Drug Monograph

Introduction

Generic Name: morphine sulfate/naltrexone hydrochloride extended-release capsule
Trade Name: Embeda®
Dosage form: Extended-release capsule
National Drug Code (NDC) #: 60793-0430-20, 60793-0431-20, 60793-0433-20, 60793-0434-20, 60793-0435-20, 60793-0437-20
Manufacturer: Actavis Elizabeth LLC for Pfizer Inc.
Classification: Agonist / Antagonist combination, Delivery System, Combination

Executive Summary

Embeda® (morphine sulfate/naltrexone hydrochloride) extended-release capsules are being evaluated by the Drug Formulary Commission to be considered for inclusion on the Massachusetts formulary of therapeutically equivalent substitutions, as outlined in Chapter 258 of the Acts of 2014, as it is currently the only abuse-deterrent formulation of extended-release morphine sulfate approved by the Food and Drug Administration (FDA) and available in the marketplace.

Embeda® (morphine sulfate/naltrexone hydrochloride) is a combination opioid agonist and opioid antagonist approved by FDA for the management of pain severe enough to require daily, around-the-clock opioid, long-term opioid treatment for which alternative treatment options are inadequate. It is not intended for use as an as-needed analgesic. The FDA has designated this drug a schedule II controlled substance due to the associated risks of addiction, abuse, and misuse, even at recommended treatment doses. Similar to other extended-release opioid analgesics, it is also associated with greater risks of overdose and death.[1]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[2] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third extended-release opioid analgesic to obtain this designation and the first among the morphine extended-release products.[3]

Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[1] Morphine sulfate is a pure opioid agonist and is relatively selective for the μ-receptor; although. at higher doses it may interact with other opioid receptors. Naltrexone is a centrally-acting, μ-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid agonists by competitively binding at the mu-opioid receptors. If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[1]

Embeda® (morphine sulfate/naltrexone hydrochloride) has been shown to be effective in treating pain and relatively safe in clinical studies.[4-10] It also demonstrated to be “less preferred” for “drug liking” and “high” effects in a crushed formulation administered as an oral solution to morphine sulfate extended-release (MS Contin®) administered in a crushed formulation as an oral solution.[7] Similarly, crushed Embeda® (morphine sulfate/naltrexone hydrochloride) pellets was rated lower for “drug liking” when administered intranasally compared with crushed morphine sulfate extended-release (MS Contin®), but was rated higher than placebo.[8]

Embeda® (morphine sulfate/naltrexone hydrochloride) is an additional long-acting morphine sulfate preparation available for the management of pain that may deter abuse by the standard means of crushing, snorting, and/or injecting. If abused or misused, it does pose a danger of accidently precipitating withdrawal

in opioid tolerant individuals. Similar to other long-acting opioids, it carries a black box warning regarding addiction, abuse, misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, and interactions with alcohol.[1]

Reference Data

Embeda® (morphine sulfate/naltrexone hydrochloride) extended-release is a combination opioid agonist and opioid antagonist approved by the Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock opioid, long-term opioid treatment for which alternative treatment options are inadequate. It is not intended for use as an as-needed analgesic. The FDA has designated this drug a schedule II controlled substance due to the associated risks of addiction, abuse, and misuse, even at recommended treatment doses. Similar to other extended-release opioid analgesics, it is also associated with greater risks of overdose and death.[1]

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Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[1] Morphine sulfate is a pure opioid agonist and is relatively selective for the μ-receptor; although at higher doses it may interact with other opioid receptors. The primary therapeutic effect of morphine is analgesia; however, it may also result in dysphoria, euphoria, somnolence, respiratory depression, changes in gastrointestinal motility, histamine release, physical dependence, and alterations in the circulatory, endocrine, and autonomic nervous systems. Naltrexone is a centrally-acting, μ-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid agonists by competitively binding at the μ-opioid receptors. When Embeda® (morphine sulfate/naltrexone hydrochloride) is taken orally as directed, the morphine relieves pain while the sequestered naltrexone passes through the body with no clinical effect. However, if Embeda® (morphine sulfate/naltrexone hydrochloride) is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death. Due to the presence of talc as one of the product excipients, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.[1]

Embeda® (morphine sulfate/naltrexone hydrochloride) is the only oral agent in an extended-release capsule formulation that utilizes a sequestered core of the μ-opioid antagonist, naltrexone. Morphine sulfate in extended-release formulations are available as MS Contin® and Kadian®.[11,12] A third extended-release formulation of morphine sulfate (Avinza®) was discontinued by the manufacturer in July 2015; however a generic version of this agent does remain commercially available.[13,14] These preparations do not currently have formulations designated by the FDA to be abuse deterrent. Table 1 outlines the currently available, long-acting opioid therapies and whether they have a designated abuse deterrent formulation available per package labelling.

Table 1. Long-Acting Opioid Availability[15]

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Buprenorphine (Belbuca®, Butrans®)	-	✓
Fentanyl (Duragesic®)	-	✓
Hydrocodone (Hysingla ER®)	✓	✓
Hydrocodone (Zohydro ER®)	-	✓
Hydromorphone (Exalgo®)	-	✓
Levorphanol (Levo-Dromoran®)	-	✓
Methadone (Diskets Dispersible®, Dolophine®, Methadose®, Methadone Intensol®)	-	✓

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Morphine sulfate (Avinza®, Kadian®, MS Contin®)	-	✓
Morphine sulfate/naltrexone (Embeda®)	✓	✓
Oxycodone (OxyContin®)	✓	✓
Oxycodone/naloxone (Targiniq®)	✓	-
Oxymorphone (Opana® ER)	-	✓
Tapentadol (Nucynta ER®)	-	✓

Therapeutic Indications/Efficacy

The available efficacy and safety studies, as well as trials assessing the abuse-deterrence of Embeda® (morphine sulfate/naltrexone hydrochloride), are outlined in Table 2.[4-10]

A multicenter, randomized, double-blind, placebo-controlled, 12-week trial involving 547 patients with osteoarthritis evaluated the efficacy of Embeda® (morphine sulfate/naltrexone hydrochloride). The mean change in weekly diary brief pain inventory (BPI) average pain scores from randomization baseline to week 12 were found to be statistically significant in the Embeda® (morphine sulfate/naltrexone hydrochloride) group compared with the placebo group (–0.2 ± 1.9 vs 0.3 ± 2.1; P=0.045). Statistically significant differences in average pain intensity, in-clinic BPI score, and weekly diary BPI (worst, least, and current pain) were seen with Embeda® (morphine sulfate/naltrexone hydrochloride) from randomization throughout week 12 of the maintenance phase. Responder rates at the time of completion of the maintenance phase favored the active treatment. A greater number of patients in the active treatment group compared to the placebo group experienced ≥30% improvement from baseline in pain scores (72.5% vs 57.8%; P=0.005); however, the rates for those with ≥20%, ≥40%, and ≥50% improvement were not statistically significant.[5]

A phase II, double-blind, multicenter, cross-over, randomized controlled trial demonstrated clinical efficacy and bioequivalence of Embeda® (morphine sulfate/naltrexone hydrochloride) with morphine sulfate extended-release (Kadian®).[4] The rate of morphine absorption was similar for Embeda® (morphine sulfate/naltrexone hydrochloride) and morphine sulfate extended-release. Summed mean scores, mean change from baseline, and daily scores for worst, least, average, and current pain were not appreciably different between treatments. There were also no significant differences between treatments in the physical function, or composite index subscale scores; however, there was a small but statistically significant difference for the stiffness subscale score, favoring Embeda® (morphine sulfate/naltrexone hydrochloride) vs morphine sulfate extended-release (2.5 vs 12.3, respectively; P=0.02).

