RATIONALE FOR INCLUSION IN PA PROGRAM

Background
Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at κ-opioid receptors. Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia. In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis, and sedation (1-2).

Regulatory Status
FDA-approved indications: Butorphanol tartrate injection is indicated for the management of pain when the use of an opioid analgesic is appropriate. Butorphanol tartrate injection is also indicated as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor (1).

Butorphanol tartrate nasal spray is indicated for the management of pain when the use of an opioid analgesic is appropriate (2).

Butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. Butorphanol tartrate, by all routes of administration has been associated with episodes of abuse. Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance and prolonged use during pregnancy can result neonatal withdrawal syndrome (2). Special care should be exercised in administering butorphanol to patients with a history of drug abuse or to patients receiving the drug on a continuous basis for an extended period (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 (3).

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 (3).
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) (4).

The FDA has determined that a REMS is necessary for all opioid analgesics intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks. The Opioid Analgesic REMS is a strategy to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics (5).

Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population (1-2).

**Summary**

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). Butorphanol tartrate injection is indicated for the management of pain when the use of an opioid analgesic is appropriate. Butorphanol tartrate injection is also indicated as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor. Butorphanol tartrate nasal spray is indicated for the management of pain when the use of an opioid analgesic is appropriate. Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence. The safety and effectiveness have not been established in the pediatric population (1-2).

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

**References**