TREZIX™ Capsules

Acetaminophen, Caffeine and Dihydrocodeine Bitartrate CIII

320.5 mg / 30 mg / 16 mg

Rx Only

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYME; HEPATOTOXICITY and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse

TREZIX™ expose 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 TREZIX™, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see Warnings]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

•complete a REMS-compliant education program,
•counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
•emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
•consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TREZIX™. Monitor for respiratory depression, especially during initiation of TREZIX™ or following a dose increase [see WARNINGS].

Accidental Ingestion

Accidental ingestion of TREZIX™, especially by children, can result in a fatal overdose of TREZIX™ [see WARNINGS].

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to CYP2D6 polymorphism [see WARNINGS and PRECAUTIONS]. TREZIX™ is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see CONTRAINDICATIONS]. Avoid the use of TREZIX™ in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TREZIX™ 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 opioid use is required for a prolonged period 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].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TREZIX™ requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Hepatotoxicity

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 4,000 milligrams per day, and often involve more than one acetaminophen-containing product [see WARNINGS].

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, PRECAUTIONS; Drug Interactions].
• Reserve concomitant prescribing of TREZIX™ 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.

DESCRIPTION:

TREZIX™ capsules are supplied in capsule form for oral administration.
Each red capsule contains:
Acetaminophen 320.5 mg
Caffeine 30 mg
Dihydrocodeine bitartrate 16 mg

Acetaminophen (4'-hydroxyacetanilide), a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

Caffeine (1,3,7-trimethylxanthine), a bitter, white crystalline powder or white glistening needles, is a central nervous system stimulant. It has the following structural formula:

Dihydrocodeine Bitartrate (4,5 a-epoxy-3-methoxy-17-methylmorphinan-6 a-ol (+)-tartrate), an odorless, fine white powder is an opioid analgesic. It has the following structural formula:

In addition, each capsule contains the following inactive ingredients: crospovidone, magnesium stearate, povidone, pregelatinized corn starch, stearic acid. The capsule is composed of FD&C Red #40, and gelatin. Imprinting ink is composed of ammonium hydroxide, isopropyl alcohol, n-butyl alcohol, pharmaceutical glaze (modified) in SD-45, propylene glycol, simethicone, and titanium dioxide.

CLINICAL PHARMACOLOGY:

TREZIX™ capsules contain dihydrocodeine which is a semi-synthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to those of codeine; the most prominent of these involve the central nervous system and organs with smooth muscle components. The principal action of therapeutic value is analgesia.
This combination product also contains acetaminophen, a non-opiate, non-salicylate analgesic and antipyretic. This combination product contains caffeine as an analgesic adjuvant. Caffeine is also a CNS and cardiovascular stimulant.

Effects on the Endocrine System

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes 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 [see ADVERSE REACTIONS].

INDICATIONS AND USAGE:

TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules are indicated for the management of 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], reserve TREZIX™ 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

CONTRAINDICATIONS:

TREZIX™ is contraindicated for:
• All children younger than 12 years of age [see WARNINGS and PRECAUTIONS]
• Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see WARNINGS and PRECAUTIONS].
TREZIX™ is also contraindicated in patients with:
• Significant respiratory depression [see WARNINGS]
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see WARNINGS]
• Known or suspected gastrointestinal obstruction, including paralytic ileus [see WARNINGS]
• Hypersensitivity to codeine, acetaminophen, or any of the formulation excipients. (e.g., anaphylaxis) [see WARNINGS]

WARNINGS:

Addiction, Abuse, and Misuse

TREZIX™ contains dihydrocodeine bitartrate , a Schedule III controlled substance. As an opioid, TREZIX™ exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TREZIX™. 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 TREZIX™, and monitor all patients receiving TREZIX™ for the development of these behaviors or 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 TREZIX™, but use in such patients necessitates intensive counseling about the risks and proper use of TREZIX™ 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 TREZIX™ 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 PRECAUTIONS; Information for Patients]. 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.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

•Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
•Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
•Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
•Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint

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]. 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 TREZIX™, 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 TREZIX™.
To reduce the risk of respiratory depression, proper dosing and titration of TREZIX™ are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the TREZIX™ dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.
Accidental ingestion of TREZIX™, especially by children, can result in respiratory depression and death due to an overdose of dihydrocodeine bitartrate.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children less than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:
• TREZIX™ is contraindicated for all children younger than 12 years of age [see CONTRAINDICATIONS].
• TREZIX™ is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see CONTRAINDICATIONS].
• Avoid the use of TREZIX™ in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
• As with adults, when prescribing codeine for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [see OVERDOSAGE].

