HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APADAZ™ safely and effectively. See full prescribing information for APADAZ.

APADAZ (benzhydrocodone and acetaminophen) tablets, for oral use, CII
Initial U.S. Approval: 1982

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; HEPATOTOXICITY, CYTOCHROME P450 3A4 INTERACTION, and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
***See full prescribing information for complete boxed warning*.**

- **APADAZ exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental ingestion of APADAZ, especially by children, can result in a fatal overdose of hydrocodone. (5.2)**
- **Prolonged use of APADAZ during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from APADAZ. (5.4, 7, 12.3)**
- **APADAZ contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. (5.5)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)**

----------INDICATIONS AND USAGE----------

APADAZ is a combination of benzhydrocodone, a prodrug of the opioid agonist hydrocodone, and acetaminophen, and is indicated 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. (1)

Limitations of Use (1)
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 [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

---------- DOSAGE AND ADMINISTRATION ----------

- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with APADAZ at 1 or 2 tablets every 4 to 6 hours as needed for pain. Dosage should not exceed 12 tablets in a 24-hour period. (2.2)
- 6.12 mg benzhydrocodone is equivalent to 4.54 mg hydrocodone or 7.5 mg hydrocodone bitartrate. If switching from immediate-release hydrocodone bitartrate/acetaminophen, substitute 6.12 mg/325 mg APADAZ for 7.5 mg/325 mg hydrocodone bitartrate/acetaminophen. Dosage of APADAZ should be adjusted according to the severity of the pain and the response of the patient.
- Do not stop APADAZ abruptly in a physically-dependent patient. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

Immediate-release tablets: 6.12 mg benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg acetaminophen (3)

----------CONTRAINDICATIONS----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to hydrocodone or acetaminophen (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of APADAZ in patients with circulatory shock. (5.9)
- Serious Skin Reactions: Discontinue APADAZ immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of APADAZ in patients with impaired consciousness or coma. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (>5%) are nausea, somnolence, vomiting, constipation, pruritus, dizziness, and headache (6)

To report SUSPECTED ADVERSE REACTIONS, contact KemPharm, Inc. at 1-321-939-3416 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue APADAZ if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with APADAZ because they may reduce analgesic effect of APADAZ or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the efects of hydrocodone. Avois concommitnat use in patietns receiving MAOIs or within 14 days of stopping treatment wit an MAOI. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: May cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: 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 CNS DEPRESSANTS

Addiction, Abuse, and Misuse

APADAZ 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 APADAZ, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of APADAZ. Monitor for respiratory depression, especially during initiation of APADAZ or following a dose increase *[see Warnings and Precautions (5.2)].*

Accidental Ingestion

Accidental ingestion of even one dose of APADAZ, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of APADAZ 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 prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of APADAZ with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving APADAZ and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Hepatotoxicity

APADAZ contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.5)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory

depression, coma, and death *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of APADAZ and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

APADAZ is indicated 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.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve APADAZ for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. The total dosage of APADAZ and any concomitant acetaminophen-containing products should not exceed 4000 mg of acetaminophen in a 24-hour period.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with APADAZ and adjust the dosage accordingly *[see Warnings and Precautions (5.2)].*

2.2 Initial Dosage

Use of APADAZ as the First Opioid Analgesic

Initiate treatment with APADAZ at 1 to 2 tablets every 4 to 6 hours as needed for pain. Dosage should not exceed 12 tablets in a 24-hour period.

2.3 Conversion from Other Opioids to APADAZ

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of APADAZ. It is

safer to underestimate a patient's 24-hour APADAZ dosage than to overestimate the 24-hour APADAZ dosage and manage an adverse reaction due to overdose.

Conversion from Hydrocodone Bitartrate/Acetaminophen to APADAZ

Hydrocodone content in 6.12 mg benzhydrocodone is 4.54 mg hydrocodone or is equivalent to 7.5 mg hydrocodone bitartrate. If switching from immediate-release hydrocodone bitartrate/acetaminophen, substitute 6.12 mg/325 mg APADAZ for 7.5 mg/325 mg hydrocodone bitartrate/acetaminophen.

2.4 Titration and Maintenance of Therapy

Individually titrate APADAZ to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving APADAZ to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. 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.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the APADAZ dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Total dosage of APADAZ and any concomitant acetaminophen-containing products should not exceed 4000 mg of acetaminophen in a 24-hour period.

