 ('do not care'), 0 represents the strongest negative response ('definitely would not') and 100 represents the strongest positive response ('definitely would').

The study demonstrated that the oral administration of manipulated ARYMO ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate extended-release tablets. However, the difference between manipulated ARYMO ER and crushed morphine sulfate extended-release tablets for Take Drug Again was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.

These results are summarized in Table 3.

Table 3: Summary of Maximum Scores (E_{max}) for Drug Liking and Take Drug Again VAS[1] Following Oral Administration of Manipulated and Intact

ARYMO ER and Crushed Morphine Sulfate Extended-Release in Non-Dependent Recreational Opioid Users

Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 38)	Placebo (n = 38)
	Manipulated (n = 38)	Intact (n = 38)		
Maximum Drug Liking (E_{max})				
Mean (SD)	68.3 (12.3)	63.2 (10.1)	73.3 (9.8)	53.3 (7.8)
Median (Q1, Q3)	67.0 (61.0, 75.0)	62.0 (56.0, 68.0)	74.0 (68.0, 79.0)	50.0 (50.0, 52.0)
Take Drug Again (E_{max})				
Mean (SD)	62.9 (19.6)	54.8 (20.8)	70.1 (17.5)	51.0 (10.2)
Median (Q1, Q3)	61.5 (51.0, 71.0)	56.0 (50.0, 65.0)	68.0 (56.0, 80.0)	50.0 (50.0, 50.0)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)
Q1=1st Quartile; Q3=3rd Quartile

Intranasal Human Abuse Potential Study

Pharmacokinetic Results

The pharmacokinetic profile of manipulated ARYMO ER compared to crushed morphine sulfate extended-release was evaluated following intranasal administration in 46 subjects. The study was conducted in a randomized cross-over design. Subjects were non-dependent recreational opioid users with insufflation experience. The preparation of ARYMO ER in this study required a multi-step procedure (mechanical and electrical manipulations) compared to morphine sulfate extended-release tablets, which were crushed in a single-step (mechanical) procedure. Treatment arms included ARYMO ER 60 mg tablet manipulated, morphine sulfate extended-release 60 mg tablet crushed, oral intact ARYMO ER 60 mg tablet, and placebo.

The pharmacokinetic parameters that were measured include C_{max}, T_{max} and overall exposure ($AUC_{0-\infty}$). The results are summarized in Table 4 and demonstrate that snorting manipulated ARYMO ER had a lower C_{max}, longer T_{max} and lower overall exposure compared to snorting crushed morphine sulfate extended-release tablets. The pharmacokinetic profile of manipulated Arymo ER is consistent with an oral intact extended-release profile.

Table 4: Pharmacokinetic Results from Intranasal Study

PK Parameter	Manipulated ARYMO ER (n = 45)	Intact ARYMO ER (Oral) (n = 46)	Crushed Morphine Sulfate Extended-Release (n = 46)
C_{max} (ng/mL)			
Mean (SD)	19.0 (9.6)	17.2 (4.3)	36.3 (12.9)
Median (Range)	19.8 (4.2-40.1)	18.1 (9.3-24.8)	34.6 (6.5-62.3)
T_{max} (h)			
Median (Range)	2.2 (1.1-6.1)	3.7 (1.1-6.2)	1.1 (0.4-2.7)
$AUC_{0-\infty}$ (h*ng/mL)			
Mean (SD)	125.2 (63.6)	149.0 (25.5)	181.6 (49.7)
Median (Range)	137.7 (20.8-244.2)	153.4 (85.6-188.6)	177.6 (29.8-286.0)

C_{max} = maximum observed plasma concentration; T_{max} = time to achieve the maximum observed plasma concentration; $AUC_{0-\infty}$ = area under the curve, zero to infinity; SD=standard deviation

Pharmacodynamic Results

In the intranasal abuse potential study, drug liking was measured on a 100 mm bipolar visual analog scale (VAS) where 50 represents a neutral response of "neither like nor dislike", 0 represents "strong disliking", and 100 represents "strong 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 ('do not care'), 0 represents the strongest negative response ('definitely would not') and 100 represents the strongest positive response ('definitely would').