Nursing Mothers

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with TREZIX™ [see PRECAUTIONS; Nursing Mothers].

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see OVERDOSAGE]. Therefore, individuals who are ultra-rapid metabolizers should not use codeine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TREZIX™ 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 PRECAUTIONS; Information for Patients, Pregnancy].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TREZIX™ requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

• Cytochrome P450 3A4 Interaction

The concomitant use of TREZIX™ with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of TREZIX™ with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving TREZIX™ and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when TREZIX™ are used in conjunction with inhibitors and inducers of CYP3A4.

If concomitant use of a CYP3A4 inhibitor is necessary or if a CYP3A4 inducer is discontinued, consider dosage reduction of TREZIX™ until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If concomitant use of a CYP3A4 inducer is necessary or if a CYP3A4 inhibitor is discontinued, consider increasing the TREZIX™ dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal [see PRECAUTIONS, Drug Interactions].

• Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of TREZIX™ with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.
Follow patients receiving TREZIX™ and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when TREZIX™ are used in conjunction with inhibitors of CYP2D6.

If concomitant use with a CYP2D6 inhibitor is necessary, follow the patient for signs of reduced efficacy or opioid withdrawal and consider increasing the TREZIX™ dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the TREZIX™ dosage and follow the patient for signs and symptoms of respiratory depression or sedation [see PRECAUTIONS; Drug Interactions].

Hepatotoxicity

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. 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.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of TREZIX™ 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 PRECAUTIONS; Drug Interactions].

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 TREZIX™ 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 PRECAUTIONS; Drug Interactions) and PRECAUTIONS; Information for Patients].

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

The use of TREZIX™ 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: TREZIX™ 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 TREZIX™ [see WARNINGS].

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].

Monitor such patients closely, particularly when initiating and titrating TREZIX™ and when TREZIX™ is given concomitantly with other drugs that depress respiration [see WARNINGS]. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 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.

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. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Usage in Ambulatory Patients

Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

Respiratory Depression

Respiratory depression is the most dangerous acute reaction produced by opioid agonist preparations, although it is rarely severe with usual doses. Opioids decrease the respiratory rate, tidal volume, minute ventilation, and sensitivity to carbon dioxide. Respiratory depression occurs most frequently in elderly or debilitated patients, usually after large initial doses in nontolerant patients, or when opioids are given in conjunction with other agents that depress respiration. This combination product should be used with caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale and in patients with a substantially decreased respiratory reserve, hypoxia hypercapnia, or respiratory depression. In such patients, alternative non-opioid analgesics should be considered, and opioids should be administered only under careful medical supervision at the lowest effective dose.

Head Injury

This combination product should be used cautiously in the presence of head injury or increased intracranial pressure. The effects of opioids on pupillary response and consciousness may obscure neurologic signs of increases in intracranial pressure in patients with head injuries. The respiratory depressant effects including carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions, or other causes of increased intracranial pressures.

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 TREZIX™ immediately and seek medical care if they experience these symptoms. Do not prescribe TREZIX™ for patients with acetaminophen allergy.

Hypotensive Effect

Dihydrocodeine, like all opioid analgesics, may cause hypotension in patients whose ability to maintain blood pressure has been compromised by a depleted blood volume or who receive concurrent therapy with drugs such as phenothiazines or other agents which compromise vasomotor tone. Acetaminophen, caffeine and dihydrocodeine bitartrate capsules may produce orthostatic hypotension in ambulatory patients. This combination product should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Drug Dependence

Dihydrocodeine can produce drug dependence of the codeine type and has the potential of being abused [see DRUG ABUSE AND DEPENDENCE].