2.5 Discontinuation of APADAZ

When a patient who has been taking APADAZ regularly and may be physically dependent no longer requires therapy with APADAZ, taper the dose gradually, by 25% to 50 % every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue APADAZ in a physically dependent patient *[see Warnings and Precautions (5.15), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Immediate-release tablet. Each capsule-shaped white tablet debossed with "KP201" on one side contains 6.12 mg benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg acetaminophen.

4 CONTRAINDICATIONS

APADAZ is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*

- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Hypersensitivity to hydrocodone or acetaminophen, or any other component of this product (e.g., anaphylaxis) *[see Warnings and Precautions (5.12), Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

APADAZ contains benzhydrocodone, a Schedule II controlled substance. As an opioid, APADAZ exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed APADAZ. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing APADAZ, and monitor all patients receiving APADAZ for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as APADAZ, but use in such patients necessitates intensive counseling about the risks and proper use of APADAZ along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing APADAZ. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of APADAZ, the risk is greatest during the initiation of therapy or following a dosage increase.

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of APADAZ.

To reduce the risk of respiratory depression, proper dosing and titration of APADAZ are essential *[see Dosage and Administration (2)]*. Overestimating the APADAZ dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of APADAZ, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of APADAZ during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information(17)]*.

5.4 Risks of Concomitant Use or Discontinuation of Cytochrome P450 CYP3A4 Inhibitors and Inducers

Concomitant use of APADAZ with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of hydrocodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of APADAZ is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in APADAZ treated patients may increase hydrocodone plasma concentrations and prolong opioid adverse reactions. When using APADAZ with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in APADAZ treated patients, monitor patients closely at frequent intervals and consider dosage reduction of APADAZ until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of APADAZ with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease hydrocodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using APADAZ with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)].*

5.5 Acetaminophen Hepatotoxicity

APADAZ contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and

often involve more than one acetaminophen-containing product *[see Overdosage (10)]*. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of APADAZ with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when APADAZ is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of APADAZ in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: APADAZ-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of APADAZ *[see Warnings and Precautions (5.2)]*.

Elderly, Cachetic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating APADAZ and when APADAZ is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

APADAZ may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is 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) *[see Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of APADAZ. In patients with circulatory shock, APADAZ may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of APADAZ in patients with circulatory shock.

5.10 Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Inform patients about the signs of serious skin reactions and discontinue use at the first appearance of skin rash or any other sign of hypersensitivity.

5.11 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), APADAZ may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with APADAZ.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of APADAZ in patients with impaired consciousness or coma.

5.12 Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue APADAZ tablets immediately and seek medical care if they experience these symptoms. Do not prescribe APADAZ tablets for patients with acetaminophen allergy.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

APADAZ is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The hydrocodone from APADAZ may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The hydrocodone from APADAZ may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occuring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during APADAZ therapy.

5.15 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g, pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist

analgesic, including APADAZ [see Drug Interactions (7)]. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing APADAZ, gradually taper the dosage [see *Dosage and Administration (2.5)*]. Do not abruptly discontinue APADAZ [see *Drug Abuse and Dependence (9.3)*].

5.16 Risks of Driving and Operating Machinery

APADAZ may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of APADAZ and know how they will react to the medication *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity*[see Warnings and Precautions (5.5]*
- Interactions with Benzodiazepines and other CNS Depressants *[see Warnings and Precautions (5.6)*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Serious Skin Reactions*[see Warnings and Precautions (5.10)]*
- Anaphylaxis and Other Hypersensitivity Reactions *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of APADAZ was evaluated in six Phase 1 studies in which a total of 200 healthy adult subjects receive at least one oral dose of APADAZ. The most common AEs (>5%) reported across these studies were: nausea (21.5%), somnolence (18.5%), vomiting (13.0%), constipation (12.0%), pruritus (11.5%), dizziness (7.5%), and headache (6.0%).

The following adverse reactions occurred with an incidence of 1% to 5% in single-dose or repeated-dose clinical trials of APADAZ.

Gastrointestinal disorder: abdominal distension, abdominal pain, flatulence

General disorders and administration site conditions: asthenia

Nervous system disorders: presyncope, tremor

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hot flush, hypotension

Adverse reactions occurring at less than 1%: the following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in APADAZ clinical trials.

