***Drug Monograph***

**Generic Name**: morphine sulfate extended-release

**Trade Name**: Arymo® ER

**Dosage Form**:Extended-release tablet

**NDCs:** 69344-0111-11, 69344-0211-11, 69344-0311-11

**Manufacturer**: Egalet Corporation

**ADF Product Classification:** Physical/Chemical Barrier

**Executive Summary**

Arymo® ER (morphine extended-release) is an opioid agonist that is Food and Drug Administration (FDA)-approved for the management of pain that is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate. This agent, like other long-acting opioids, should be reserved 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. It is not indicated for use on an as-needed basis.1 Arymo® ER (morphine extended-release) is being evaluated by the Drug Formulary Commission, as it is a relatively new FDA-labeled abuse-deterrent formulation (ADF) in the marketplace to be considered for inclusion on the Massachusetts formulary of interchangeable abuse-deterrent drugs, as outlined in Chapter 258 of the Acts of 2014.

Arymo® ER (morphine extended-release) is formulated as a tablet and utilizes Egalet’s proprietary GuardianTM Technology, which combines a polymer matrix with an injection molding process to make the tablet more difficult to manipulate for abuse.2 *In vitro* testing indicates that Arymo® ER (morphine extended-release) tablets have an increased resistance to cutting, crushing, grinding, or breaking using a variety of tools, and form a viscous hydrogel that resists passage through a hypodermic needle when subjected to a liquid environment. The results of *in vitro* testing demonstrate that Arymo® ER (morphine extended-release) has properties that are expected to make abuse via the intravenous (IV) route difficult.1

Arymo® ER (morphine extended-release) was FDA-approved through the 505(b)(2) pathway after pharmacokinetic studies demonstrated its bioequivalence to equivalent doses of MS Contin® (morphine sulfate controlled-release).3 Safety and efficacy studies for Arymo® ER (morphine extended-release) are not currently available; however, Arymo® ER (morphine extended-release) was studied in two randomized, double-blind, active and placebo-controlled, crossover studies in non-dependent recreational opioid users in order to evaluate its potential for abuse via the oral and intranasal routes.4,5 In the oral human abuse potential study, the oral administration of manipulated Arymo® ER (morphine extended-release) was associated with significantly lower median “drug liking” scores, but not significantly lower median “take drug again scores,” compared to manipulated morphine extended-release.4 In the intranasal human abuse potential study, the intranasal administration of manipulated Arymo® ER (morphine extended-release) was associated with significantly lower mean “drug liking” and median “take drug again” scores compared to manipulated morphine extended-release.5 Despite the data suggesting Arymo ER® (morphine extended-release) may potentially deter abuse via the IV, intranasal and oral routes and the FDA Advisory Committee voting in favor of approval of labeling for all three routes, the FDA only approved labeling that indicates Arymo ER® (morphine extended-release) is abuse-deterrent via the IV route.1,6 This is in part due to marketing exclusivity of MorphaBond ER® as a single-entity morphine extended-release product that is expected to deter intranasal abuse via its physicochemical properties.7

**Reference Data**

Arymo® ER (morphine extended-release) is an extended-release tablet formulation of morphine. Morphine is an opioid agonist that is relatively selective for the µ opioid receptor; although, other opioid receptor subtypes may be stimulated at higher doses.1 Stimulation of the µ opioid receptors results in analgesia, decreased gastrointestinal motility, euphoria, physical dependence, respiratory depression and sedation.8 The abuse-deterrent properties of Arymo® ER (morphine extended-release) are most comparable to those of MorphaBond® ER (morphine extended-release), OxyContin® (oxycodone extended-release) and Hysingla ER® (hydrocodone extended-release) in that all four of these medications are formulated as tablets that resist crushing, cutting or breaking, and attempts to dissolve these formulations results in the formation of a viscous material that resists passage through a needle.1,9,10,11 Similar drugs within the long-acting opioid class are listed in Table 1.

**Table 1. Long-Acting Opioid Availability12,13**

| **Generic Name (Trade name)** | **Abuse Deterrent Formulation Available** | **Commercially Available** |
| --- | --- | --- |
| Buprenorphine (Belbuca®, Butrans®) | - | ✓ |
| Fentanyl (Duragesic®) | - | ✓ |
| Hydrocodone (Hysingla ER®) | ✓ | ✓ |
| Hydrocodone (Vantrela® ER) | ✓ | ✓\* |
| Hydrocodone (Zohydro ER®) | - | ✓ |
| Hydromorphone (Exalgo®) | - | ✓ |
| Levorphanol (Levo-Dromoran®) | - | ✓ |
| Methadone (Diskets Dispersible®, Dolophine®, Methadose®, Methadone Intensol®) | - | ✓ |
| Morphine sulfate (Avinza®, Kadian®, MS Contin®) | - | ✓ |
| Morphine sulfate (Arymo® ER) | ✓ | ✓\* |
| Morphine sulfate (MorphaBond® ER) | ✓ | ✓\* |
| Morphine sulfate/naltrexone (Embeda®) | ✓ | ✓ |
| Oxycodone (OxyContin®) | ✓ | ✓ |
| Oxycodone (Xtampza ER®) | ✓ | ✓ |
| Oxycodone/naloxone (Targiniq ER®) | ✓ | - |
| Oxycodone/naltrexone (Troxyca® ER) | ✓ | ✓\* |
| Oxymorphone (Opana® ER) | - | ✓ |
| Tapentadol (Nucynta ER®) | - | ✓ |