Embeda® (morphine sulfate/naltrexone hydrochloride) has been evaluated in abuse deterrent studies.[6-10] In a study evaluating intact morphine sulfate/naltrexone hydrochloride capsules administered orally compared to orally-administered crushed morphine sulfate/naltrexone hydrochloride pellets as an oral solution, morphine sulfate oral solution, and placebo, the mean effects of treatment based on the visual analogue scale (VAS) for drug likability were: 67.6, 68.1, 89.5, and 52.2 for the intact capsules, crushed pellets, morphine sulfate solution, and placebo groups, respectively (P<0.001 for all comparisons except intact vs. crushed pellets, P=not significant).[6]

In a drug likability study comparing crushed Embeda® (morphine sulfate/naltrexone hydrochloride) 120 mg/4.8 mg pellets administered as an oral solution with crushed morphine sulfate controlled-release (CR) (MS Contin®) 120mg administered as an oral solution and placebo, higher VAS scores for “drug liking” and “drug high” were reported for crushed morphine sulfate CR over placebo, crushed morphine sulfate CR over crushed Embeda® (morphine sulfate/naltrexone hydrochloride) pellets, and crushed Embeda® (morphine sulfate/naltrexone hydrochloride) pellets over placebo.[7]

Crushed Embeda® (morphine sulfate/naltrexone hydrochloride) 30 mg/1.2 mg pellets administered intranasally was compared with crushed morphine sulfate CR (MS Contin®) 30 mg tablets administered intranasally and placebo to evaluate the "drug liking" and "high" effects among recreational opioid users. The maximum effect for "drug liking" on the VAS scale rated crushed intranasal morphine sulfate CR higher than crushed intranasal morphine sulfate/naltrexone hydrochloride, and both agents higher than placebo (69.6, 87.6, and 50.9, respectively; (P<0.001 all comparisons). The same preferential ratings observed on the VAS scale (86.6, 55.2, and 3.7, respectively; P<0.001 all comparisons).[8]

Among experienced, non-dependent, male opioid users in a clinical simulation study aimed to mimic the effects of injected morphine sulfate/naltrexone hydrochloride. Patients received one of three, single-dose courses of a 30mg intravenous (IV) bolus of morphine immediately followed by an IV bolus of naltrexone placebo within 30 seconds, a 30mg IV bolus of morphine immediately followed by a 1.2 mg IV bolus of naltrexone, and an IV bolus of morphine placebo immediately followed by an IV bolus of naltrexone placebo. The primary endpoint of assessing "How high are you now?" the mean maximum effect for the morphine sulfate/naltrexone hydrochloride, morphine, and placebo groups were: 29.8 ± 26.4 (P<0.0001 vs morphine; P<0.0001 vs placebo), 85.2 ± 12.9 (P<0.0001 vs placebo), and 0.0 ± 0.0, respectively. Both the morphine sulfate/naltrexone hydrochloride and morphine groups had similar time to maximum effect of 6 minutes compares with 0 minutes for the placebo group.[9]

A pharmacokinetic study assessing the bioavailability of crushed morphine sulfate/naltrexone hydrochloride pellets with intact morphine sulfate/naltrexone hydrochloride capsules and naltrexone oral solution was conducted by Johnson et al.[10] In this study, plasma concentrations of naltrexone were not significantly different between crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution at any assessment time. After the administration of the intact morphine sulfate/naltrexone hydrochloride capsules, plasma naltrexone was below the lower level of quantitation (4 pg/mL) in all but one patient who had a single value of 5.50 pg/mL at 72 hours post-dose. The first quantifiable plasma naltrexone concentrations occurred at 0.5 hour after administration, and peak concentrations were attained at one hour after the administration of crushed morphine sulfate/ naltrexone hydrochloride pellets and naltrexone solution. The area und the curve for morphine not significantly different whether morphine sulfate/naltrexone hydrochloride was crushed or administered whole; however, peak exposure to morphine after the administration of the crushed pellets was approximately three-fold greater than that with the intact capsules. The maximum plasma concentration was reached by 2.00 hours with the crushed morphine sulfate/naltrexone hydrochloride pellets compared to 7.03 hours with intact morphine sulfate/naltrexone hydrochloride capsules.

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Katz et al[4] Morphine sulfate/naltrexone hydrochloride titrated to effective dose between 20 mg and 160 mg BID vs morphine sulfate CR (Kadian®) titrated to effective dose between 20 mg and 160 mg BID This trial consisted of five periods: washout, dose titration, first active treatment, OL morphine sulfate extended-release, cross over to alternate active treatment, OL morphine sulfate extended-release.	Phase II, DB, MC, RCT, XO Adults in good health based upon medical history, physical examination, laboratory profile, and ECG who had chronic pain due to OA of the knee or hip based upon ACR criteria and required treatment with non-opioid analgesics or received opioid therapy equivalent to ≤40 mg/day of oral morphine	N=113 Two 14-day treatment periods	Primary: Pharmacokinetic assessment of morphine sulfate and naltrexone after multiple doses Secondary: Mean change from baseline of in-clinic pain intensity; least, worst, and current pain intensity based on BPI scores, and mean change from baseline WOMAC scores	Primary: Overall, mean morphine concentrations over time on day 14 of periods two and four were similar for both treatments. Mean morphine C_{max} was 14.1 ng/mL for morphine sulfate/naltrexone hydrochloride and 12.4 ng/mL for morphine sulfate CR. Rate of morphine absorption was similar for morphine sulfate/naltrexone hydrochloride and morphine sulfate CR (median T_{max}, 4.0 and 5.0 hours, respectively). Steady state plasma morphine exposure over the 12-hour dosing interval, demonstrated comparable bioavailability (AUC mean ratio, 0.93; 95% CI, 0.824 to 1.069). Plasma naltrexone concentrations were below the LLOQ (4.00 pg/mL) for most patients. Among 55 patients with quantifiable 6-β-naltrexol levels, mean C_{max} and AUC of 6-β -naltrexol were 31.3 pg/mL and 308.6 pg*h/mL. Median T_{max} was 3.0 hours. Secondary: After the washout period, the mean in-clinic pain intensity scores were 7.1 ± 1.5. After dose stabilization on morphine sulfate CR, mean scores for in-clinic pain were 2.1 ± 1.0 and remained low for both treatment groups. At day 14, summed mean scores, mean change from baseline, and daily scores for worst, least, average, and current pain were not appreciably different between treatments (data not reported). Daily diary scores were also similar between treatments for worst, least, average, and current pain (data not reported).

