Apadaz™ (benzhydrocodone/acetaminophen) – New drug approval

- On February 23, 2018, KemPharm announced the FDA approval of Apadaz (benzhydrocodone/acetaminophen [APAP]) for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

    — Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Apadaz for use in patients for whom alternative treatment options [eg, non-opioid analgesics] have not been or are not expected to be tolerated, or have not provided adequate analgesia, or are not expected to provide adequate analgesia.

- Apadaz is an immediate-release, fixed-dose combination of benzhydrocodone and APAP, and is a Schedule II controlled substance.

    — Other currently available immediate-release hydrocodone/APAP products include Lorcet®, Lortab®, Norco®, and Vicodin®.

- Apadaz contains benzhydrocodone, a prodrug of hydrocodone, and is converted to active hydrocodone by enzymes in the gastrointestinal (GI) tract.

- The *in vitro* studies that evaluated physical manipulation and extraction for the purpose of preparing Apadaz for abuse by the intravenous route or by smoking did not find an advantage for Apadaz over the hydrocodone/APAP control.

    — The results of the oral and intranasal human abuse potential studies do not support a finding that Apadaz can be expected to deter abuse by the oral or nasal routes of administration.

- The approval of Apadaz was based in part on pharmacokinetic studies with Vicoprofen® (hydrocodone/ibuprofen), Ultracet® (tramadol/APAP), and Norco in which Apadaz demonstrated exposure to hydrocodone and APAP that is expected to result in therapeutic effects equivalent to currently approved immediate-release hydrocodone/APAP combination products when administered orally as intended.

- Apadaz carries a boxed warning regarding addiction abuse and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; cytochrome P450 3A4 interaction; hepatotoxicity; and risks from concomitant use with benzodiazepines or other central nervous system depressants.

- Apadaz is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment; known or suspected GI obstruction, including paralytic ileus; and hypersensitivity to hydrocodone or APAP.

- Warnings and precautions of Apadaz include life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients; adrenal insufficiency; severe hypotension; serious skin reactions; risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness; hypersensitivity/anaphylaxis; risks of use in patients with GI conditions; increased risk of seizure in patients with seizure disorders; withdrawal; and risks of driving and operating machinery.

- The most common adverse reactions (> 5%) with Apadaz use were nausea, somnolence, vomiting, constipation, pruritus, dizziness, and headache.

Continued . . .

- The recommended starting dose of Apadaz is 1 to 2 tablets every 4 to 6 hours as needed for pain. The dose should not exceed 12 tablets in a 24 hour period.

    - The lowest effective dosage should be used for the shortest duration consistent with individual patient treatment goals. The total dosage of Apadaz and any concomitant APAP-containing products should not exceed 4,000 mg of APAP in a 24-hour period.
    - The dosage regimen should be individualized, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.
    - Patients should be monitored closely for respiratory depression, especially within the first 24 - 72 hours of initiating therapy and following dosage increases with Apadaz, and the dose adjusted accordingly.
    - Refer to the drug label on how to convert patients from other opioids to Apadaz.

- KemPharm's launch plans for Apadaz are pending. Apadaz (benzhydrocodone/ acetaminophen) will be available as a 6.67 mg (equivalent to 7.5 mg of hydrocodone)/325 mg tablet.