\*Manufacturer reports launch scheduled for first half of 2017

**Therapeutic Indications/Efficacy**

*In vitro* laboratory studies were conducted to assess the ability to manipulate, extract and smoke Arymo® ER (morphine extended-release). In the manipulation/particle size reduction (PSR) study, 10 commonly available household tools were used to attempt PSR of Arymo® ER (morphine extended-release) tablets by both single-tool and multiple-tool manipulations. The same single-tool manipulations were performed on MS Contin® (morphine extended-release) tablets as a comparator. No tools were able to produce PSR less than 500 microns of Arymo® ER (morphine extended-release), compared to six of the ten tools that produced PSR of at least 50% of particles less than 500 microns with MS Contin® (morphine extended-release). Nine of ten tools produced yields that were considered suitable for insufflation with MS Contin® (morphine extended-release) compared to no tools with Arymo ER® (morphine extended-release). Three combinations of tools were used to attempt PSR with Arymo® ER (morphine extended-release), and the maximum yield of particles smaller than 500 microns was approximately 5% with one combination. Results were similar (3 to 5% of particles smaller than 500 microns) with multiple-tool manipulations after pre-treatment of Arymo® ER (morphine extended-release) tablets with heating (microwave and oven) and freezing. Effort needed to manipulate the products was rated on a 100-point scale, where 0 represented easy to manipulate and 100 means very difficult to manipulate, and ratings for Arymo® ER (morphine extended-release) ranged from 70 to 99 for different tools. In contrast, no tool rated higher than a 20 for manipulation of MS Contin® (morphine extended-release).2

Both small and large-volume extraction studies were performed to assess ability to prepare Arymo® ER (morphine extended-release) for intravenous (IV) injection. In the small-volume study, the extractability of morphine from Arymo® ER (morphine extended-release) and MS Contin® (morphine extended-release) was assessed using injectable solvents, tap water and 3% hypertonic saline in volumes of 2 mL, 5 mL and 10 mL under room temperature and near boiling point temperatures for the solvents. Needle gauges ranging from 27 gauge (27G) to 18 gauge (18G), where higher numbers for gauge represents smaller bore size. The maximum amount of morphine recovered for Arymo® ER (morphine extended-release) in this study was between 16 and 18% with an 18G needle (largest needle) due to the gel formation that occurred when manipulated tablets were subjected to liquid. In contrast, MS Contin® (morphine extended-release) was consistently prepared for injection under all conditions tested.2

In the large-volume extraction study, the extractability of morphine from Arymo® ER (morphine extended-release) and MS Contin® (morphine extended-release) using a panel of 18 solvents (ingestible and non-ingestible) to prepare a solution for oral administration was assessed. Under multiple temperature and agitation conditions, less than 60% of morphine was extracted from Arymo® ER (morphine extended-release) in ingestible solvents by 30 minutes. The FDA Guidance to industry for evaluation of the abuse deterrent properties states that ≥80% extraction at 30 minutes is the threshold that indicates failure or defeat of abuse-deterrent properties. Arymo® ER (morphine extended-release) was below this threshold for all ingestible solvents and conditions tested; however, it is not clear what amount of morphine could be extracted with longer extraction times.2

A simulated smoking study and isolation of free-base morphine study was performed with Arymo® ER (morphine extended-release). In the free-base morphine isolation study, investigators were unable to isolate free-base morphine after three separate attempts due to formation of a cloudy solution, rather than a precipitate. This was attributed to the gelling effects of the excipient. In the *in vitro* simulated smoking study, less than 3% of the morphine was released from simulated smoking of manipulated Arymo® ER (morphine extended-release). This indicates Arymo® ER (morphine extended-release) does not appear to be prone to abuse by smoking.2

Two human abuse potential studies were performed for Arymo® ER (morphine extended-release) of the oral and intranasal routes. The oral human abuse potential study was a randomized, double-blind, active and placebo-controlled study in 38 non-dependent, adult opioid users. After a naloxone challenge and drug discrimination phase, subjects were randomized in a 1:1:1:1 fashion to manipulated Arymo® ER (morphine extended-release), intact Arymo® ER (morphine extended-release), manipulated morphine ER tablet, or placebo. All subjects were assigned to complete each treatment. The primary endpoint assessed was the median peak effect (Emax) for drug liking score on the Visual Analogue Scale (VAS). Secondary endpoints assessed were time to Emax (TEmax) for drug liking, Emax for changes in pupil diameter, TEmax for changes in pupil diameter, willingness to take drug again bipolar VAS scores, overall drug liking bipolar VAS scores and responses to the Drug Effects Questionnaire (DEQ) on the unipolar VAS. The median drug liking Emax for manipulated Arymo® ER (morphine extended-release) was significantly lower compared to manipulated morphine ER tablets (67 versus 74, respectively; P=0.007). Similarly, the median drug liking Emax for intact Arymo® ER (morphine extended-release) was significantly lower compared to manipulated morphine ER tablets (62 versus 74, respectively; P<0.0001). There was no significant difference in drug liking Emax between manipulated and intact Arymo® ER (morphine extended-release) (67 versus 62, respectively; P=not reported). Median scores for take drug again were significantly lower for manipulated and intact Arymo® ER (morphine extended-release) compared to manipulated morphine ER tablets (61.5 and 56.0 versus 68.0, respectively; P=0.05 and P<0.001, respectively). Similar results were seen for other secondary endpoints.4