The study results demonstrated that subjects who snorted manipulated ARYMO ER reported statistically significantly lower maximum scores (E_{max}) for drug liking and take drug again compared to snorting crushed morphine sulfate extended-release tablets. These results are summarized in Table 5.

Table 5: Summary of Maximum Scores (E_{max}) for Drug Liking and Take Drug Again[1] following Intranasal Administration of Manipulated ARYMO ER and

Crushed Morphine Sulfate Extended-Release Tablets in Non-Dependent Recreational Opioid Users

Parameter	Manipulated ARYMO ER (n = 46)	Crushed Morphine Sulfate Extended-Release (n = 46)	Placebo (n = 46)
Maximum Drug Liking (E_{max})			
Mean (SD)	65.5 (14.3)	77.7 (11.7)	54.7 (10.6)
Median (Q1, Q3)	62.0 (52.0, 76.0)	77.5 (70.0, 85.0)	51.0 (50.0, 58.0)
Take Drug Again (E_{max})			
Mean (SD)	43.1 (29.6)	69.9 (27.4)	52.5 (12.7)
Median (Q1, Q3)	50.0 (19.0, 66.0)	73.0 (57.0, 90.0)	50.0 (50.0, 51.0)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)
Q1=1st Quartile; Q3=3rd Quartile

Summary

The in vitro data demonstrate that ARYMO ER has physical and chemical properties expected to make abuse by injection difficult. The data from the in vitro studies and the intranasal clinical abuse potential study indicate that ARYMO ER has physical and chemical properties that are expected to reduce abuse via the intranasal route.

Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that ARYMO ER has physical and chemical properties that are expected to reduce abuse via the oral route.

Abuse of ARYMO ER by the intravenous and nasal routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of ARYMO ER 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 dose 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 (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine).

Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

ARYMO ER should not be abruptly discontinued *[see Dosage and Administration (2.4)]*. If ARYMO ER 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 overdosage with morphine 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, partial or complete airway obstruction, atypical snoring, 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 ARYMO ER, carefully monitor the patient until spontaneous respiration is reliably re-established. ARYMO ER 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 an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended 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 initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

ARYMO ER (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: polyethylene oxide 400,000, butylated hydroxytoluene, polyvinyl alcohol, polyethylene glycol 3350, talc, and titanium dioxide.

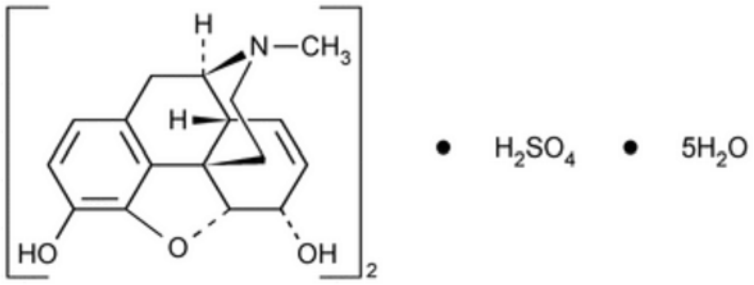
The tablet strengths describe the amount of morphine per tablet as the pentahydrated sulfate salt (morphine sulfate).

The 15 mg tablets also contain: FD&C Blue No. 2 and ferric oxide yellow.

The 30 mg tablets also contain: ferric oxide red, FD&C Blue No. 2, and ferrosoferric oxide.

The 60 mg tablets also contain: ferric oxide yellow, and ferric oxide red.

Morphine sulfate is an odorless, white crystalline solid with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, and practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pK_a 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 is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when ARYMO ER 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 opioid 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 both increases in carbon dioxide tension, and electrical stimulation.

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 hypoxia in overdose situations.

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, resulting in constipation. Other opioid-induced effects may include a reduction in 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.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

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.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.3)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

12.3 Pharmacokinetics

ARYMO ER is an extended-release tablet containing morphine sulfate. Morphine is released from ARYMO ER 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 ARYMO ER 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 ARYMO ER 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 ARYMO ER has been evaluated. In a food effect study with ARYMO ER 60 mg, there was no significant difference in peak plasma concentration (C_{max}) or overall exposure (AUC_{0-24h}). There was a 2-hour delay in median T_{max} value (6.5 hour with food compared to 4.5 hour without food) when ARYMO ER was administered with a high fat meal compared to the fasted state. The extent of food effect is not considered clinically significant so ARYMO ER can be taken without regard to food.

