RATIONAL FOR INCLUSION IN PA PROGRAM

Background
Embeda is an extended-release capsule consisting of morphine sulfate and naltrexone hydrochloride. Embeda is indicated for the management of moderate to severe pain when a continuous around-the-clock long term opioid analgesic is needed and for which alternative treatment options are inadequate. It is not approved for as-needed pain relief. Embeda capsules contain pellets of morphine sulfate, an opioid receptor agonist with a sequestered core of naltrexone hydrochloride, an opioid receptor antagonist (1).

Regulatory Status
FDA-approved indication: Embeda is indicated for the management of moderate to severe pain that requires daily, around the clock, long-term opioid treatment and for which alternative treatment options are inadequate (1).

Limitations of use:
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Embeda 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. Embeda is not indicated as an as-needed (prn) analgesic (1).

Embeda carries several boxed warnings regarding addiction, abuse, and misuse; life-threatening respiratory depression; accidental exposure; neonatal opioid withdrawal syndrome; and interaction with alcohol (1).

Embeda is contraindicated in patients who have significant respiratory depression, acute or severe bronchial asthma, and in patients who have or are suspected of having paralytic ileus and gastrointestinal obstruction (1).

Care should be taken to use low initial doses of Embeda in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives,
or other CNS active medications. Embeda 100 mg/4mg capsules are for use in opioid tolerant patients only (1).

CDC guidelines find that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (2).

CDC guidelines finds that given uncertain benefits and substantial risks that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue longer than 3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care (2).

FDA warns that opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see Appendix 1 for list of drugs) (3).

The safety and effectiveness of Embeda in pediatric patients below the age of 18 years have not been established (1).

**Summary**
Embeda is an extended release oral formulation used in the treatment moderate to severe pain. It should not be used for as needed pain relief. The potential for developing substance abuse and addiction is extreme. Patients should be thoroughly assessed for their risk of developing severe respiratory depression, as well as substance abuse prior to being prescribed Embeda and should be routinely monitored for signs of misuse, abuse and addiction during therapy (1).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Embeda while maintaining optimal therapeutic outcomes.

**References**

Appendix 1 - List of Serotonergic Medications

**Selective Serotonin Reuptake Inhibitors (SSRIs)**
- paroxetine  
  Paxil, Paxil CR, Pexeva, Brisdelle
- fluvoxamine  
  Luvox, Luvox CR
- fluoxetine  
  Prozac, Prozac Weekly, Sarafem, Selfemra, Symbyax
- sertraline  
  Zoloft
- citalopram  
  Celexa
- escitalopram  
  Lexapro

**Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**
- venlafaxine  
  Effexor XR
- desvenlafaxine  
  Pristiq, Khedezla
- duloxetine  
  Cymbalta
- milnacipran  
  Savella

**Tricyclic Antidepressants (TCAs)**
- amitriptyline  
  No brand name currently marketed
- desipramine  
  Norpramin
- clomipramine  
  Anafranil
- imipramine  
  Tofranil, Tofranil PM
- nortriptyline  
  Pamelor, Aventyl
- protriptyline  
  Vivactil
- doxepin  
  Zonalon, Silenor
- trimipramine  
  Surmontil

**Monoamine Oxidase Inhibitors (MAOIs)**
- isocarboxazid  
  Marplan
- phenelzine  
  Nardil
- selegiline  
  Emsam, Eldepryl, Zelapar
- tranylcypromine  
  Parnate

**Other Psychiatric Medicines**
- amoxapine  
  No brand name currently marketed
- maprotiline  
  No brand name currently marketed
- nefazodone  
  No brand name currently marketed
- trazodone  
  Oleptro
- buspirone  
  No brand name currently marketed
- vilazodone  
  Viibryd
- mirtazapine  
  Remeron, Remeron Soltab
- lithium  
  Lithobid
**EMBEDA**  
(morphine sulfate and naltrexone hydrochloride)

### Migraine Medicines

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<tr>
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<tr>
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<td>frovatriptan</td>
<td>Frova</td>
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<tr>
<td>naratriptan</td>
<td>Amerge</td>
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<tr>
<td>rizatriptan</td>
<td>Maxalt, Maxalt-MLT</td>
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<td>sumatriptan</td>
<td>Imitrex, Imitrex Statdose, Alsuma, Sumavel Dosepro, Zecuity, Treximet</td>
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<td>zolmitriptan</td>
<td>Zomig, Zomig-ZMT</td>
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### Antiemetics

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<td>ondansetron</td>
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<td>granisetron</td>
<td>Kytril, Sancuso</td>
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<td>dolasetron</td>
<td>Anzemet</td>
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<td>palonosetron</td>
<td>Aloxi</td>
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### Other Serotonergic Medicines

<table>
<thead>
<tr>
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<th>Brand(s)</th>
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<tr>
<td>dextromethorphan</td>
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<td>Zyvox</td>
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<td>cyclobenzaprine</td>
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<td>Amrix</td>
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<tr>
<td>tryptophan</td>
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