The intranasal clinical abuse potential study was a randomized, double-blind, active and placebo-controlled study in 46 non-dependent, adult opioid users. After a naloxone challenge and drug discrimination phase, subjects were randomized in a 1:1:1:1 fashion to receive high-volume manipulated Arymo® ER (morphine extended-release), low-volume manipulated Arymo® ER (morphine extended-release) intranasal, low-volume manipulated morphine ER, intact Arymo® ER (morphine extended-release) by mouth and placebo in one of four sequences. The primary endpoint assessed was the median maximum drug liking score (Emax) on the Visual Analogue Scale (VAS). Secondary endpoints included overall drug liking scores on the bipolar VAS, willingness to take drug again scores on the bipolar VAS, peak effect for changes in pupil diameter, time to peak effect for changes in pupil diameter, ease of snorting scores on the bipolar VAS and nasal effects assessed by responses to questions concerning nasal sensations rated on a four-point scale (0=non, 1=mild, 2=moderate, 3=severe). The median drug liking E­max was significantly lower for high volume manipulated Arymo® ER (morphine extended-release) intranasally, low volume manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (62.0, 52.5, 68.0 versus 77.5, respectively; P<0.0001, P<0.0001, P=0.0001, respectively). Median overall drug liking scores were significantly lower for high volume manipulated Arymo® ER (morphine extended-release) intranasally, low volume manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (51.0, 50.5, 59.0 compared to 71.0, respectively; P<0.0001 for all). Other secondary endpoints followed this trend.5

**Table 2. Clinical Trials**

| **Study and Drug Regimen** | **Study Design and**  **Demographics** | **Sample Size**  **and Study Duration** | **End Points** | **Results** |
| --- | --- | --- | --- | --- |
| Smith et al4  manipulated Arymo® ER (morphine extended-release) oral  vs  manipulated morphine ER tablets oral  vs  intact Arymo® ER (morphine extended-release) oral  vs  placebo  All volunteers must have passed a naloxone challenge and drug discrimination phase prior to randomization  At randomization, subjects were randomized to one of the four groups, but completed each treatment. | AC, DB, PC, RCT, SC, SiD, XO  Nondependent, experienced recreational opioid users aged 18 to 55 years | N=38  Single doses | Primary:  Emax drug liking on VAS  Secondary:  TEmax for drug liking, Emax for changes in pupil diameter, TEmax for changes in pupil diameter, Emax for take drug again, Emax for overall drug liking and Emax for responses to the DEQ | Primary:  Median drug liking Emax for manipulated Arymo® ER (morphine extended-release) was significantly lower compared to manipulated morphine ER tablets (67 versus 74, respectively; P=0.007). Median drug liking Emax for intact Arymo® ER (morphine extended-release) was significantly lower compared to manipulated morphine ER tablets (62 versus 74, respectively; P<0.0001). There was no significant difference in drug liking Emax between manipulated and intact Arymo® ER (morphine extended-release) (67 versus 62, respectively; P=NR).  Secondary:  TEmax for drug liking was significantly shorter for manipulated morphine ER tablets compared to both manipulated and intact Arymo® ER (morphine extended-release) (P=0.004 and P<0.0001, respectively; numerical values for TEmax not reported in text [only in graphic format]).  Median Emax for pupillary miosis was the same for manipulated morphine ER tablets and manipulated Arymo® ER (morphine extended-release) (numerical values not reported). Comparison of Emax for pupillary miosis between manipulated morphine ER tablets and intact Arymo® ER (morphine extended-release) was not reported.  TEmax for pupillary miosis was significantly shorter for manipulated morphine ER tablets compared to both manipulated and intact Arymo® ER (morphine extended-release) (P<0.0001 for both; numerical values not reported).  Median Emax for take drug again were significantly lower for manipulated and intact Arymo® ER (morphine extended-release) compared to manipulated morphine ER tablets (61.5 and 56.0 versus 68.0, respectively; P=0.05 and P<0.001, respectively).  There was no significant difference in median Emax for overall drug liking between manipulated morphine ER and manipulated Arymo® ER (morphine extended-release) (67.5 versus 63.5, respectively; P=0.13). Median Emax for overall drug liking was significantly lower with manipulated morphine ER compared to intact Arymo® ER (morphine extended-release) (63.5 versus 57.0, respectively; P<0.001).  Median Emax DEQ responses to “I can feel a drug effect” were significantly higher with manipulated morphine ER tablet compared to both manipulated and intact Arymo® ER (morphine extended-release) (55.5 versus 39.0 and 17.5, respectively; P=0.001 and P<0.0001, respectively). Median Emax responses to “I can feel good drug effects” were significantly higher with manipulated morphine ER tablet compared to both manipulated and intact Arymo® ER (morphine extended-release) (52.0 versus 25.5 and 17.5, respectively; P=0.0025 and P<0.0001, respectively). Median Emax responses to “I am feeling high” were significantly higher with manipulated morphine ER tablet compared to both manipulated and intact Arymo® ER (morphine extended-release) (49.0 versus 38.0 and 18.5, respectively; P=0.0035 and P<0.0001, respectively). There were no significant differences in responses to the questions “I can feel bad drug effects,” “I am feeling sick,” “I am feeling nauseous,” “I am feeling sleepy” and “I am feeling dizzy.” |
| Webster LR, et al.5  HV manipulated Arymo® ER (morphine extended-release) intranasal  vs  LV manipulated Arymo® ER (morphine extended-release) intranasal  vs  manipulated morphine ER tablets intranasal  vs  intact Arymo® ER (morphine extended-release) oral  vs  placebo  All volunteers must have passed a naloxone challenge and drug discrimination phase prior to randomization  At randomization, subjects were randomized to one of the four sequences, but completed each treatment. | AC, DB, PC, RCT, SC, SiD, XO  Nondependent, experienced recreational opioid users aged 18 to 55 years | N=46  Single doses | Primary:  Emax drug liking on VAS  Secondary:  Emax overall drug liking on VAS, Emax take drug again on VAS, Emax for changes in pupil diameter, TEmax for changes in pupil diameter, Emax for responses to the DEQ, ease of snorting scores on VAS and nasal effects assessed by responses to questions concerning nasal sensations | Primary:  Median E­max for drug liking was significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasally, LV manipulated Arymo® ER (morphine extended-release) intranasal and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (62.0, 52.5, 68.0 versus 77.5, respectively; P<0.0001, P<0.0001, P=0.0001, respectively).  Secondary:  Median Emax overall drug liking was significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasal, LV manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasal (51.0, 50.5, 59.0 versus 71.0, respectively; P<0.0001 for all).  Median Emax take drug again was significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasally, LV manipulated Arymo® ER (morphine extended-release) intranasal and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasal (50.0, 50.0, 56.0 versus 73.0, respectively; P<0.0001, P<0.0001, P=0.0003, respectively).  Emax for changes in pupil diameter of HV manipulated Arymo® ER (morphine extended-release) were approximately 80% of measurements for manipulated morphine ER tablets. Low levels of pupillary miosis were observed after insufflation of LV manipulated Arymo® ER (morphine extended-release). Numerical values were not reported.  Values for TEmax were only reported in graphic format.  Median Emax DEQ responses to “I can feel a drug effect” were significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasal, LV manipulated Arymo® ER (morphine extended-release) intranasal and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasal (23.5, 6.5, 38.0 versus 64.0, respectively; P<0.0001 for all). Median Emax responses to “I can feel good drug effects” were significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasal, LV manipulated Arymo® ER (morphine extended-release) intranasal and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasal (17.0, 4.5, 32.5 versus 62.0, respectively; P<0.0001 for all). Median Emax responses to “I can feel bad drug effects” were significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasally, LV manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (1.0, 0, 3.0 versus 7.5, respectively; P=0.0017, P=0.0001, P=0.0092, respectively). Median Emax responses to “I am feeling high” were significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasally, LV manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (20.0, 5.0, 30.0 versus 65.5, respectively; P<0.0001 for all). Median Emax responses to “I am feeling dizzy” were significantly lower for HV manipulated Arymo® ER (morphine extended-release) intranasally, LV manipulated Arymo® ER (morphine extended-release) intranasally and intact Arymo® ER (morphine extended-release) by mouth compared to manipulated morphine ER intranasally (0, 0, 0 versus 9.0, respectively; P<0.0001, P<0.0001, P=0.0021, respectively). Results for Emax responses to other questions on the DEQ were mixed.  Subjects rated HV manipulated Arymo® ER (morphine extended-release) intranasally as “difficult” to snort (median rating 9.5, scale 0 to 100 with lower as more difficult) and “unpleasant to snort” (median rating 32.0, scale 0 to 100 with lower as more unpleasant). Subjects rated LV manipulated Arymo® ER (morphine extended-release) intranasally and manipulated morphine ER tablets as “easy” to snort (median rating 77.0 and 81.5, respectively) and neither pleasant nor unpleasant to snort (median rating 50.5 and 59.0, respectively).  Median Emax ratings for “need to blow your nose at this moment” and “rate any nasal congestion this moment” after insufflation HV manipulated Arymo® ER (morphine extended-release) intranasally were rated as moderate (median rating 2.0, scale 0 to 3 with higher numbers representing increased severity). Emax ratings for LV manipulated Arymo® ER (morphine extended-release) intranasally and manipulated morphine ER intranasally on these questions were mild (median rating 1.0). |