				There were no significant differences between treatments in change from baseline scores for pain, physical function, or composite index subscales (data not reported). There was a small but statistically significant difference for the stiffness subscale score, favoring morphine sulfate/naltrexone hydrochloride vs morphine sulfate CR (2.5 vs 12.3, respectively; P=0.02). On the Global Assessment of Study Medication rating, most patients in the morphine sulfate/naltrexone hydrochloride and morphine sulfate CR groups rated their treatment as good, very good, or excellent (91.5% and 78.9%, respectively). A total of 83.8% of patients experienced an adverse event during open-label morphine sulfate CR, 45.1% during double-blind morphine sulfate CR, and 46.5% during double-blind morphine sulfate/naltrexone hydrochloride. The top three reported events were constipation, nausea, and somnolence.
Katz, Hale, et al[5] Morphine sulfate/naltrexone hydrochloride; original formulation (dose determined during titration phase for opioid naïve and opioid-experienced patients up to a maximum of 160 mg daily) vs placebo	DB, MC, PC, RCT Patients ≥21 years of age with osteoarthritis of the hip or knee (functional class I to III) requiring chronic treatment within the prior 90 days, who were unable to control the pain with non-opioid analgesics, tramadol, or another at a dose equivalent	N=547 12 weeks (maintenance phase)	Primary: Mean change in weekly diary BPI average pain score from randomization baseline to week 12 Secondary: In-clinic BPI, and weekly diary BPI (worst, least, current, and average pain scores over the past 24 hours), average pain scores over maintenance	Primary: The mean change in weekly diary BPI average pain scores from randomization baseline to week 12 were found to be statistically significant in the morphine sulfate/naltrexone hydrochloride compared with placebo group (–0.2 ± 1.9 vs 0.3 ± 2.1; P=0.045). Secondary: Statistically significant differences in average pain intensity, in-clinic BPI score, and weekly diary BPI (worst, least, current pain) were seen with morphine sulfate/naltrexone hydrochloride from randomization throughout week 12 of the maintenance phase. The mean score change (SD) in diary pain scores from baseline to week 12 for the morphine sulfate/naltrexone hydrochloride and placebo groups, respectively were the following: “Worst pain” score: 0.3 (2.0) vs 0.9 (2.0); P=0.003 “Least pain” score: 0.3 (1.8) vs 0.8 (1.8); P=0.036

This trial followed an enriched-enrollment, randomized withdrawal (EERW) design and consisted of three periods: washout, titration, and maintenance	of ≤40 mg/day of oral morphine sulfate, had an average 24-hour pain intensity score ≥5 (on 11-point pain scale [0=no pain; 10=pain as bad as you can imagine]) at baseline after cessation of previous medications		phase, and patient assessments of WOMAC Osteoarthritis Index	"Current pain" score: 0.4 (2.0) vs 0.9 (2.1); P=0.026 "Average pain" score: 0.3 (1.9) vs 0.9 (1.9); P0.003 "In-clinic pain" score: 0.7 (2.3) vs 1.5 (2.3); P=0.002. The diary average-pain score averaged over the entire maintenance period was 0.1 (1.4) vs 0.7 (1.5); P=0.001, for the morphine sulfate/naltrexone hydrochloride and placebo groups, respectively. Changes from randomization baseline in WOMAC composite index and pain subscale scores favored the morphine sulfate/naltrexone hydrochloride group vs the placebo group (P=0.031 and P=0.023, respectively) at week 12 of maintenance. Responder rates at the time of completion of the maintenance phase favored the active treatment. More patients in the active treatment group than the placebo group experienced ≥30% improvement from the titration baseline visit in-clinic assessment of pain scores (72.5% vs 57.8%; P=0.005). The rates for those with ≥20%, ≥40%, and ≥50% improvement were not statistically significant. A total of 63.4% of patients during the titration phase experienced ≥1 adverse event, most commonly constipation, nausea, and somnolence. Three patients had a serious adverse event, of which only one event (hypotension) was deemed possibly or probably related to the study drug. During the maintenance period, the incidence of adverse events was similar between the morphine sulfate/naltrexone hydrochloride and placebo groups (53.2% vs 48.6%, respectively, P=0.391). The most common events were diarrhea and nausea. During the study, there were no patients experiencing opioid withdrawal while taking morphine sulfate/naltrexone

				hydrochloride as directed.
Stauffer et al[6] Morphine sulfate/naltrexone hydrochloride 120 mg (two-60 mg intact capsules) vs morphine sulfate/naltrexone hydrochloride 120 mg as crushed pellets dissolved in apple juice vs morphine sulfate oral solution 120 mg vs placebo This trial consisted of three periods: screening/ qualifying period, double-blind treatment sessions (i.e., four 2-night inpatient treatment sessions, each separated by a 14- to 21-day washout period) and post-treatment follow-up.	DB, PC, TD, XO RTC Patients (men and non-pregnant and non-lactating women) ages 18 to 55 years with a BMI of 21 to 31 kg/m^2 and weight >55 kg who were opioid users, not currently physically dependent based on DSM-IV criteria, and had used opioids non-therapeutically for psychoactive effects on ≥10 occasions within the previous year and at least once in the previous 12 weeks	N=32 Four SiD treatment sessions	Primary: Drug-liking visual analogue scale score, scores on items from the ARCI-MBG, Cole/ARCI stimulation-euphoria and abuse potential scales, SDV (at 12- and 24-hours after dosing), and pupillometry Secondary: Not reported	Primary: The mean (SD) effects of treatment based on the VAS for drug liking (scale 0 to 100) were: 67.6 (13.1), 68.1 (17.5), 89.5 (12.6), and 52.2 (4.5) for the intact capsules, crushed pellets, MSS, and placebo groups, respectively (P<0.001 for all comparisons except intact vs. crushed pellets, P=NS). The mean (SD) effects of treatment based on the ARCI-MBG scale (17-item questionnaire scored 0 to 3) were: 13.4 (12.5), 15.7 (13.5), 23.8 (12.8), and 9.4 (9.8) for the intact capsules, crushed pellets, MSS, and placebo groups, respectively (P<0.001 for all comparisons except intact capsules vs crushed pellets [P=NS], crushed pellets vs placebo [P=0.002] and intact capsules vs placebo [P=NS]). The mean (SD) effects of treatment based on the Cole/ARCI stimulation-euphoria scale (15-item questionnaire scored 0 to 3) were: 10.8 (11.2), 11.9 (11.3), 18.4 (11.6), and 6.9 (8.2) for the intact capsules, crushed pellets, MSS, and placebo groups, respectively (P<0.001, all comparisons except intact capsules vs crushed pellets [P=NS], crushed pellets vs placebo [P=0.007] and intact capsules vs placebo [P=NS]). The mean (SD) effects of treatment based on the Cole/ARCI abuse potential scale (12-item questionnaire scored 0 to 3) were: 5.9 (3.7), 6.3 (4.7), 8.7 (4.0), and 3.4 (2.9) for the intact capsules, crushed pellets, MSS, and placebo groups, respectively (P<0.001 for all comparisons except intact capsules vs crushed pellets [P=NS] and crushed pellets vs MSS [P=0.002]). The mean (SD) effects of treatment based on the SDV scale (6-item questionnaire) were: 14.22 (15.46). 13.72 (16.98), 28.85 (14.55), and 2.73 (7.08) for the intact capsules, crushed pellets, MSS, and placebo groups,