PRECAUTIONS:

General

Selection of patients for treatment with TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules should be governed by the same principles that apply to the use of similar opioid/non-opioid fixed combination analgesics. As with any such opioid analgesic, the dosing regimen should be adjusted for each patient [see DOSAGE AND ADMINISTRATION]. This combination product should be used with caution in elderly or debilitated patients or those with any of the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); asthma; central nervous system depression or coma; chronic obstructive pulmonary disease; decreased respiratory reserve (including emphysema, severe obesity, cor pulmonale, or kyphoscoliosis); delirium tremens; head injury; hypotension; increased intracranial pressure; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; and toxic psychosis. The benefits and risks of using opioids in patients taking monoamine oxidase inhibitors and in those with a history of drug abuse should be carefully considered. The administration of an analgesic containing an opioid may obscure the diagnosis or clinical course in patients with acute abdominal conditions. This combination product may aggravate convulsions in patients with convulsive disorders and, like all opioids, may induce or aggravate seizures in some clinical settings.
Acetaminophen is relatively non-toxic at therapeutic doses, but should be used with caution in patients with severe renal or hepatic disease. Care should be observed when using large doses of acetaminophen in malnourished patients or those with a history of chronic alcohol abuse because they may be more susceptible to hepatic damage similar to that observed with toxic overdosage. Caffeine in high doses may produce central nervous system and cardiovascular stimulation and gastrointestinal irritation.

Information for Patients/Caregivers

Addiction, Abuse, and Misuse

Inform patients that the use of TREZIX™ even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see WARNINGS]. Instruct patients not to share TREZIX™ with others and to take steps to protect TREZIX™ 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 TREZIX™ or when the dosage is increased, and that it can occur even at recommended dosages [see WARNINGS]. 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]. Instruct patients to take steps to store TREZIX™ securely. Advise patients to properly dispose of the TREZIX™ in accordance with local state guidelines and/or regulations.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise patients that TREZIX™ is contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving TREZIX™ to monitor for signs of respiratory depression [see WARNINGS].

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if TREZIX™ is used with benzodiazepines or other CNS depressants, including alcohol, and not to use such drugs unless supervised by a health care provider [see WARNINGS and PRECAUTIONS; Drug Interactions].

Serotonin Syndrome

Inform patients that TREZIX™ 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 physicians if they are taking, or plan to take serotonergic medications [see PRECAUTIONS; Drug Interactions].

Adrenal Insufficiency

Inform patients that TREZIX™ 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].

Important Administration Instructions
Instruct patients how to properly take TREZIX™ [see DOSAGE AND ADMINISTRATION]
• Advise patients not to adjust the dose of TREZIX™ without consulting a physician or other health-care professional.
• If patients have been receiving treatment with TREZIX™ for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication [see Warnings].

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of TREZIX™ during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see WARNINGS, PRECAUTIONS; Pregnancy]

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that TREZIX™ can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [see PRECAUTIONS; Pregnancy].

Lactation
Advise women that breastfeeding is not recommended during treatment with TREZIX™ [see PRECAUTIONS; Nursing Mothers].

Disposal of Unused TREZIX™
Advise patients to properly dispose of unused TREZIX™. Advise patients to throw the drug in the household trash following these steps.
1) Remove them from their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs).
2) Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag, or to dispose of in accordance with the local state guidelines and/or regulations.

Patients receiving TREZIX™ capsules should be given the following information:
1. Do not take TREZIX™ if you are allergic to any of its ingredients. If you develop signs of allergy such as a rash or difficulty breathing stop taking TREZIX™ and contact your healthcare provider immediately.
2. Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.
3. Patients should be advised that TREZIX™ capsules may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
4. Patients should be advised to report adverse experiences occurring during therapy.
5. Patients should be advised not to adjust the dose of TREZIX™ capsules without consulting the prescribing professional.
6. Patients should be advised that TREZIX™ capsules are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
7. Advise patients that some people have a genetic variation that results in dihydrocodeine changing into dihydromorphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid dihydrocodeine metabolizer or not. These higher-than-normal levels of dihydromorphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Dihydrocodeine-containing products are contraindicated in all children who undergo tonsillectomy and/or adenoidectomy.
Advise caregivers of children receiving dihydrocodeine-containing products for other reasons to monitor for signs of respiratory depression.