Eye disorders: eye pruritus

Gastrointestinal disorders: diarrhea, gastrooesophageal reflux disease, haematemesis

General disorders and administration site conditions: chest discomfort

Infections and infestations: rhinitis

Nervous system disorders: hypoesthesia, syncope

Psychiatric disorders: agitation, euphoric mood, nightmare

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of hydrocodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis*:* Anaphylaxis has been reported with ingredients contained in APADAZ.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)].*

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with APADAZ.

Table 1. Clinically Significant Drug Internactions with APADAZ

CYP3A4 and 2D6 Inhibitors	
Clinical Impact:	The concomitant use of APADAZ and CYP3A4 inhibitors can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of APADAZ and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of APADAZ is achieved *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)], resulting* in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of APADAZ until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the APADAZ dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir) etc.
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of APADAZ and CYP3A4 inducers can decrease the plasma concentration of hydrocodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone] *[see Warnings and Precautions (5.15)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the APADAZ dosage until stable drug effects are achieved *[see Dosage and Administration (2)]*. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider APADAZ dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin etc.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol,

	increases the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Dosage and Administration (2.5), Warnings and Precautions (5.6)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue APADAZ if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precauitons (5.2)]*. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Intervention:	The use of APADAZ is not recommended for patietns taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of APADAZ and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Hydrocodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of APADAZ and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when APADAZ is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available human data on hydrocodone or APADAZ use during pregnancy to inform any drug associated risks. However, neonatal opioid withdrawal and other adverse reactions during pregnancy and labor can occur with use of APADAZ *[see Clinical Considerations].*

Published studies with oral acetaminophen use during pregnancy have not reported an association with major congenital malformations. No reproductive or developmental toxicology studies in animals have been conducted with benzhydrocodone or the combination of benzhydrocodone and acetaminophen. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice and rats treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproductive capacity were reported. In mice, a reduction in number of litters of the parental mating pair was observed as well as retarded growth, abnormal sperm in their offspring, and reduced birth weight in the next generation. In rats, female fertility was decreased following in utero exposure to acetaminophen [see *DATA*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse

outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. APADAZ is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including APADAZ, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

Acetaminophen:

Published data from a large population-based prospective cohort study and a population-based, case-control study do not clearly report an association with oral acetaminophen and major birth defects, miscarriage, or adverse maternal or fetal outcomes when acetaminophen is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including recall bias.

Animal Data

No reproductive or developmental toxicology studies were conducted with benzhydrocodone or the combination of benzhydrocodone and acetaminophen. The following data are based on findings from studies performed with acetaminophen alone.

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.88 the maximum human daily dose (MHDD) of 3.9 grams/day based on a body surface area comparison showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related

increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2 times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3 times the MHDD, based on a body surface area comparison. In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.45, 0.89, and 1.78 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Lactation

Risk Summary

Hydrocodone is present in human milk. A published lactation study reports variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of hydrocodone to nursing mothers in the early post-partum period. This lactation study did not assess breastfed infants for potential adverse drug reactions. There is potential for sedation and respiratory depression resulting from infant exposure to hydrocodone and its metabolites in breast milk.

Acetaminophen is present in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 to 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for APADAZ and any potential adverse effects on the breastfed child from APADAZ or from the underlying maternal condition.

Clinical Considerations

Infants exposed to APADAZ through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2),*

Clinical Pharmacology (12.2)].

Published animal studies report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to hydrocodone. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of APADAZ slowly in geriatric patients and monitor closely for signs of respiratory depression *[see Warnings and Precautions (5.2)]*.

Hydrocodone and acetaminophen are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of the APADAZ has not been determined. Patients with hepatic impairment may have higher plasma concentrations than those with normal function. Use a low initial dose of APADAZ in patients with hepatic impairment or active liver disease and monitor closely for adverse events such as respiratory depression and hepatotoxicity *[see Warnings and Precautions (5.2and 5.5)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of the APADAZ has not been determined. Patients with renal impairment may have higher plasma concentrations than those with normal function. Use a low initial dose of APADAZ in patients with renal impairment and monitor closely for adverse events such as respiratory depression.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

APADAZ contains benzhydrocodone, a Schedule II controlled substance.

9.2 Abuse

APADAZ contains benzhydrocodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. APADAZ can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)].*

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

APADAZ, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

<u>Risks Specific to Abuse of APADAZ</u>

APADAZ is for oral use only. Abuse of APADAZ poses a risk of overdose and death. The risk is increased with concurrent use of APADAZ with alcohol and other central nervous system depressants.