Abbreviations: AC=active-controlled, DB=double-blind, DEQ=Drug Effects Questionnaire, Emax=peak effect, ER=extended-release, HV=high volume, LV=low volume PC=placebo-controlled, RCT=randomized controlled trial, SC=single-center, SiD=single dose, TEmax=time to peak effect, VAS=Visual Analogue Scale, XO=crossover

**Pharmacokinetics/Pharmacogenomics**

*Absorption*

The oral bioavailability of morphine is approximately 20 to 40%. When Arymo® ER (morphine extended-release) is given at a fixed dose and frequency steady-state is achieved in approximately one day.1

*Distribution*

The volume of distribution (VD) for oral morphine is approximately 3 to 4 L/kg. Plasma protein binding of morphine is approximately 30 to 35%. After absorption, morphine is distributed to the skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. In addition, morphine has been found to cross the placenta and be excreted into the breast milk.1

*Metabolism*

Morphine undergoes glucuronidation to morphine-3-glucuronide (M3G, approximately 50%) and morphine-6-glucuronide (M6G, approximately 5 to 15%). Minor pathways of metabolism include sulfation to morphine-3-etheral sulfate and demethylation. M6G is an active metabolite, but has poor ability to cross the blood-brain barrier.1

*Excretion*

Morphine is primarily excreted as M3G in the urine; however, approximately 10% of a dose of morphine is excreted unchanged in the urine. A minor pathway of excretion occurs as glucuronide conjugate in the bile. In addition, there is a minor amount of enterohepatic recycling.1