Drug Interactions
CYP2D6 Inhibitors
Dihydrocodeine in TREZIX™ is metabolized by CYP2D6 to form dihydromorphine. The concomitant use of TREZIX™ and CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, paroxetine bupropion) can increase the plasma concentration of dihydrocodeine, but can decrease the plasma concentration of active metabolite dihydromorphine which could result in reduced analgesic efficacy or symptoms of opioid withdrawal, particularly when an inhibitor is added after a stable dose of TREZIX™ is achieved.

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the dihydrocodeine plasma concentration will decrease but the active metabolite dihydromorphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

If concomitant use with a CYP2D6 inhibitor is necessary or if a CYP2D6 inhibitor is discontinued after concomitant use, consider dosage adjustment of TREZIX™ and monitor patients closely at frequent intervals.

If concomitant use with CYP2D6 inhibitors is necessary, follow the patient for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the TREZIX™ as needed.

After stopping use of a CYP2D6 inhibitor, consider reducing the TREZIX™ and monitor the patient for signs and symptoms of respiratory depression or sedation.

CYP3A4 Inhibitors
The concomitant use of TREZIX™ with CYP3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), may result in an increase in dihydrocodeine plasma concentration with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater dihydromorphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of TREZIX™ is achieved.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower dihydrocodeine plasma levels, greater dihydronorcodeine levels, and less metabolism via 2D6 with resultant lower dihydromorphine levels, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to dihydrocodeine. If concomitant use with CYP3A4 inhibitor is necessary, consider dosage reduction of TREZIX™ 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 TREZIX™ dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

CYP3A4 Inducers
The concomitant use of TREZIX™ and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin), can result in lower dihydrocodeine levels, greater dihydronorcodeine levels, and less metabolism via 2D6 with resultant lower dihydromorphine levels, resulting in decreased efficacy or a withdrawal syndrome in patients who had developed physical dependence to dihydrocodeine.

After stopping a CYP3A4 inducer, as the effects of the inhibitor decline, the dihydrocodeine plasma concentration may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater dihydromorphine levels, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use with CYP3A4 inducer is necessary, follow the patient for reduced efficacy and signs of opioid withdrawal and consider increasing the TREZIX™ dosage as needed.

If a CYP3A4 inducer is discontinued, consider TREZIX™ dosage reduction and monitor for signs of respiratory depression and sedation at frequent intervals.

Benzodiazepines and Other Central Nervous System (CNS) Depressants
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
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 WARNINGS].

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (used to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see PRECAUTIONS; Information for Patients].
If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue TREZIX™ immediately if serotonin syndrome is suspected.

Dihydrocodeine with Monoamine Oxidase Inhibitors
Dihydrocodeine, like all opioid analgesics, interacts with monoamine oxidase inhibitors causing central nervous system excitation and hypertension.

Dihydrocodeine with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) may reduce the analgesic effect of this combination product.

Acetaminophen Drug Interactions
Chronic and excessive consumption of alcohol may increase the hepatotoxic risk of acetaminophen. The potential for hepatotoxicity with acetaminophen also may be increased in patients receiving anticonvulsants that induce hepatic microsomal enzymes (including phenytoin, barbiturates, and carbamazepine) or isoniazide. Chronic ingestion of large doses of acetaminophen may slightly potentiate the effects of warfarin-and indandione-derivative anticoagulants. Severe hypothermia is possible in patients receiving acetaminophen concomitantly with phenothiazines.