				respectively (P<0.001 for all comparisons except intact vs. crushed pellets, P=NS). The mean (SD) effects of treatment on minimum pupil diameter were: 3.20 (0.81), 3.43 (0.81), 2.70 (0.64), and 4.71 (0.92) for the intact capsules, crushed pellets, MSS, and placebo groups, respectively (P<0.001 for all comparisons except intact vs. crushed pellets, P=NS). Secondary: Not reported.
Setnik et al[7] Morphine sulfate/naltrexone hydrochloride 120 mg/4.8 mg pellets crushed and dissolved in cranberry juice x 1 for each treatment session vs morphine sulfate CR 120mg (MS Contin®) crushed and dissolved in cranberry juice x 1 for each treatment session vs placebo This study consisted of five phases: screening, naloxone challenge, drug discrimination, treatment, and follow-up.	DB, PC, RCT, SC, XO Patients 18 to 55 years of age with a BMI of 18.0 to 33.0 kg/m^2 who were recreational, non-physically dependent opioid users (determined by DSM-IV criteria and naloxone challenge test) who had used opioids for non-therapeutic purposes on ≥10 occasions within the past year and at least once in the 12 weeks prior to screening.	N=36 (treatment phase) Three SiD treatment sessions	Primary: "Drug liking" (at the moment) and "high" using 100-mm VAS Secondary: 100-mm unipolar VAS items (good drug effects, any drug effects, bad drug effects, feel sick, nausea, sleepy, and dizzy) measuring positive, negative, and any subjective effects, global assessments of take drug again and overall drug liking, Pupillometry, and safety	Primary: The effect of crushed morphine sulfate CR on each measure peaked within two hours after dosing and gradually declined to placebo levels by 24 hours post-dose. Participants receiving crushed morphine sulfate/naltrexone hydrochloride had reduced "drug liking" and "high" VAS scores vs those receiving crushed morphine sulfate CR at all time points, but higher scores vs those receiving placebo. Crushed morphine sulfate CR had significantly higher ratings than placebo on "drug liking" and "high" for E_{max} and AUE (0 to 2 hour) (P<0.0001). Crushed morphine sulfate/naltrexone hydrochloride had significantly lower scores for both E_{max} and AUE (0 to 2 hour) compared with crushed morphine sulfate CR (P<0.0001). The LSM difference for "Drug liking" E_{max} and "high" E_{max} comparing crushed morphine sulfate/naltrexone hydrochloride and crushed morphine sulfate CR was -15.7 (95% CI, -20.2 to -11.1; P<0.0001) and -34.9 (95% CI, -42.1 to -27.7; P<0.0001), respectively. The LSM difference for "Drug liking" AUE (0 to 2 hour) and "high" AUE (0 to 2 hour) comparing crushed morphine sulfate/naltrexone hydrochloride and crushed morphine

				sulfate CR was -24.9 (95% CI, -31.7 to -18.1; P<0.0001) and -51.1 (95% CI, -61.2 to -41.0; P<0.0001), respectively. Secondary: The mean VAS ratings of E_{max} and AUC (0–2h) for good drug effects, overall drug liking (24 hours post-dose), and take drug again (24 hours post-dose) were significantly lower for crushed morphine sulfate/naltrexone hydrochloride vs crushed morphine sulfate CR (P<0.005). The VAS ratings for crushed morphine sulfate/naltrexone hydrochloride were generally higher vs placebo, and significant differences were observed for good effects and overall drug liking (P<0.03) but not for take drug again. Crushed morphine sulfate/naltrexone hydrochloride resulted in significantly lower peak scores on all measures vs crushed morphine sulfate CR. Similar results were seen with AUE (0 to 2 hour) except for feel sick and nausea, where crushed morphine sulfate/naltrexone hydrochloride did not differ significantly from crushed morphine sulfate CR. Peak pupil diameter was significantly smaller for both crushed MSN and crushed morphine sulfate CR vs placebo (P<0.0001), but was significantly larger for crushed morphine sulfate/naltrexone hydrochloride vs crushed morphine sulfate CR (P<0.0001). Approximately 85% of the crushed morphine CR-treated patients reported TEAEs compared with approximately 31% of the crushed morphine sulfate/naltrexone hydrochloride-treated patients. The most commonly reported TEAEs (≥10% occurrence) after crushed morphine sulfate CR were nausea, vomiting, pruritus, dizziness, and hiccups. Somnolence was the only TEAE reported by ≥10% of participants after crushed

				morphine sulfate/naltrexone hydrochloride. No clinically important mean changes in vital sign values following treatment were observed.
Setnik, Goli et al[8] Morphine sulfate/naltrexone hydrochloride 30 mg/1.2 mg crushed pellets IN once vs morphine sulfate CR (MS Contin®) 30 mg crushed tablet IN once vs placebo This trial consisted of three phases: dose selection, drug discrimination and treatment.	DB, PC, SiD, RCT, XO Recreational opioid users (men and non-pregnant, non-lactating women) ages 18 to 55 years with a BMI of 18 to 33 kg/m^2 and weight ≥50 kg who used opioids for non-therapeutic purposes on ≥10 occasions within the past year and at least once in the 12 weeks, but were not dependent on opioids based on DSM-IV criteria naloxone challenge confirmation, and who were experienced with intranasal drug administration, defined as self-reported intranasal use on	N=33 Three SiD treatment sessions	Primary: "Drug liking" VAS and "high" VAS Secondary: Pupillometry, and VAS measures of: good and bad drug effects, any drug effects, feelings of sick, nausea, sleepy, and dizzy, and adverse events	Primary: Mean scores for each measure peaked within 1 hour after dosing with crushed morphine sulfate CR given IN and then gradually declined to near-placebo levels by 6 to 8 hour post-dose for "drug liking" VAS and by 12 hour post-dose for "high" VAS. Crushed morphine sulfate/naltrexone hydrochloride IN was associated with lower "drug liking" and "high" VAS scores compared with crushed morphine sulfate at all time points, including the mean peaks. The E_{max} for "drug liking" on the VAS scale for morphine sulfate/naltrexone hydrochloride, morphine sulfate CR, and placebo were: 69.6 (95% CI, 63.9 to 75.3), 87.6 (95% CI, 81.9 to 93.2), and 50.9 (95% CI, 45.3 to 56.5), respectively; representing significant differences between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR, morphine sulfate/naltrexone hydrochloride and placebo, and morphine sulfate CR and placebo (P<0.001 all comparisons). The E_{max} for "high" on the VAS scale for morphine sulfate/naltrexone hydrochloride, morphine sulfate CR, and placebo were: 55.2 (95% CI, 45.5 to 64.9), 86.6 (95% CI, 77.03 to 96.3), and 3.7 (95% CI, -6.0 to 13.3), respectively; representing significant differences between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR, morphine sulfate/naltrexone hydrochloride and placebo, and morphine sulfate CR and placebo (P<0.001 all comparisons). The AUE (0 to 2 hour) for "drug liking" on the VAS scale for morphine sulfate/naltrexone hydrochloride, morphine sulfate CR, and placebo were: 86.3 (95% CI, 77.7 to 94.9), 120.6 (95% CI, 112.2 to 129.0), and 73.1 (95% CI, 64.5 to