*Food Effects*

In a food effect study, after administration of a single dose of Arymo® ER (morphine extended-release) 60 mg there was no significant difference in peak plasma concentration (Cmax) of morphine or overall exposure (AUC) in the fed state compared to the fasted state. There was a delay in median time to peak plasma concentration (Tmax) in the fed state (6.5 hours) compared to the fasted state (4.5 hours). The effect of food is not considered clinically significant. As such, Arymo® ER (morphine extended-release) may be taken without regard to food.1

*Effects of Tampering*

In an oral clinical abuse potential study, the mean (SD) Tmax for morphine was shorter for manipulated Arymo® ER (morphine extended-release) taken by mouth (2.0 [0.7] hours) compared to intact Arymo® ER (morphine extended-release) by mouth (3.6 [1.1] hours). The mean (SD) AUC was numerically lower for manipulated Arymo® ER (morphine extended-release) by mouth compared to intact Arymo® ER (morphine extended-release) (159.3 [36.8] ng●hr/mL versus 168.0 [53.6] ng●hr/mL, respectively). Conversely, the mean (SD) Cmax for morphine was numerically higher with manipulated Arymo® ER (morphine extended-release) by mouth (28.7 [9.1] ng/mL) compared to intact Arymo® ER (morphine extended-release) by mouth (17.8 [6.8] ng/mL).1

In an intranasal clinical abuse potential study, the mean (SD) Tmax was shorter for a high volume of manipulated Arymo® ER (morphine extended-release) intranasally (2.4 [0.8] hours) compared to intact Arymo® ER (morphine extended-release) by mouth (3.5 [1.1] hours). The mean (SD) AUC was lower for a high volume of manipulated Arymo® ER (morphine extended-release) intranasally (125.2 [63.6] ng●hr/mL) than for intact Arymo® ER (morphine extended-release) by mouth (149.0 [25.5] ng●hr/mL); however, the mean (SD) Cmax for a high volume of manipulated Arymo® ER (morphine extended-release) intranasally was higher compared to intact Arymo® ER (morphine extended-release) (19.0 [9.6] ng/mL versus 17.2 [4.3] ng/mL, respectively).1

***Pharmacogenomic Considerations:***

Evidence is available that suggests certain genetic variants may be related to requirement of higher doses of morphine for adequate analgesia; however this evidence is based on studies with small sample sizes. A large study of 2,294 cancer patients, 830 of which were on morphine, was conducted to evaluate whether genetic variants were associated with opioid doses. The study failed to replicate previous findings of genetic associations related to opioid efficacy (including morphine), suggesting that pharmacogenetics of opioids need not be considered in clinical decision making.14,15

**Table 2. Pharmacokinetics1,13,16**

| **Generic Name** | **T­max**  **(hours)\*** | **Duration**  **(hours)** | **Clearance**  **(mL/min/kg)** | **Active Metabolites** | **Serum Half-Life**  **(hours)\*** |
| --- | --- | --- | --- | --- | --- |
| Morphine | 4.5 | 8 to 12 | 20 to 30 | Morphine-6-glucuronide (M6G) | 9.57 |

\*Mean Tmax and serum half-life for single dose of 60 mg

**Special Populations**

**Table 3. Special Populations1**

| **Population** | **Precaution** |
| --- | --- |
| Pregnancy/Lactation | The prolonged use of opioids during pregnancy may result in physical dependence in the neonate and neonatal opioid withdrawal syndrome after birth. Opioids cross the placenta and may result in respiratory depression and psycho-physiologic effects in neonates. Based upon animal data, advise pregnant women of the potential risk to a fetus. Data from a population-based prospective cohort study that included 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy did not indicate increased risk for congenital malformations. This study does not establish the absence of risk because of methodological limitations, including the small sample size and non-randomized design. There are no data available for Arymo® ER (morphine extended-release) in pregnant women regarding potential for birth defects or miscarriage.  Morphine is present in breast milk; lactation studies have not been conducted with extended-release formulations of morphine, including Arymo® ER (morphine extended-release). Because of the potential serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with Arymo® ER (morphine extended-release). |
| Females and Males of Reproductive Potential | Chronic use of opioids may cause reduced fertility in males and females of reproductive potential. It is not known whether effects on fertility are reversible. Animal data indicates morphine adversely affected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats. |
| Children | Safety and efficacy of Arymo® ER (morphine extended-release) have not been established in patients below the age of 18 years. |
| Elderly | Clinical studies of morphine extended-release did not include a sufficient amount of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Morphine is substantially excreted by the kidney, and risk of adverse reactions to morphine may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function. As such, care should be taken in dose selection, and it may be useful to monitor renal function. |
| Hepatic Impairment | The pharmacokinetics of morphine is known to be significantly altered in patients with cirrhosis. Start these patients at a lower than usual dosage of Arymo® ER (morphine extended-release) and titrate slowly, monitoring for signs of respiratory depression, sedation and hypotension. |
| Renal Impairment | The pharmacokinetics of morphine is altered in patients with renal impairment. Start these patients at a lower than usual dosage of Arymo® ER (morphine extended-release) and titrate slowly, monitoring for signs of respiratory depression, sedation and hypotension. |

**Dosage Forms**

**Table 4. Availability, Storage and Handling1**

| **Dosage Form** | **Strength** | **Special Handling or Storage** |
| --- | --- | --- |
| Extended-release tablet | 15 mg  30 mg  60 mg | Store at 25°C (77°F); excursions between 15° and 30°C (59° and 86°F) are permitted.  Dispense and store in tight, light-resistant container with child-resistant closure. |