Caffeine Drug Interactions
Caffeine may enhance the cardiac inotropic effects of beta-adrenergic stimulating agents. Co-administration of caffeine and disulfiram may lead to a substantial decrease in caffeine clearance. Caffeine may increase the metabolism of other drugs such as phenobarbital and aspirin. Caffeine accumulation may occur when products or foods containing caffeine are consumed concomitantly with quinolones such as ciprofloxacin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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].

Pregnancy:
Teratogenic Effects – Pregnancy Category C.
Animal reproduction studies have not been conducted with TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules. It is also not known whether this combination product can cause fetal harm when administered to pregnant women or can affect reproduction capacity in males and females. This combination product should be given to pregnant women only if clearly needed, especially during the first trimester.

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].

Labor and 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. TREZIX™ is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including TREZIX™, and 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.

Nursing Mothers
Dihydrocodeine bitartrate and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of dihydrocodeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal dihydrocodeine metabolism (normal CYP2D6 activity), the amount of dihydrocodeine secreted into human milk is low and dose-dependent.

There is no information on the effects of the dihydrocodeine on milk production. Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with TREZIX™ [see WARNINGS].

Clinical Considerations
If infants are exposed to TREZIX™ through breast milk, they 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.
Acetaminophen and caffeine are also excreted in breast milk in small amounts. Because of the potential for serious adverse reactions in nursing infants from this combination product, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of TREZIX™ in pediatric patients have not been established.

Life-threatening respiratory depression and death have occurred in children who received codeine [see WARNINGS]. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine.

Because of the risk of life-threatening respiratory depression and death:
• TREZIX™ is contraindicated for all children younger than 12 years of age [see CONTRAINDICATIONS].
• TREZIX™ is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see CONTRAINDICATIONS].
• Avoid the use of TREZIX™ in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression [see WARNINGS].

Geriatric Use
Elderly patients (aged 65 years or older) may have increased sensitivity to TREZIX™. 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 TREZIX™ slowly in geriatric patients and monitor closely for signs of central nervous system and central nervous system depression [see WARNINGS].

Hepatic Impairment
TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules should be given with caution to patients with hepatic insufficiency. Since dihydrocodeine is metabolized by the liver and since acetaminophen potentially causes hepatotoxicity, the effects of this combination product should be monitored closely in such patients.

Renal Impairment
TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules should be used with caution and at reduced dosage in the presence of impaired renal function.

Pancreatic/Biliary Tract Disease
Opioids may cause spasms of the sphincter of Oddi and should be used with caution in patients with biliary tract disease including pancreatitis.

ADVERSE REACTIONS
Dihydrocodeine:
The most frequently observed adverse reactions include lightheadedness, dizziness, drowsiness, headache, fatigue, sedation, sweating, nausea, vomiting, constipation, pruritus, and skin reactions. With the exception of constipation, tolerance develops to most of these effects. Other reactions that have been observed with dihydrocodeine or other opioids include respiratory depression, orthostatic hypotension, cough suppression, confusion, diarrhea, miosis, abdominal pain, dry mouth, indigestion, anorexia, spasm of biliary tract, and urinary retention. Physical and psychological dependence are possibilities. Hypersensitivity reactions (including anaphylactoid reactions), hallucinations, vivid dreams, granulomatous interstitial nephritis, severe narcosis and acute renal failure have been reported rarely during dihydrocodeine administration.

Acetaminophen
Acetaminophen in therapeutic doses rarely causes adverse reactions. The most serious adverse reaction is hepatoxicity from overdosage (see OVERDOSAGE). Thrombocytopenia, leukopenia, pancytopenia, neutropenia, thrombocytopenic purpura, and agranulocytosis have been reported in patients receiving acetaminophen or p-aminophenol derivatives. Hypersensitivity reactions including urticarial or erythematous skin reactions, laryngeal edema, angioedema, or anaphylactoid reactions are rare.

Caffeine
Adverse reactions associated with caffeine use include anxiety, anxiety neurosis, excitement, headaches, insomnia, irritability, lightheadedness, restlessness, tenseness, tremor, extrasystoles, palpitations, tachycardia, diarrhea, nausea, stomach pain, vomiting, diuresis, urticaria, scintillating scotoma, and tinnitus.