With intravenous abuse the inactive ingredients in APADAZ can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrent Studies

In vitro and human abuse potential studies comparing APADAZ to an immediate-release hydrocodone/acetaminophen tablet control were conducted to assess the potential abuse deterrent properties of APADAZ.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to extract and convert benzyhydrocodone to hydrocodone for the purpose of preparing APADAZ for abuse by the intravenous route or by smoking. The efficiency of extracting benzhydrocodone from APADAZ was similar compared to the efficiency of extracting hydrocodone from the non-abuse-deterrent hydrocodone/acetaminophen control. Further conversion (hydrolysis) of benzhydrocodone to hydrocodone in vitro is a difficult process. Overall, these studies showed no advantage for APADAZ over the hydrocodone/acetaminophen control.

Oral Clinical Abuse Potential Study

In an oral, single-center, randomized, double-blind, active- and placebo-controlled, 7-period, crossover, human abuse potential study, 71 recreational opioid users were randomized into the Treatment Phase; 62 subjects completed the study. Treatment arms included APADAZ (4, 8, and 12 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), hydrocodone/acetaminophen (4, 8 and 12 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen), and placebo. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone. The rate (C_{max}) and extent (AUC_{last}, AUC_{inf}) of hydrocodone exposure following APADAZ administration was comparable to that for hydrocodone/acetaminophen across all 3 dosage strengths. There were no statistically significant differences nor any clinically meaningful differences between APADAZ and the hydrocodone/acetaminophen control for the pre-specified primary endpoint of maximal score (E_{max}) for Drug Liking VAS or secondary endpoints of Emax for High VAS and Take Drug Again VAS. The results do not support a finding that APADAZ can be expected to deter abuse by the oral route of administration.

Intranasal Clinical Abuse Potential Study

In an intranasal single-center, randomized, double-blind, double-dummy, two-part human abuse potential study, 46 recreational opioid users were randomized into the Treatment Phase; 42

subjects completed the study. Five treatment arms included intranasal crushed and oral APADAZ (2 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), intranasal crushed and oral hydrocodone/acetaminophen (2 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen), and intranasal placebo powder. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone.

The pharmacokinetic data showed that overall (AUC_{last}, AUC_{inf}, and C_{max}) hydrocodone exposure was comparable between intranasal crushed APADAZ and intranasal crushed hydrocodone/acetaminophen. These treatments were also comparable with cumulative hydrocodone exposure at the timepoints of 4, 8, and 24 hours (AUC_{0-4}, AUC_{0-8}, AUC_{0-24}). Over the first 2 hours post-dosing ($AUC_{0-0.5}$, AUC_{0-1}, and AUC_{0-2}), the cumulative hydrocodone exposure was lower following intranasal APADAZ compared to intranasal hydrocodone/ acetominophen.

There were numerically small but not statistically significant differences between APADAZ and the hydrocodone-acetaminophen control observed for the pre-specified primary endpoint, maximum effect on Drug Liking VAS (E_{max}), and the secondary endpoints of E_{max} for High VAS and Take Drug Again VAS.

Table 2: Summary Statistics of Maximum Scores (E_{max}) on Drug Liking, High and Take Drug Again, Following Intranasal Administration of Apadaz, Hydrocodone/APAP, and Placebo

VAS Scale (100 point) *intranasal (n=42)*	Apadaz Crushed	Hydrocodone/APAP Crushed	Placebo
Drug Liking *			
Mean (SE)	75.9 (2.3)	79.0 (2.7)	53.0 (1.2)
Median (Range)	74.0 (50-100)	80.0 (50-100)	51.0 (50-85)
High**			
Mean (SE)	61.8 (4.6)	59.1 (5.1)	8.8 (3.8)
Median (Range)	68.5 (0-100)	67.5 (0-100)	0.0 (0-100)
Take Drug Again*			
Mean (SE)	69.5 (3.9)	74.5 (3.9)	48.2 (2.2)
Median (Range)	68.0 (0-100)	81.5 (0-100)	50.0 (0-100)

*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)
** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Additional secondary analyses of Drug Liking based on area under the effect curve analyses (AUE) for the first half hour, hour, and 2 hours post-dosing, demonstrated numerically small differences between intranasal APADAZ and intranasal hydrocodone/acetaminophen. However, there were no differences between these two treatments with respect to the cumulative High experienced over the first 2 hours post-dosing using similar AUE analyses. There are no data to support that small differences in the early Drug Liking experience over the first 2 hours are clinically relevant findings consistent with possible abuse-deterrent effects, particularly in the

setting of the E_{max} analyses for Drug Liking, Take Drug Again, and High that do not support a deterrent effect. Based on the overall results, APADAZ cannot be expected to deter abuse by the intranasal route of administration.