**Dosage Range**

**Table 5. Dosing and Administration1**

| **Adult Dose** | **Pediatric Dose** | **Renal Dose** | **Hepatic Dose** |
| --- | --- | --- | --- |
| Management of pain that is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate:  Initial: 15 mg every 8 or 12 hours  Maintenance: individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions every 1 to 2 days | Safety and efficacy in pediatric patients have not been established. | Start with lower than usual dosage and titrate slowly while monitoring for respiratory depression, sedation and hypotension. | Start with lower than usual dosage and titrate slowly while monitoring for respiratory depression, sedation and hypotension. |

***Dosing Considerations:***

Conversion from other oral morphine formulations to Arymo® ER (morphine extended-release)

Patients receiving other oral morphine formulations may be converted to Arymo® ER (morphine extended-release) by administering one-half of the patient's total daily oral morphine dose as Arymo® ER (morphine extended-release) every 12 hours or one-third of the patient’s total daily oral morphine dose as Arymo® ER (morphine extended-release) every 8 hours.1

Conversion from other opioids to Arymo® ER (morphine extended-release)

Discontinue all other around-the-clock opioid drugs when Arymo® ER (morphine extended-release) therapy is initiated.1

There are no established conversion ratios for conversion from other opioids to Arymo® ER (morphine extended-release) defined by clinical trials. Initiate dosing using Arymo® ER (morphine extended-release) 15 mg every 12 hours.1

It is safer to underestimate a patient’s 24-hour oral morphine dosage and provide rescue medication 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 relative potency of opioid drugs and formulations.1

Conversion from parenteral morphine or other opioids (parenteral or oral) to Arymo® ER (morphine extended-release)

When converting from parenteral morphine to Arymo® ER (morphine extended-release) consider that 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.1

When converting from other parenteral or oral non-morphine opioids to Arymo® ER (morphine extended-release) specific recommendations for ratios 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.1

Conversion from methadone to Arymo® ER (morphine extended-release)

Close monitoring is of particular importance when converting from 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.1

Discontinuation of Arymo® ER (morphine extended-release)

When a patient no longer requires therapy with Arymo® ER (morphine extended-release), 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 (morphine extended-release).1

**Precautions**

**Boxed Warning for Arymo® ER (morphine extended-release)1**

|  |
| --- |
| **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** |
| * Arymo® ER (morphine extended-release) exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing and monitor regularly for development of these behaviors and conditions. * Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow tablets whole. Crushing, chewing, or dissolving Arymo® ER (morphine extended-release) can cause rapid release and absorption of a potentially fatal dose of morphine. * Accidental ingestion of even one dose of Arymo® ER (morphine extended-release), especially by children, can result in fatal overdose of morphine. * Prolonged maternal use of Arymo® ER (morphine extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and which requires management according to protocols developed by neonatology experts. 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. * Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of Arymo® ER (morphine extended-release) 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 and follow patients for signs and symptoms of respiratory depression and sedation. |

**Table 6. Warnings/Precautions1**

|  |  |
| --- | --- |
| **Warning/Precaution** | Addiction, abuse and misuse; as an opioid, Arymo® ER (morphine extended-release) exposes users to the risks of addiction, abuse and misuse. Extended-release products such as Arymo® ER (morphine extended-release) deliver the opioid over an extended period of time, and there is a greater risk of overdose and death due to the larger quantity of morphine present. Although the risk of addiction in any individual is not known, it can occur in patients appropriately prescribed Arymo® ER (morphine extended-release) at the recommended dosages. Patients at increased risk may be prescribed opioids, but use in such patients necessitates intensive counseling regarding the risks and appropriate use of Arymo® ER (morphine extended-release), along with intensive monitoring for signs of addiction, abuse, and misuse. Abuse or misuse of Arymo® ER (morphine extended-release) by crushing, snorting, or injecting the dissolved product may compromise some of the extended-release properties and cause delivery of morphine that could result in overdose and death. |
| Neonatal opioid withdrawal syndrome; prolonged use of Arymo® ER (morphine extended-release) during pregnancy can result in withdrawal in the neonate. 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 appropriate treatment will be available. |
| Risks due to interactions with CNS depressants; hypotension, profound sedation, coma, respiratory depression, and death may result if Arymo® ER (morphine extended-release) is used concomitantly with alcohol or other CNS depressants (e.g. benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids). If prescribing a benzodiazepine or other CNS depressant concomitantly with an opioid, prescribe the lowest effective dosages and the minimum durations of concomitant use. Monitor patients for signs and symptoms of respiratory depression and sedation. |
| Risk of life-threatening respiratory depression in the elderly, cachectic and debilitated patients and patients with significant chronic obstructive pulmonary disease or cor pulmonale; life-threatening respiratory depression is more likely to occur in elderly, cachectic or debilitated patients and patients with significant chronic obstructive pulmonary disease or cor pulmonale. Monitor these patients closely when initiating and titrating Arymo® ER (morphine extended-release) and when this agent is given concomitantly with other drugs that cause respiratory depression. |
| Adrenal insufficiency; cases of adrenal insufficiency have been reported with opioid use, often after at least one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms, such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. The patient should be weaned off of the opioid and corticosteroid treatment should be continued until adrenal function recovers. |
| Severe hypotension; Arymo® ER (morphine extended-release) 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 is already compromised by a reduced blood volume or concomitant CNS depressant drugs. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Arymo® ER (morphine extended-release). Avoid use in patients with circulatory shock, as Arymo® ER (morphine extended-release) may cause vasodilation that further reduces cardiac output and blood pressure in these patients. |
| Increased intracranial pressure, brain tumors, head injury, or impaired consciousness; in patients who may be susceptible to the intracranial effects of CO2 retention (e.g. those with evidence of increased intracranial pressure or brain tumors), Arymo® ER (morphine extended-release) may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor these patients for signs of sedation and respiratory depression. |
| Difficulty in swallowing and risk for obstruction in patients at risk for a small gastrointestinal lumen; the stickiness of moistened Arymo® ER (morphine extended-release) tablets may lead to difficulty in swallowing the tablets, and may also predispose patients to intestinal obstruction and exacerbation of diverticulitis, especially in patients with underlying gastrointestinal disorders, such as esophageal cancer or colon cancer with a small gastrointestinal lumen. Consider use of an alternative analgesic in patients who have difficulty swallowing and in those at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen. |
| Increased risk of seizures in patients with seizure disorders; Arymo® ER (morphine extended-release) 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 treatment. |
| Withdrawal; Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing Arymo® ER (morphine extended-release), gradually taper the dosage; do not abruptly discontinue. |
| Risks of driving and operating machinery; Arymo® ER (morphine extended-release) may impair the mental or physical abilities necessary to perform potentially hazardous activities, such as driving a car or operating machinery. Patients should be warned not to drive or operate dangerous machinery unless they are tolerant to this agent and know how they will be affected by its use. |