	at least three occasions within the past year			81.6), respectively; representing significant differences between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR (P<0.001), morphine sulfate/naltrexone hydrochloride and placebo (P=0.022), and morphine sulfate CR and placebo (P<0.001). The AUE (0 to 2 hour) for "high" on the VAS scale for morphine sulfate/naltrexone hydrochloride, morphine sulfate CR, and placebo were: 66.7 (95% CI, 50.5 to 82.8), 132.9 (95% CI, 116.6 to 149.1), and 6.1 (95% CI, -10.1 to -22.4), respectively; representing significant differences between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR, morphine sulfate/naltrexone hydrochloride and placebo, and morphine sulfate CR and placebo (P<0.001 all comparisons). Secondary: Pupil diameter remained consistent throughout the assessment time for placebo. Morphine sulfate CR was associated with a gradual decrease in mean pupil size up to 2 hour post-dose, the decrease was sustained up to 8 hour post-dose, and returned to near baseline levels at 24 hour post-dose. Mean pupil size decreased with morphine sulfate/naltrexone hydrochloride, but was less than morphine sulfate CR. The peak reduction (Emin) was significantly less after morphine sulfate/naltrexone hydrochloride vs morphine sulfate CR, but greater than that with placebo. The Emin for pupillometry for morphine sulfate/naltrexone hydrochloride, morphine sulfate CR, and placebo were: 3.8 (95% CI, 3.6 to 4.0), 3.3 (95% CI, 3.1 to 3.5), and 4.5 (95% CI, 4.3 to 4.7), respectively; representing significant differences between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR (P=0.002), morphine sulfate/naltrexone hydrochloride and placebo (P<0.001), and morphine sulfate CR and placebo (P<0.001).

				Bad drug effects, feeling sick, nausea, and dizzy on the VAS scale were not significantly different between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR or morphine sulfate/naltrexone hydrochloride and placebo. Morphine sulfate CR was associated with significantly higher E_{max} on bad drug effects and dizzy compared with placebo. The overall incidence of adverse events during the treatment phase was comparable between morphine sulfate/naltrexone hydrochloride and morphine sulfate CR (77 vs 79%, respectively); although morphine sulfate/naltrexone hydrochloride resulted in a lower incidence of euphoric mood vs morphine sulfate CR morphine sulfate CR (39% v 59%, respectively) and dizziness (3% vs 21%, respectively). The incidence of adverse events with placebo was 10%. TEAEs in vital signs were mild, transient and not clinically relevant.
Webster et al[9] Morphine 30 mg IV bolus once immediately followed by naltrexone placebo IV bolus vs morphine 30 mg IV bolus immediately followed naltrexone 1.2 mg IV bolus vs morphine placebo IV bolus immediately followed by naltrexone placebo IV bolus	DB, RCT, SC, XO Men ages 18 to 50 years who used prescription opioids to get a 'high' ≥5 times in the last 12 months, but were not physically opioid dependent, who were recreational abusers (only used opioids orally or snorted), in generally good health, and who had negative	N=28 Three SiD treatment sessions	Primary: Assessment of response to DEQ question #5 ("How high are you now?) Secondary: Response to the Cole/ARCI Stimulation-Euphoria Subscale, drug likability assessment from DEQ	Primary: The mean (±SD) E_{max} for the DEQ question #5 among the morphine + naltrexone, morphine, and placebo groups were: 29.8 ± 26.4 (P<0.0001 vs morphine; P<0.0001 vs placebo), 85.2 ± 12.9 (P<0.0001 vs placebo), and 0.0 ± 0.0, respectively. The median TE_{max} was six minutes (0.1 hour) for both of the morphine + naltrexone and morphine groups, and 0 minutes for placebo group. Secondary: The mean (±SD) E_{max} for Cole/ARCI stimulation-euphoria among the morphine + naltrexone, morphine, and placebo groups were: 13.7 ± 9.5 (P<0.0001 vs morphine; P<0.0001 vs placebo), 27.8 ± 11.2 (P<0.0001 vs placebo), and 1.3 ± 3.1, respectively. The median (±SD) T_{max} for Cole/ARCI stimulation-euphoria among the morphine + naltrexone, morphine, and placebo

This trial consisted of three phases: naloxone challenge, drug discrimination, and treatment.	urine drug screens for amphetamines, barbiturates, benzodiazepines, cocaine, and opioids			groups were: 0.1 hour, 0.3 hour, and 0.0 hour, respectively. The mean (±SD) E_{max} for the DEQ question #4 ("drug liking") among the morphine + naltrexone, morphine, and placebo groups were: 38.9 ± 30.5 (P<0.0001 vs morphine; P<0.0001 vs placebo), 81.4 ± 17.1 (P<0.0001 vs placebo), and 0.0 ± 0.0, respectively. The median (±SD) T_{max} for the DEQ question #4 ("drug liking") among the morphine + naltrexone, morphine, and placebo groups were: 0.1 hour, 0.3 hour, and 0.0 hour, respectively. A total of 75% of patients experienced a total of 69 adverse event; corresponding to 33.3% in the morphine + naltrexone group, 67.9% in the morphine group, and 7.4% in the placebo group.
Johnson et al[10] Morphine sulfate/naltrexone hydrochloride 60 mg/2.4 mg as crushed pellets dissolved in apple juice vs morphine sulfate/naltrexone hydrochloride 60 mg/2.4 mg intact capsule vs naltrexone hydrochloride 2.4 mg solution	OL, SC, SiD, RCT, XO Men and women (non-pregnant, non-lactating) ages 18 to 55 years who were deemed "healthy" and had no abnormal finding on physical examination, medical history taking, or clinical laboratory analysis, including positive urine samples for drugs of abuse (i.e.,	N=23 Three SiD treatment sessions	Primary: Pharmacokinetic assessments Secondary: Not reported	Plasma concentrations of naltrexone were not significantly different between crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution at any assessment time. The first quantifiable plasma naltrexone concentrations occurred at 0.5 hour after administration, and peak concentrations were attained at one hour after the administration of crushed morphine sulfate/ naltrexone hydrochloride pellets and naltrexone solution. The maximum mean (SD) naltrexone concentrations were 599 (408) and 629 (439) pg/mL with the crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution, respectively. After the administration of the intact morphine sulfate/naltrexone hydrochloride capsule, plasma naltrexone was below the LLOQ (4 pg/mL) in all but one patient who had a single value of 5.50 pg/mL at 72 hours post-dose.

	amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opioids).			The 90% CIs for the treatment (crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution) ratios of the natural logarithm-transformed naltrexone C_{max} (mean ratio, 98.5% [90% CI, 83.8 to 115.9]) and AUC (93.1% [90% CI, 84.4 to 102.7]) were within the regulatory range for assuming bioequivalence. Plasma concentrations of 6-β-naltrexol appeared similar after oral administration of crushed morphine sulfate/ naltrexone hydrochloride pellets and naltrexone solution. The first quantifiable plasma 6-β-naltrexol concentrations occurred at 0.5 hour post-dose and peak concentrations were attained at hour after the administration crushed morphine sulfate/naltrexone hydrochloride pellets and 1.5 hours after the administration of oral naltrexone solution. The maximum mean (SD) 6-β-naltrexol concentrations were 3,120 (994) and 3,570 (1360) pg/mL with crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution, respectively. The 90% CIs of the ratios for 6-β-naltrexol C_{max} and AUC (94.7% [90% CI, 86.3 to 104.0] and 92.2% [90% CI, 85.5 to 99.5], respectively) fell within the regulatory range for assuming bioequivalence of the crushed morphine sulfate/naltrexone hydrochloride pellets and naltrexone solution. The plasma morphine concentration–time profiles differed between crushed morphine sulfate/naltrexone hydrochloride pellets and the morphine sulfate/naltrexone hydrochloride intact capsules. At two hours post-dose, the mean plasma morphine concentration with crushed morphine sulfate/naltrexone hydrochloride pellets was approximately 15-fold greater than that with morphine sulfate/naltrexone hydrochloride

				intact capsules (26.1 vs 1.75 ng/mL, respectively). C_{max} was reached by 2.00 hours with the crushed morphine sulfate/naltrexone hydrochloride pellets, while T_{max} with the morphine sulfate/naltrexone hydrochloride intact capsule was 7.03 hours (range; 6.00 to 12.00 hours). The observed mean C_{max} with crushed morphine sulfate/ naltrexone hydrochloride pellets was 24.5 ng/mL, while mean C_{max} with the morphine sulfate/naltrexone hydrochloride intact capsule was 7.7 ng/mL, with natural logarithmic-transformed ratios for C_{max} outside of the regulatory range to assume bioequivalence (80 to 125%; ratio, 314%; 90% CI, 289 to 342). The systemic exposure based on AUC was significantly lower with crushed morphine sulfate/naltrexone hydrochloride pellets versus morphine sulfate/naltrexone hydrochloride intact capsules (mean ratio, 87.6% [90% CI, 78.0 to 98.3]). A total of 89 TEAEs were reported by 63% of patients. Of the reported TEAEs, 52% were deemed by investigators to be definitely related to the study treatment, (11%) probably related, 10% possibly related, and 27% unrelated. The most common adverse events were nausea (35%, 42%, and 13%) and emesis (26%, 29%, and 9%) in the crushed pellets, intact, and naltrexone groups, respectively. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: ACR=American College of Rheumatology, ARCI=Addiction Research Center Inventory, ARCI-MBG=Addiction Research Center Inventory-Morphine Benzedrine Group, AUC=area under the curve, AUE=area under the effective curve, BMI=body mass index, BPI=Brief Pain Inventory, Cole/ARCI=Cole/ Addiction Research Center Inventory, CI=confidence interval, C_{max}=maximum plasma concentration, CR=controlled (extended) release, DB=double-blind, MC=multicenter, DEQ=drug effects questionnaire, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th edition, ECG=electrocardiogram, E_{max}=maximum effect, Emin=peak reduction, IN=intranasally, LLOQ=lower limit of quantification, MSS=morphine sulfate solution, NS=not significant, OA=osteoarthritis, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, SC=single center, SD=standard deviation, SDV=subjective drug value, SiD=single dose, TD=triple dummy, TEAEs= treatment-emergent adverse events, TE_{max}=time to maximum effect, T_{max}=time to maximum concentration, VAS=visual analogue scale, WOMAC=Western Ontario and McMaster Universities, XO=crossover

Pharmacokinetics/Pharmacogenomics[1,16]

Absorption
Following the administration of morphine sulfate/naltrexone hydrochloride to healthy volunteers, approximately 50% of the morphine absorbed reached the systemic circulation after an average of eight hours. However, because of pre-systemic elimination, only about 20% to 40% of the morphine administered actually reaches systemic circulation. This is comparable with most forms of oral morphine.

Morphine sulfate/naltrexone hydrochloride (Embeda®) is bioequivalent to similar morphine sulfate extended-release capsule products such as Kadian®, with regard to the rate and extent of plasma morphine absorption. Median time to peak plasma morphine levels was shorter for morphine sulfate/naltrexone hydrochloride, (7.5 hours) as compared to Kadian® (10 hours).

Following single dose administration of intact morphine sulfate/naltrexone hydrochloride 60 mg/2.4 mg to 120 mg/4.8 mg, approximately 2% of blood samples had low plasma naltrexone levels (median=7.74 pg/mL; range 4 to 132 pg/mL); naltrexone was not detected in the remaining samples. Compared to 2.4 mg naltrexone oral solution, which produced mean (± standard deviation) naltrexone plasma levels of 689 (± 429 pg/mL) and mean (±SD) 6-β-naltrexol plasma levels of 3,920 (±1,350 pg/mL), administration of intact morphine sulfate/naltrexone hydrochloride 60 mg produced no naltrexone plasma levels and mean 6β-naltrexol plasma levels of 16.7 (±13.5 pg/mL). Trough levels of plasma naltrexone and 6-β-naltrexol did not accumulate upon repeated administration.

While co-administration with high fat foods reduces the rate and extent of morphine absorption, the total bioavailability is not affected. The sequestered naltrexone core is not consistently absorbed into systemic circulation following single dose administration when morphine sulfate/naltrexone hydrochloride is taken as directed, and administration with high-fat meals does not affect the sequestered naltrexone drug component.

Distribution
The volume of distribution of morphine is approximately 3 to 4 L/kg, and once absorbed, morphine is distributed to the skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Morphine is 30 to 35% reversibly bound to plasma proteins and primarily acts in the central nervous system (CNS) with only small quantities passing the blood brain barrier. Morphine also crosses the placental membrane.