Postmarketing Experience
• 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 TREZIX™.
• Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see CLINICAL PHARMACOLOGY].

DRUG ABUSE AND DEPENDENCE

Controlled Substance
TREZIX™ contains dihydrocodeine bitartrate, a Schedule III controlled substance.

Abuse
TREZIX™ contains dihydrocodeine bitartrate, a substance with a high potential for abuse similar to other Schedule III opioids. TREZIX™ can be abused and is subject to misuse, addiction, and criminal diversion [see WARNINGS].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since 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 health care 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.
TREZIX™, 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.

Risks Specific to Abuse of TREZIX™
TREZIX™ is for oral use only. Abuse of TREZIX™ poses a risk of overdose and death. The risk is increased with concurrent use of TREZIX™ with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

TREZIX™ should not be abruptly discontinued [see DOSAGE AND ADMINISTRATION]. If TREZIX™ 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 PRECAUTIONS; Pregnancy].

OVERDOSAGE
Following an acute overdosage with TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules, toxicity may result from the dihydrocodeine or the acetaminophen. Toxicity due to the caffeine is less likely, due to the relatively small amounts in this formulation.

Clinical Presentation
Acute overdose with TREZIX™ 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.

Signs and Symptoms
Toxicity from dihydrocodeine poisoning includes the opioid triad of: pinpoint pupils, respiratory depression, and loss of consciousness. Convulsions, cardiovascular collapse, and death may occur. A single case of acute rhabdomyolysis associated with an overdose of dihydrocodeine has been reported. In acetaminophen overdosage: dose-dependent potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. 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. Acute caffeine poisoning may cause insomnia, restlessness, tremor, delirium, tachycardia, and extrasystoles.

Because overdose information on this combination product is limited, it is unclear which of the signs and symptoms of toxicity would manifest in any particular overdose situation.

Treatment of Overdose
A single or multiple drug overdose with TREZIX™ (acetaminophen, caffeine and dihydrocodeine bitartrate) capsules is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

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 TREZIX™ overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to TREZIX™ overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of dihydrocodeine bitartrate in TREZIX™, 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.

For respiratory depression due to unusual sensitivity to dihydrocodeine, parenteral naloxone is a specific and effective antagonist.

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.

DOSAGE AND ADMINISTRATION:

Important Dosage and Administration Instructions
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see WARNINGS].

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].

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with TREZIX™ and adjust the dosage accordingly [see WARNINGS].

Initial Dosage
Initiating treatment with TREZIX™

The usual adult dosage is two (2) TREZIX™ (acetaminophen, caffeine, and dihydrocodeine bitartrate) capsules orally every four (4) hours, as needed. No more than five (5) doses, or ten (10) capsules should be taken in a 24-hour period.

Conversion from Other Opioids to TREZIX™
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 TREZIX™. It is safer to underestimate a patient's 24-hour TREZIX™ dosage than to overestimate the 24-hour TREZIX™ dosage and manage an adverse reaction due to overdose.

Titration and Maintenance of Therapy
Individually titrate TREZIX™ to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving TREZIX™ 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]. 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 TREZIX™ 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.

Discontinuation of TREZIX™
When a patient who has been taking TREZIX™ regularly and may be physically dependent no longer requires therapy with TREZIX™, 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 TREZIX™ in a physically-dependent patient [see WARNINGS, DRUG ABUSE AND DEPENDENCE].

HOW SUPPLIED:
TREZIX™ capsules, containing acetaminophen 320.5 mg, caffeine 30 mg and dihydrocodeine bitartrate 16 mg, are supplied in bottles of 100 capsules (NDC #66992-840-10) and 30 capsules (NDC #66992-840-30).
Capsules are imprinted "TREZIX" on the red cap in white ink.

Store at 20°C to 25°C (68°F to 77°F). [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container with a child-resistant closure. Protect from moisture.

Rx Only

Manufactured for:
WraSer Pharmaceuticals LLC
Ridgeland, MS 39157
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