**Contraindications**

**Table 7. Contraindications1**

|  |  |
| --- | --- |
| **Contraindication** | Arymo® ER (morphine extended-release) is contraindicated in patients with significant respiratory depression. |
| Arymo® ER (morphine extended-release) is contraindicated in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment. |
| Arymo® ER (morphine extended-release) is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. |
| Arymo® ER (morphine extended-release) is contraindicated in patients with hypersensitivity to morphine or any other components of Arymo® ER (morphine extended-release). |
| Arymo® ER (morphine extended-release) is contraindicated in patients using MAOIs or that have used MAOIs within the last 14 days. |

**Adverse Effects**

The safety and efficacy of Arymo® ER (morphine extended-release) was based upon data for MS Contin® (morphine extended-release). As such, there are no adverse reactions that have been reported that are specific to Arymo® ER (morphine extended-release), and the adverse effect profile is expected to be similar to that of MS Contin® (morphine extended-release) and other morphine products.

In clinical trials, the most common adverse reactions associated with morphine extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoric mood.1

**Drug Interactions**

**Table 8. Drug Interactions1,16**

| **Interacting Medication or Disease** | **Interaction Severity Rating\*** | **Potential Result** |
| --- | --- | --- |
| Anticholinergic Drugs | Major | The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when using opioids concomitantly with anticholinergic agents. |
| Benzodiazepines/ Other CNS Depressants | Major | Due to their additive pharmacologic effect, the concomitant use of opioids and benzodiazepines or other CNS depressants may increase the risk of respiratory depression, profound sedation, coma and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, and limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. |
| Cimetidine | Major | Concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma and death. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dose of Arymo® ER (morphine extended-release) and/or cimetidine as necessary. |
| Cyclosporine | Major | Concurrent use of cyclosporine and morphine may result in increased morphine exposure, increased risk of abnormalities or malfunction of the nervous system. |
| Donepezil | Major | The use of donepezil has been associated with a reduction in the seizure threshold. When donepezil is used with other agents that may lower the seizure threshold, treatment should be initiated at low doses and increases in dose should take place gradually. |
| Mixed Agonist/Antagonist and Partial Agonist Opioids | Major | The use of these agents may reduce the analgesic effect of Arymo® ER (morphine extended-release) or precipitate withdrawal symptoms. Avoid concomitant use with these agents. |
| Monoamine Oxidase Inhibitors (MAOIs) | Major | MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). Do not use Arymo® ER (morphine extended-release) in patients taking MAOIs or within 14 days of stopping MAOIs. |
| Muscle Relaxants | Major | Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and result in an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected. Decrease the dose of Arymo® ER (morphine extended-release) and/or the muscle relaxant as necessary. |
| P-glycoprotein (P-gp) inhibitors (e.g., quinidine) | Major | Concomitant use of P-gp inhibitors can increase the exposure to morphine by approximately two-fold and can increase the risk of hypotension, respiratory depression, profound sedation, coma and death. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Arymo® ER (morphine extended-release) and/or the P-gp inhibitor as necessary. |
| Serotonergic Drugs | Major | Concomitant use of opioids and serotonergic drugs has resulted in serotonin syndrome. If concomitant use is necessary, carefully observe the patient, particularly during treatment initiation and dose adjustments. If serotonin syndrome is suspected, discontinue Arymo® ER (morphine extended-release). |
| Diuretics | Moderate | Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure. Increase the dose of the diuretic as necessary. |
| Esmolol | Moderate | Concurrent use of esmolol and morphine may result in esmolol toxicity (bradycardia, hypotension). |
| Gabapentin | Moderate | Concurrent use of gabapentin and morphine may result in increased gabapentin concentrations. |
| Ginseng | Moderate | Concomitant use of opioids with ginseng may result in decreased efficacy of analgesia of opioids. |
| Kava | Moderate | Concomitant use of opioids with kava may result in increased CNS depression. |
| Rifampin | Moderate | Concomitant use of morphine and rifampin may result in loss of morphine efficacy. |
| Somatostatin | Moderate | Concurrent use of somatostatin and morphine may result in reduced analgesia with morphine. |
| Trospium | Moderate | Concurrent use of morphine and trospium may result in increased serum concentrations of morphine and/or trospium, potentially increasing risk of paralytic ileus. |
| Valerian | Moderate | Concomitant use of opioids with valerian may result in increased CNS depression. |
| Yohimbine | Moderate | Concurrent use of morphine and yohimbine may result in increased analgesic and adverse effects of morphine. |