Metabolism
Morphine is mainly metabolized by glucuronidation in the liver to 50% morphine-3-glucuronide (M3G), 5% to 15% morphine-6-glucuronide (M6G), and sulfation in the liver to morphine-3-etheral sulfate. A small fraction of less than 5% of morphine is demethylated. While M3G has not been shown to have any cause significant analgesic activity, M6G, which does not readily cross the blood brain barrier, has been shown to have opioid agonist and analgesic activity in humans. Naltrexone is extensively metabolized into 6-β-naltrexol.

Elimination
Elimination of morphine mainly occurs via hepatic metabolism and results in 55% to 65% glucuronide metabolites M3G and M6G, which are then renally excreted. Approximately 10% of morphine is excreted unchanged in the urine. A small amount of glucuronide metabolites are eliminated in the bile and there is minor enterohepatic cycling. Following a single dose, morphine has a terminal elimination half-life of approximately 29 hours.

There are no specific pharmacogenomics data reported for Embeda® (morphine sulfate/naltrexone hydrochloride).

Special Populations

Table 3. Special Populations[1]

Population	Precaution
Elderly	Clinical studies did not include sufficient numbers of individuals ≥65 years to determine whether they respond differently from younger individuals. The pharmacokinetic parameters in elderly individuals have not been evaluated.
Renal dysfunction	The pharmacokinetics of morphine may be altered in patients with renal failure. Individuals with renal failure were found to have an increase in the AUC of morphine. Metabolites, M3G and M6G, may also accumulate several-fold as compared with healthy subjects.
Hepatic dysfunction	The pharmacokinetics may be significantly altered in individuals with alcoholic cirrhosis, including reduced drug clearance with a corresponding increase in half-life. M3G and M6G to morphine plasma AUC ratios may also decrease in this population, indicating a decrease in metabolic activity.
Pregnancy / nursing	Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Opioids cross the placenta and may produce respiratory depression in neonates. Morphine is excreted in breast milk, with a milk-to-plasma morphine AUC ratio of approximately 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant and extent of first pass metabolism.
Children	The safety and efficacy in individuals less than 18 years of age have not been established.
Gender / Race	No meaningful differences were noted between male and female individuals in the analysis of pharmacokinetic data of morphine from clinical trials. No race-specific differences in pharmacokinetic data have been identified.

Dosage Forms[1]

Table 4.

Dosage form	Strengths	Special handling or storage
Capsule	20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg	Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F). Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Dosage Range[1]

Embeda® (morphine sulfate/naltrexone hydrochloride) is administered at a frequency of either once daily (every 24 hours) or twice daily (every 12 hours).

Adults:

Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate:

Initial dosage as the first opioid analgesic or in patients who are not opioid tolerant;

Embeda® (morphine sulfate/naltrexone hydrochloride) 20 mg/0.8 mg capsule orally every 24 hours.

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, or an equianalgesic dose of another opioid.

Conversion from other opioids to Embeda® (morphine sulfate/naltrexone hydrochloride)
There are no established conversion ratios from other opioids to Embeda® (morphine sulfate/naltrexone hydrochloride) defined by clinical trials. Discontinue all other around-the-clock opioid drugs when Embeda® therapy is initiated and initiate dosing using 30 mg orally every 24 hours.

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

Conversion from other oral morphine formulations to Embeda® (morphine sulfate/naltrexone hydrochloride)
Administer one-half of the patient's total daily oral morphine dose as Embeda® (morphine sulfate/naltrexone hydrochloride) twice daily, or by administering the total daily oral morphine dose as Embeda® (morphine sulfate/naltrexone hydrochloride) once daily. There are no data to support the efficacy or safety of prescribing this agent more frequently than every 12 hours.

Conversion from parenteral morphine or other opioids to Embeda® (morphine sulfate/naltrexone hydrochloride)
When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to Embeda® (morphine sulfate/naltrexone hydrochloride), consider the following general points:

- Parenteral to Oral Morphine Ratio: Between 2 mg and 6 mg of oral morphine may be required to provide analgesia equivalent to 1 mg of parenteral morphine. Typically, a dose of oral morphine that is three times the daily parenteral morphine requirement is sufficient.

- Other Oral or Parenteral Opioids to Oral Morphine Ratios: 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 Embeda® (morphine sulfate/naltrexone hydrochloride)
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.

The first dose of Embeda® (morphine sulfate/naltrexone hydrochloride) may be taken with the last dose of any immediate-release opioid medication due to the extended-release characteristics of the Embeda® (morphine sulfate/naltrexone hydrochloride) formulation.

Titration and maintenance dosing
Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. Continually re-evaluate and reassess the ongoing need for opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the Embeda® (morphine sulfate/naltrexone hydrochloride) dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 24 to 36 hours, Embeda® (morphine sulfate/naltrexone hydrochloride) doses may be adjusted every one to two days.

Discontinuation of therapy

Use a gradual downward titration of the dose every two to four days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue.

For breakthrough pain, increase the dose of Embeda® (morphine sulfate/naltrexone hydrochloride) or administer 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 Embeda® dose. In patients experiencing inadequate analgesia with once daily dosing of Embeda®(morphine sulfate/naltrexone hydrochloride), consider a twice daily regimen.

Elderly:
No specific dosing recommendations are available for individuals ≥65 years of age.

Pediatrics:
No specific dosing recommendations are available for individuals <18 years of age.

Renal or Hepatic Insufficiency:
No specific dosing recommendations are available for patients with either renal or hepatic insufficiency.

Gender:
No specific dosing recommendations are available based upon gender.

Special administration requirements:
Administer capsules whole. Do not crush, chew, or dissolve capsules. If unable to swallow capsules whole, sprinkle the capsule contents on applesauce and immediately swallow without chewing. Rinse the mouth to ensure all pellets have been swallowed.

Discard any unused portion of the Embeda® (morphine sulfate/naltrexone hydrochloride) capsules after the contents have been sprinkled on applesauce.

Do not administer Embeda® (morphine sulfate/naltrexone hydrochloride) pellets through a nasogastric or gastric tube.

Reserve the 100 mg/4 mg capsules only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.

Use the lowest effective dose to achieve pain control and prescribe the drug in the smallest appropriate quantity.

Precautions[1]
Embeda® (morphine sulfate/naltrexone hydrochloride) is a Schedule II controlled substance due to the morphine component and the risk of addiction, abuse, and misuse. Since modified-release products such as Embeda® (morphine sulfate/naltrexone hydrochloride) deliver the opioid component over an extended period of time, there is a greater risk for overdose and death due to the larger amount of morphine present. Misuse by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the morphine and can result in overdose and death and these methods of misuse and abuse may also release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Strategies to reduce the risks of addiction, abuse, and misuse include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.