Summary
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/acetaminophen 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.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

APADAZ should not be abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2.5)].* If APADAZ is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Hydrocodone
Acute overdose with APADAZ can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted

pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Acetaminophen
In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

A single or multiple drug overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, assisted ventilation, and other supportive measures should be employed as indicated.

Hydrocodone
In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydrocodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydrocodone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of hydrocodone from APADAZ, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Acetaminophen
If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

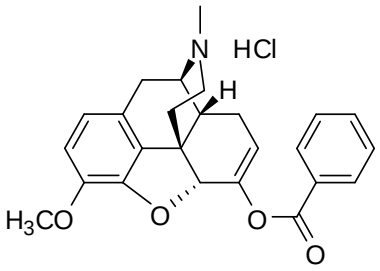
Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

11 DESCRIPTION

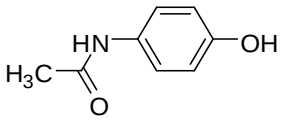
APADAZ (benzhydrocodone and acetaminophen) tablet is an immediate-release, fixed-dose combination of an opioid agonist and acetaminophen. APADAZ tablets are white to off-white, capsule shaped tablets with KP201 debossed on one side and contain 6.12 mg of benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg of acetaminophen for oral administration.

Benzhydrocodone hydrochloride is a prodrug of hydrocodone. It occurs as a fine white powder and is not affected by light. The chemical name is 6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-yl benzoate hydrochloride. The molecular formula is $C_{25}H_{26}ClNO_4$, which corresponds to a molecular weight of 439.93 g/mol. It has the following chemical structure:



Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. The molecular formula for acetaminophen is

$C_8H_9NO_2$, which corresponds to a molecular weight of 151.16 g/mol. It has the following structural formula:



APADAZ tablets contain 6.12 mg of benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg of acetaminophen and are white to off-white in color. In addition, each tablet contains the following inactive ingredients: crospovidone, microcrystalline cellulose, pregelatinized starch, Povidone K30, and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Benzhydrocodone

Benzhydrocodone is a prodrug of hydrocodone.

Hydrocodone

Hydrocodone is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Acetaminophen

Acetaminophen is a non-opioid, non-salicylate analgesic. The site and mechanism for the analgesic effect of acetaminophen has not been determined but is thought to primarily involve central actions.

12.2 Pharmacodynamics

Hydrocodone

Effects on the Central Nervous System

Hydrocodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because hydrocodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to

an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.5)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.4)]*.

12.3 Pharmacokinetics

APADAZ has met the bioequivalence criteria for hydrocodone AUC and C_{max} to other immediate-release hydrocodone combination products. Benzhydrocodone was not detectable in plasma after oral administration in clinical studies, indicating that exposure to benzhydrocodone was minimal and transient. Steady state with APADAZ is attained within 24 to 36 hours of dosing. The systemic exposure to hydrocodone from APADAZ increases linearly after administration of single and multiple doses of 2 tablets of APADAZ.

Absorption

Single–Dose Studies
In 2 comparative bioavailability studies following oral administration of single dose to healthy subjects under fasted conditions, 6.67 mg/325 mg APADAZ tablet met the bioequivalence criteria for hydrocodone AUC and C_{max} to immediate-release tablet of 7.5 mg hydrocodone/200 mg ibuprofen (N = 28); and the bioequivalence criteria for acetaminophen AUC and C_{max} to immediate-release tablet of 37.5 mg tramadol/325 mg acetaminophen (N = 27)

In a comparative bioavailability study following oral administration of single dose under fasted conditions in 24 healthy subjects comaparing 6.67 mg/325 mg APADAZ to immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen, APADAZ met the bioequivalence criteria for hydrocodone C_{max} and AUC; and met the bioequivalence criteria for acetaminophen AUC, with comaparble acetaminophen C_{max}.