\*Severity rating per Micromedex

**Patient Monitoring Guidelines**

Before starting therapy with an opioid, individuals should be evaluated for potential signs of addiction, abuse or misuse of medications; risks are increased in patients with a personal or family history of substance abuse or mental illness, but the potential for these risks should not prevent the proper management of pain. If therapy with an opioid is started, they should continue to be monitored frequently for any changes in behavior. While the individual is receiving opioid analgesics they should be monitored for adequacy of analgesia as well as continually assessed for the need of continued opioid treatment.1

The following signs and symptoms should be monitored during therapy with opioids:

* respiratory depression and sedation; especially within the first 24 to 72 hours after initiating therapy and following dose increases; and particularly in high risk patients (elderly, cachectic, or debilitated patients, those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve, and those who may be susceptible to the intracranial effects of CO2 retention)
* exacerbation of biliary tract disease
* hypotension; in ambulatory patients and in those whose ability to maintain blood pressure has been compromised; especially after initiating therapy or titrating the dose
* worsened seizure control; in patients with a history of seizure disorders
* signs of abuse, misuse and addiction

**References**

1. Arymo® ER [package insert]. Wayne (PA): Egalet US Inc; 2017 Jan.
2. Arymo® ER (morphine sulfate extended-release) product Dossier. 2017 Mar. Egalet Corporation. Data on file.
3. Egalet Announces FDA Acceptance of New Drug Application for ARYMO™ ER (Morphine Sulfate) Extended-Release Tablets [press release on the internet]. PR Newswire Association LLC; 2016 Feb 29 [cited 2017 May 9]. Available from: <http://www.prnewswire.com/news-releases/egalet-announces-fda-acceptance-of-new-drug-application-for-arymo-er-morphine-sulfate-extended-release-tablets-300227415.html>.
4. Smith MD, Webster LR, Lawler J, Lindhardt K, Dayno JM. Human Abuse Potential of an Abuse-Deterrent (AD), Extended-Release (ER) Morphine Product Candidate (Morphine-ADER Injection-Molded Tablets) versus Extended-Release Morphine Administered Orally in Nondependent Recreational Opioid Users. Pain Medicine. 2016 Sep 13;00:1-10.
5. Webster LR, Smith MD, Lawler J, Lindhardt K, Dayno JM. Human Abuse Potential of an Abuse-Deterrent (AD), Extended-Release (ER) Morphine Product Candidate (Morphine-ADER Injection-Molded Tablets) vs Extended-Release Morphine Administered Intranasally in Nondependent Recreational Opioid Users. Pain Medicine. 2016 Sep 20;00:1-11.
6. Egalet Announces FDA Advisory Committees Recommend Approval of Abuse-Deterrent ARYMO™ ER (Morphine Sulfate) and Reports Second Quarter 2016 Financial Results [press release on the internet]. Wayne (PA): Egalet Corporation. 2016 Aug 4 [cited 2017 May 9]. Available from: <http://egalet.investorroom.com/2016-08-04-Egalet-Announces-FDA-Advisory-Committees-Recommend-Approval-of-Abuse-Deterrent-ARYMO-ER-Morphine-Sulfate-and-Reports-Second-Quarter-2016-Financial-Results>.
7. U.S. Food and Drug Administration. Impact of Exclusivity on Approval of Arymo ER [press release on the internet]. Silver Spring (MD): U.S Food and Drug Administration; 2017 Jan 9 [cited 2017 May 9]. Available from: <https://www.fda.gov/Drugs/DrugSafety/ucm535708.htm>.
8. Trescot AM, Datta S, Lee M, Hansen H. Opioid Pharmacology. Pain Physician. 2008 Mar;11(2 Suppl):S133-153.
9. MorphaBond® ER [package insert]. Basking Ridge (NJ): Daiichi Sankyo, Inc.; 2017 Feb.
10. Hysingla ER® [package insert]. Stamford (CT): Purdue Pharma L.P.; 2016 Dec.
11. OxyContin® [package insert]. Stamford (CT): Purdue Pharma L.P.; 2016 Dec.
12. U.S. Food and Drug Administration. Opioid Medications; Information on Opioid Medications [webpage on the internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 Nov 25 [cited 2017 May 9]. Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm.
13. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017 [cited 2017 May 9]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/.
14. Vuilleumier PH, Stamer UM and Landau R. Pharmacogenomic considerations in opioid analgesia. Pharmacogenomics and Personalized Medicine. 2012;5:73-87.
15. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, Dale O, et al. Influence from genetic variability on opioid use for cancer pain: A European genetic association study of 2294 cancer pain patients. PAIN. 2011;152(5): 1139-1145.
16. Micromedex® Healthcare Series [database on the internet]. Cambridge (MA): Truven Health Analytics; Updated periodically [cited 2017 May 9]. Available from: http://www.thomsonhc.com/.