Morphine preparations have the risk of impaired respiration due to respiratory depression. Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Thus, this medication should be used with caution in patients with

chronic obstructive pulmonary disease and in patients with significant respiratory impairments, including cor pulmonale, decreased respiratory reserve, hypoxia, and hypercapnia. Respiratory depressant effects may be exaggerated in the presence of head injury, pre-existing increases in intracranial pressure, the elderly, cachexia, and debilitated individuals. Interactions with other CNS depressants (e.g., alcohol, sedatives, anxiolytics, hypnotics, neuroleptics, and other opioids) may also increase the risk of respiratory depression, as well as hypotension and profound sedation or coma.

Embeda® (morphine sulfate/naltrexone hydrochloride) 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). It may also aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures

The use of mixed agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist analgesics (e.g., buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic should be avoided since the concomitant use may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Similar to all opioid therapies, Embeda® (morphine sulfate/naltrexone hydrochloride) impairs the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Due to possible spasms in the sphincter of Oddi, morphine sulfate/naltrexone hydrochloride should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Prolonged use during pregnancy may result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome may be life-threatening if not recognized and treated, particularly by neonatology experts.

Naltrexone does not interfere with thin-layer, gas-liquid, and high performance liquid chromatographic methods which may be used for the separation and detection of morphine, methadone, or quinine in the urine. Naltrexone may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Consult the test manufacturer for specific details.

Due to the potential for addiction, abuse, and misuse, the potential for life-threatening respiratory depression, the possibility of accidental ingestion, the risks of neonatal opioid withdrawal syndrome, and the significant interaction with alcohol consumption, this product also has a Black Box Warning.

Black Box Warning[1]

WARNING
Addiction, Abuse, and Misuse Embeda® (morphine sulfate/naltrexone hydrochloride) 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 Embeda®, (morphine sulfate/naltrexone hydrochloride) 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 Embeda®. Monitor for respiratory depression, especially during initiation of Embeda® (morphine sulfate/naltrexone hydrochloride) or following a dose increase. Instruct patients to swallow Embeda® (morphine sulfate/ naltrexone hydrochloride) capsules whole, or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving Embeda® (morphine sulfate/ naltrexone hydrochloride) can cause rapid release and absorption of a potentially fatal dose of morphine.

WARNING
Accidental Ingestion Accidental ingestion of even one dose of Embeda® (morphine sulfate/naltrexone hydrochloride), especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of Embeda® (morphine sulfate/naltrexone hydrochloride) 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 Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Embeda® (morphine sulfate/naltrexone hydrochloride). The co-ingestion of alcohol with Embeda® (morphine sulfate/naltrexone hydrochloride) may result in increased plasma level and a potentially fatal overdose of morphine.

Contraindications[1]

Embeda® (morphine sulfate/naltrexone hydrochloride) is contraindicated in patients with a known hypersensitivity (e.g., anaphylaxis) to morphine or naltrexone, significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, and in patients who have or are suspected of having paralytic ileus.

Adverse Drug Events

The adverse events reported in ≥2.0% of individuals in a long-term (12-week), open-label, safety study of non-malignant pain among 465 individuals, of which 124 individuals were treated for up to one year are outlined in Table 5.

Table 5. Adverse Reactions Reported by ≥2% of Subjects Treated with Embeda in a 12-Week Safety Study[1]

Adverse Event	Reported Frequency %; (N=465)
Constipation	31
Nausea	22
Vomiting	8
Somnolence	7
Headache	7
Pruritus	6
Fatigue	4
Dizziness	4
Dry mouth	4
Hyperhidrosis	3
Insomnia	3
Diarrhea	2
Anxiety	2

Drug Interactions

Table 6. Drug and Food Interactions[1,16]

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Alcohol (ethanol)	Major	Concomitant use of alcohol may result in increased morphine plasma levels and potentially fatal overdose of morphine. Counsel patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol.
Central nervous system (CNS) Depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, etc.)	Major	Caution should be used in patients concurrently taking other CNS depressants as they can increase the risk of respiratory depression, profound sedation, coma, and death. When used together, the dose of one or both agents should be reduced by at least 50%.
Mixed Agonist/Antagonist (pentazocine, nalbuphine, & butorphanol) and Partial Agonist (e.g., buprenorphine) Opioid Analgesics	Major	May reduce the analgesic effect and/or may precipitate withdrawal symptoms.
Muscle Relaxants	Major	Opioids may result in enhanced neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Monoamine Oxidase Inhibitors (MAOIs)	Major	May potentiate the effects of morphine, including respiratory and central nervous system depression, anxiety, confusion, and significant depression of respiration or coma. Concurrent use with MAOIs or use within 14 days of discontinuing MAOI treatment should be avoided.
Cimetidine	Major	Cimetidine may potentiate morphine-induced respiratory depression. There is a report of confusion and severe respiratory depression when a patient on hemodialysis was concurrently administered morphine and cimetidine.
Diuretics	Moderate	Morphine can induce the release of antidiuretic hormone, which may reduce the efficacy of diuretics. Morphine may also lead to acute retention of urine by causing a spasm of the sphincter of the bladder, particularly in men with enlarged prostates.
Anticholinergics	Major	An increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus may result from concurrent use with anticholinergics or other medications with anticholinergic activity.
P-Glycoprotein Inhibitors (e.g., quinidine,	Major	May result in an increase in the absorption and/or exposure of morphine sulfate by approximately two-fold.

etc.)		
Sodium oxybate	Major	Concurrent use may result in additive respiratory depression.
Yohimbine	Moderate	Concurrent use with naltrexone may result in increased symptoms of anxiety or nervousness and may result in increased analgesic and adverse effects of morphine.
Rifampin & rifapentine	Moderate	Concurrent use may result in loss of morphine efficacy.
Esmolol	Moderate	Concurrent use with morphine may result in esmolol toxicity (e.g., bradycardia, hypotension).
Somatostatin	Moderate	Concurrent use may result in reduced analgesic effect of morphine.
Ginseng	Moderate	Concurrent use may result in reduced opioid analgesic effectiveness.
Kava	Moderate	Concurrent use may result in increased central nervous system depression.
Tylophora	Moderate	Concurrent use with morphine may result in enhanced analgesia and possibly increased adverse effects.
Valerian	Moderate	Concurrent use may result in additive central nervous system depression.

*Severity rating per Micromedex

Patient Monitoring Guidelines[1]

Assess each patient's risk for opioid addiction, abuse, or misuse prior to initiating therapy and monitor all patients for the development of these behaviors or conditions. “Drug seeking” behaviors should also be monitored to help identify these potential concerns.

Continually re-evaluate patients to assess the maintenance of pain control and the development of adverse reactions. 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 opioid analgesics.

Continuously monitor patients for new or worsening adverse events or changes in medication efficacy, particularly with changes in drug doses and/or frequency. Closely monitor patients when there is the addition or elimination of other agents that may alter the efficacy or adverse event profile of the interacting agent(s).

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