In a study to assess the effect of food on the bioavailability and pharmacokinetics of APADAZ in 38 healthy subjects, compared to fasted condition, coadministration of APADAZ with a high-fat, high-calorie meal showed a slight decrease in the rate but no change in the extent of hydrocodone absorption; and no difference in rate and extent of acetaminophen absorption. The effect of a high-fat, high-calorie meal on pharmacokinetics is similar between APADAZ and immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen. APADAZ can be administered without regard to food. The PK parameters for hydrocodone and acetaminophen after oral administration of APADAZ tablet, 6.67 mg/325 mg under fasted and fed conditions are shown in Table 3 below.

Table 2. PK parameters of hydrocodone and acetaminophen after oral administration of APADAZ tablet, 6.67 mg/325 mg under fasted and fed conditions.

Parameter[a]	Fed	Fasted
Hydrocodone		
C_{max} (ng/mL)	16.04 ± 3.60 (40)	19.18 ± 4.84 (38)
T_{max} (h)	2.50 (40) [0.50–4.00]	1.25 (38) [0.50–3.00]
AUC_{inf} (h·ng/mL)	130.91 ± 29.45 (40)	125.73 ± 36.78 (38)
$t_{½}$ (h)	4.53 ± 0.70 (40)	4.33 ± 0.67 (38)
Acetaminophen		
C_{max} (µg/mL)	3.34 ± 1.01 (39)	4.05 ± 1.30 (38)
T_{max} (h)	1.50 (39) [0.50–4.00]	1.00 (38) [0.50–3.00]
AUC_{inf} (h·µg/mL)	15.0 ± 3.53 (36)	14.7 ± 3.87 (36)
$t_{½}$ (h)	5.64 ± 1.58 (36)	4.78 ± 1.30 (36)

[a] Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported

Multiple-Dose Study

A multiple-dose study in 24 healthy subjects showed no measurable exposure to benzhydrocodone, when 2 tablets of APADAZ, 6.67 mg/325 mg, was administered orally every 4 hours for a total of 13 doses. Steady state for hydrocodone and acetaminophen was achieved after 24 hours and between 24 and 36 hours, respectively. The accumulation ratios for hydrocodone C_{max} and AUC values were 1.85-fold and 2.03-fold, respectively. The accumulation ratios for acetaminophen C_{max} and AUC values were 1.38-fold and 1.80-fold, respectively.

Elimination

Hydrocodone is eliminated primarily from the kidneys. Elimination of acetaminophen is principally by liver metabolism and subsequent renal excretion of metabolites.

Metabolism

Benzhydrocodone is a prodrug of hydrocodone and is converted to active hydrocodone by enzymes in the intestinal tract.

Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The O- and N- demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively. *[see Drug Interactions (7)]*.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then

further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Excretion
Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Specific Populations

Age
For hydrocodone, no significant pharmacokinetic differences based on age have been demonstrated. For APAP, a population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen, which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of acetaminophen in elderly patients with normal renal and hepatic function *[see Use in Specific Populations (8.5)].*

Sex
For hydrocodone, no significant pharmacokinetic differences based on gender have been demonstrated.

Renal Impairment
The effect of renal insufficiency on the pharmacokinetics of APADAZ has not been determined *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment
Because acetaminophen is extensively metabolized by the liver, the use of APADAZ in patients with severe hepatic impairment or severe active liver disease is contraindicated. The pharmacokinetics and tolerability of APADAZ in patients with impaired hepatic function have not been studied *[see Contraindications (4), Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of benzhydrocodone or the combination of benzhydrocodone and acetaminophen have not been conducted.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 3.9 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.3-1.5 times the MHDD, based on a body surface area comparison).

Mutagenesis

Benzhydrocodone was positive in an in vitro mammalian cell chromosome aberration assay in the presence of a metabolic activation (S9 mix) and negative in the absence of metabolic activation. Benzhydrocodone was negative in an in vitro bacterial mutation assay as well as in the in vivo rat micronucleus and comet assays.

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (3.7-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.9-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility

No nonclinical fertility studies have been conducted with benzhydrocodone or the combination of benzhydrocodone and acetaminophen.

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.8 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.8 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment.

In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.06 times the MHDD) reduced the number of primordial follicles in female offspring and reduced the percentage of full term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

In a published study, pregnant rats oral administration of 350 mg/kg acetaminophen (0.9 times the MHDD) from Gestation Day 13 to 21 (dams), reduced the number of germ cells in the fetal ovary and decreased ovary weight and reduced number of pups per litter in F1 females as well as reduced ovary weights in F2 females.

