Abuse-Deterrent Opioids – Evidence Evaluation & Labeling

Medication: Embeda® (morphine/naltrexone extended-release capsule)

Evaluation Date: 04/07/2016 Evaluation History: ☒ Initial Version 1.0, or ☐ Version _____

Current Product Labeling established: (select one) [☒ Prior to] or [☐ After] publication of FDA Guidance to Industry Document (4/2015)

This is a: (Check all that apply)

- ☐ New product
- ☐ Existing product, new formulation
- ☐ Existing product with new/updated labeling
- ☒ Other: Initial evaluation of existing product

Product Abuse Deterrent Property Classification: – Check all that apply

- ☐ Physical / Chemical barrier
- ☒ Agonist / Antagonist combination
- ☐ Aversion
- ☐ Delivery System
- ☐ New Molecular entity or Prodrug
- ☐ Combination (check combined items)
- ☐ Novel Approach

Product Labeling:

Does the product have FDA abuse deterrent labeling? ☒ Yes or ☐ No Year obtained: 2014

Abuse Deterrent Evidence provided. Summary of in-depth literature review and product evaluation based on FDA Guidance to Industry Document

☒ Laboratory-based in vitro manipulation and extraction studies (Category 1)
Description of Research: Study data indicates that crushing Embeda® pellets results in simultaneous release of morphine and naltrexone.

☒ Pharmacokinetic Studies (Category 2)
Description of Research: Study data indicates that crushed Embeda® pellets resulted in plasma naltrexone concentrations that were not significantly different from administration of naltrexone solution.

☒ Clinical Abuse potential studies (Category 3)
Description of Research: Oral clinical abuse potential study assessed Drug Liking as primary endpoint after oral administration of crushed Embeda®, intact Embeda®, morphine solution and placebo.

☒ Clinical Abuse potential studies (Category 3)
Description of Research: Oral clinical abuse potential study assessed Drug Liking and Drug High as primary endpoints after oral administration of crushed Embeda® in solution, crushed MS Contin® in solution and placebo.

☒ Clinical Abuse potential studies (Category 3)
Description of Research: Intranasal clinical abuse potential study assessed Drug Liking and Drug High as primary endpoints after intranasal administration/insufflation of crushed Embeda®, crushed MS Contin® and placebo.

☒ Clinical Abuse potential studies (Category 3)
Description of Research: Intravenous clinical abuse potential study assessed primary endpoint of answer to the question, "How high are you now?" after administration of simulated solution of Embeda®, morphine or placebo.

☐ Additional Studies / Post Market data which assessed the impact of abuse-deterrent formulation (Category 4)

☐ Post market

☐ Formal studies included recommended study design features (see page 19 FDA Guidance document)
Description of Research: _____

☐ Determination if use of product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death
Description of Research: _____

☒ Outcome Measures and Data Interpretation in Abuse Potential Studies

- Standardized Instruments

☒ Visual Analogue Scales (VAS)
Description of Research: Maximum effect (E_{max}) Drug Liking within 2 hours of dosing, E_{max} Drug High within 2 hours, Drug Liking, Drug High, Take Drug Again, Good Effects, Any Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, Dizzy, Nasal Effects, "How high are you right now?" and "Do you like the drug?".

☐ Profile of Mood States
Description of Research: _____

- Data Interpretation

☒ Primary Analysis
Description of Research: Difference of mean E_{max} Drug Liking, ARCI scale scores, Cole/ARCI scale scores, pupil diameter (Study 1); least squares mean difference E_{max} Drug Liking and Drug High (Study 2 and 3); least squares mean difference E_{max} "How high are you now?" (Study 4).

☒ Statistical Analysis
Description of Research: Linear mixed-effect ANCOVA with fixed-effect terms for treatment, period and sequence, and a random effect term for subjects nested within sequence (Study 1); mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence (Study 2, 3 and 4).

☒ Data and dropout for non-completers
Description of Research: Data regarding dropout and non-completers was provided in all clinical abuse potential studies.

☐ None of the above

Strength of Evidence of Abuse Deterrent Properties:

☐ Evidence is based on physical/chemical property, theoretical assumptions or manufacturer's claims and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category III)

☒ Evidence is based on physical/chemical property, clinical abuse potential studies or laboratory manipulation studies and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without-abuse-deterrent properties were available (Category II)

☐ There is evidence, supported by scientifically sound outcome data, which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category I)