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.

Elimination

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.

Specific Populations

Sex

A sex 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: Long-term 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 and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDD) were reported. Female rats that were administered morphine sulfate intraperitoneally prior to mating exhibited prolonged estrous cycles at 10 mg/kg/day (1.6 times the HDD).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation and following mating to untreated females, smaller litters, increased pup mortality, and/or changes in reproductive endocrine status in adult male offspring have been reported (estimated 5 times the plasma levels at the HDD).

16 HOW SUPPLIED/STORAGE AND HANDLING

ARYMO ER (morphine sulfate) extended-release tablets 15 mg are blue film coated, capsule shaped tablets debossed with “EGLT 15”. They are supplied as:

NDC 69344-111-11: opaque plastic bottles containing 100 tablets

ARYMO ER (morphine sulfate) extended-release tablets 30 mg are light purple film coated, capsule shaped tablets debossed with “EGLT 30”. They are supplied as:

NDC 69344-211-11: opaque plastic bottles containing 100 tablets

ARYMO ER (morphine sulfate) extended-release tablets 60 mg are light orange film coated, capsule shaped tablets debossed with “EGLT 60”. They are supplied as:

NDC 69344-311-11: 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.

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 ARYMO ER, 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 ARYMO ER with others and to take steps to protect ARYMO ER 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 ARYMO ER or when the dosage is increased, and that it can occur even at recommended doses *[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 ARYMO ER securely and to dispose of unused ARYMO ER by flushing the tablets down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ARYMO ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking ARYMO ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking ARYMO ER *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.7)]*.

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

Instruct patients how to properly take ARYMO ER, including the following:

- Use ARYMO ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Warnings and Precautions (5.2)]*.
- ARYMO ER is designed to work properly only if swallowed intact. Attempting to cut, break, crush, chew, or dissolve the tablets may result in a fatal overdose *[see Dosage and Administration (2.1)]*.
- ARYMO ER tablets should be taken one tablet at a time *[see Dosage and Administration (2.1)]*.
- Do not pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Dosage and Administration (2.1)]*.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2.1)]*.
- Do not discontinue ARYMO ER without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.4)]*.

Hypotension

Inform patients that ARYMO ER 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 (5.8)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in ARYMO ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of ARYMO ER 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 ARYMO ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with ARYMO ER *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that ARYMO ER 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 (5.14)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unused ARYMO ER

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

Healthcare professionals can telephone Egalet US Inc.'s Medical Information Department (1-800-518-1084) for information on this product.

Distributed by:

Egalet US Inc.
Wayne, PA 19087

LBL # 301.XX
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Medication Guide
ARYMO® ER (AIR ĭ mow) (morphine sulfate) extended-release tablets, CII

ARYMO ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about ARYMO ER:

- **Get emergency help right away if you take too much ARYMO ER (overdose).** When you first start taking ARYMO ER, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking ARYMO ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your ARYMO ER. They could die from taking it. Store ARYMO ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away ARYMO ER is against the law.

Do not take ARYMO ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking ARYMO ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of ARYMO ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with ARYMO ER. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ARYMO ER with certain other medicines can cause serious side effects and could lead to death.

When taking ARYMO ER:

- Do not change your dose. Take ARYMO ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 8 to 12 hours, as directed by your healthcare provider. Do not take more than your prescribed dose. If you miss a dose, take your next dose at the usual time.
- Swallow ARYMO ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject ARYMO ER because this may cause you to overdose and die.
- ARYMO ER should be taken one tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking ARYMO ER without talking to your healthcare provider.**
- After you stop taking ARYMO ER, flush any unused tablets down the toilet.

While taking ARYMO ER DO NOT:

- Drive or operate heavy machinery, until you know how ARYMO ER affects you. ARYMO ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ARYMO ER may cause you to overdose and die.

The possible side effects of ARYMO ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of ARYMO ER. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**
Distributed by: Egalet US Inc., Wayne, PA 19087, **www.egalet.com or call 1-800-518-1084**

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