16 HOW SUPPLIED/STORAGE AND HANDLING

APADAZ (benzhydrocodone and acetaminophen) is capsule-shaped white tablet debossed with "KP201" on one side. Each tablet contains 6.12 mg benzhydrocodone and 325 mg acetaminophen.

The tablets are supplied as:

NDC 70040-0167-1:	Bottles of 100 Tablets
NDC 70040-0167-3:	Blister Wallet Pack of 18 Tablets

Flush expired or unused APADAZ tablets that is no longer needed down the toilet or contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539).

Storage

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Administration Instructions

Instruct patients how to properly take APADAZ *[see Dosage and Administration (2), Warnings and Precautions (5)].*

- Do not take more than 4,000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.
- Use APADAZ exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Do not discontinue APADAZ without first discussing the need for a tapering regimen with your doctor.

Addiction, Abuse, and Misuse

Inform patients that the use of APADAZ, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)].* Instruct patients not to share APADAZ with others and to take steps to protect APADAZ from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting APADAZ or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store APADAZ securely and to dispose of unused APADAZ by flushing the tablets down the toilet.

Maximum Daily Acetaminophen Use

Advise patients not to take more than 4,000 milligrams of acetaminophen per day and call their doctor if they have taken more than the recommended dose. Advise patients not to take APADAZ in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations (*see Warnings and Precautions* (5.5)].

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients that potentially fatal additive effects may occur if APADAZ is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these unless supervised by a healthcare provider *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking APADAZ while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking APADAZ *[see Drug Interactions (7)]*.
Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

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Hypotension

Inform patients that APADAZ may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.9)]*.

Serious Skin Reactions

Advise patients to stop APADAZ immediately if they develop any type of rash and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.10)]*.

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in APADAZ. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Warnings and Precautions (5.12), Adverse Reactions (6)].*

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of APADAZ during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)].*

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that APADAZ can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)].*

Driving or Operating Heavy Machinery

Inform patients that APADAZ may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.17)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused APADAZ

Advise patients to flush the unused tablets down the toilet when APADAZ is no longer needed or to contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539).

Manufactured for:
KemPharm, Inc.
2500 Crosspark Road
Coralville, IA 52241

Medication Guide
APADAZ™ (ap' ah daz) (benzhydrocodone and acetaminophen) tablet, CII

APADAZ is:

- A strong prescription pain medicine that contains an opioid (narcotic) and the medicine acetaminophen. APADAZ is used to manage short-term pain (no more than 14 days), when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about APADAZ:

- **Get emergency help right away if you take too much APADAZ (overdose)**. When you first start taking APADAZ, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking APADAZ with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your APADAZ. They could die from taking it. Store APADAZ away from children and in a safe place to prevent stealing or abuse. Selling or giving away APADAZ is against the law.
- Get emergency help right away if you take more than 4,000 mg of acetaminophen in 1 day. Taking APADAZ with other products that contain acetaminophen can lead to serious liver problems and death.

Do not take APADAZ if you have:

- severe asthma, trouble breathing, or other lung problems.
- an allergy to hydrocodone or acetaminophen.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking APADAZ, tell your healthcare provider if you have a history of:

- head injury, seizures
- severe liver problems
- problems urinating
- kidney, thyroid, pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of APADAZ during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** APADAZ passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking APADAZ with certain other medicines can cause serious side effects that could lead to death.

When taking APADAZ:

- Do not change your dose. Take APADAZ exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 to 6 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **If you have been taking APADAZ regularly, do not stop taking APADAZ without talking to your healthcare provider.**
- After you stop taking APADAZ, flush any unused tablets down the toilet or contact the Drug Enforcement Agency (DEA) at 1-800—882-9539 for an authorized collector.

While taking APADAZ DO NOT:

- Drive or operate heavy machinery, until you know how APADAZ affects you. APADAZ can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with APADAZ may cause you to overdose and die.
- Do not take other products that contain acetaminophen while taking APADAZ.

The possible side effects of APADAZ:

- itching, constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, and skin rash. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- rash with hives, sores in your mouth or eyes, or your skin blisters and peels.

These are not all the possible side effects of APADAZ. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured for: KemPharm, Inc, Coralville, IA 52241. For more information go to www.kempharm.com or call 1-321-939-3416.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 02/2018