HCP IMPORTANT SAFETY 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

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

Accidental Ingestion

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

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.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

- **Reserve concomitant prescribing of 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.**

Indications

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, 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.

Contraindications

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

Warnings and Precautions

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.

Life-Threatening Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (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. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following and dosage increases with ARYMO ER.

To reduce the risk of respiratory depression, proper dosing and titration of ARYMO ER are essential. 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.

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.

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.

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.

Elderly, Cachetic, 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.

Monitor such patients closely, particularly when initiating and titrating ARYMO ER and when ARYMO ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

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

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.

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). 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.

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.

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.

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.

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.

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. Do not abruptly discontinue ARYMO ER.

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.

Adverse 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.

Additional Drug Interactions

Serotonergic Drugs: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: May reduce the analgesic effect of ARYMO ER and/or precipitate withdrawal symptoms; avoid concomitant use.

Muscle Relaxants: Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Cimetidine: The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.

Diuretics: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Anticholinergic Drugs: The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

P-Glycoprotein (P-gp) Inhibitors: 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.

Use in Specific Populations

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

Geriatrics: The pharmacokinetics of ARYMO ER have not been studied in elderly patients. Elderly patients (aged 65 years or older) may have increased sensitivity to morphine.

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.

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

Overdosage

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.

Please see Full Prescribing Information, including BOXED WARNING and MEDICATION GUIDE.