PENTAZOCINE AND NALOXONE- pentazocine hydrochloride and naloxone hydrochloride tablet
Actavis Pharma, Inc.

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Pentazocine and Naloxone Tablets USP C-IV

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Analgesic for Oral Use Only
WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
Pentazocine and naloxone tablets 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 pentazocine and naloxone tablets, and monitor all patients regularly for the development of these behaviors or conditions [see WARNINGS].

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of pentazocine and naloxone tablets. Monitor for respiratory depression, especially during initiation of pentazocine and naloxone tablets or following a dose increase [see WARNINGS].

Accidental Ingestion
Accidental ingestion of even one dose of pentazocine and naloxone tablets, especially by children, can result in a fatal overdose of pentazocine and naloxone tablets [see WARNINGS].

Neonatal Opioid Withdrawal Syndrome
Prolonged use of pentazocine and naloxone tablets 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].

Cytochrome P450 3A4 Interaction
The concomitant use of pentazocine and naloxone tablets with all cytochrome P450 3A4 inhibitors may result in an increase in pentazocine and naloxone 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 pentazocine and naloxone plasma concentration. Monitor patients receiving pentazocine and naloxone tablets and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

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 pentazocine and naloxone tablets 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
Pentazocine and naloxone tablets USP contain pentazocine hydrochloride, USP, equivalent to 50 mg base and is a member of the benzazocine series (also known as the benzomorphan series), and naloxone hydrochloride, USP, equivalent to 0.5 mg base.
Pentazocine and naloxone tablets USP are an analgesic for oral administration.

Chemically, pentazocine hydrochloride, USP is (2R*,6R*,11R*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride, a white, crystalline substance soluble in acidic aqueous solutions, and has the following structural formula:

\[
\text{C}_{19}\text{H}_{27}\text{NO}\cdot\text{HCl} \quad \text{Molecular Weight: 321.88}
\]

Chemically, naloxone hydrochloride, USP is Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α). It is a slightly off-white powder, and is soluble in water and dilute acids, and has the following structural formula:

\[
\text{C}_{19}\text{H}_{21}\text{NO}_4\cdot\text{HCl} \quad \text{Molecular Weight: 363.84}
\]

Inactive Ingredients: colloidal silicon dioxide, dibasic calcium phosphate, D&C Yellow No. 10 Al-lake, FD&C Blue No. 1 Al-lake, FD&C Yellow No. 6 Al-lake, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium lauryl sulfate.
Pentazocine is a Schedule IV opioid analgesic which when administered orally in a 50 mg dose appears equivalent in analgesic effect to 60 mg of codeine.

Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.

Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually three hours or longer.

Pentazocine is well absorbed from the gastrointestinal tract. Concentrations in plasma coincide closely with the onset, duration, and intensity of analgesia. The time to mean peak concentration in 24 normal volunteers was 1.7 hours (range 0.5 to 4 hours) after oral administration and the mean plasma elimination half-life was 3.6 hours (range 1.5 to 10 hours).

Pentazocine is metabolized in the liver and excreted primarily in the urine. The products of the oxidation of the terminal methyl groups and glucuronide conjugates are excreted by the kidney. Elimination of approximately 60% of the total dose occurs within 24 hours. Pentazocine passes into the fetal circulation.

Naloxone when administered orally at 0.5 mg has no pharmacologic activity. Naloxone hydrochloride administered parenterally at the same dose is an antagonist to pentazocine and a pure antagonist to narcotic analgesics.

Pentazocine and naloxone tablets are a potent analgesic when administered orally. However, the presence of naloxone in pentazocine and naloxone tablets is intended to prevent the effect of pentazocine if the product is misused by injection.

Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized.

INDICATIONS AND USAGE

Pentazocine and naloxone tablets are indicated for the management of moderate to severe 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 pentazocine and naloxone tablets 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

Pentazocine and naloxone tablets USP is indicated for oral use only.

CONTRAINDICATIONS

Pentazocine and naloxone tablets are 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]
- Hypersensitivity to either pentazocine or naloxone.
WARNINGS

Addiction, Abuse, and Misuse

Pentazocine and naloxone tablets contain pentazocine, a Schedule IV controlled substance. As an opioid, pentazocine and naloxone tablets expose 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 pentazocine and naloxone tablets. 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 pentazocine and naloxone tablets, and monitor all patients receiving pentazocine and naloxone tablets 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 pentazocine and naloxone tablets, but use in such patients necessitates intensive counseling about the risks and proper use of pentazocine and naloxone tablets 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 pentazocine and naloxone tablets. 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.

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 (CO₂) 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 pentazocine and naloxone tablets, 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 to 72 hours of initiating therapy with and following dosage increases of pentazocine and naloxone tablets.

To reduce the risk of respiratory depression, proper dosing and titration of pentazocine and naloxone tablets are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the pentazocine and naloxone tablets 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 pentazocine and naloxone tablets, especially by children, can result in respiratory depression and death due to an overdose of pentazocine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of pentazocine and naloxone tablets 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. 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
Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of pentazocine and naloxone tablets 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 pentazocine and naloxone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see WARNINGS], particularly when an inhibitor is added after a stable dose of pentazocine and naloxone is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in pentazocine and naloxone-treated patients may increase pentazocine and naloxone plasma concentrations and prolong opioid adverse reactions. When using pentazocine and naloxone with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in pentazocine and naloxone-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of pentazocine and naloxone until stable drug effects are achieved [see PRECAUTIONS; Drug Interactions].

Concomitant use of pentazocine and naloxone with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease pentazocine and naloxone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to pentazocine and naloxone. When using pentazocine and naloxone 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 PRECAUTIONS; Drug Interactions].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of pentazocine and naloxone tablets 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 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 pentazocine and naloxone tablets are 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 pentazocine and naloxone tablets 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:* Pentazocine and naloxone-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 pentazocine and naloxone tablets [see WARNINGS].

*Elderly, Cachectic, 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 pentazocine and naloxone tablets and when pentazocine and naloxone tablets are 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.

**Use In Head Injury and Increased Intracranial Pressure**

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of pentazocine and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly increased. Furthermore, pentazocine can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. In such patients, pentazocine must be used with extreme caution and only if its use is deemed essential.

**Interactions with Alcohol and Drugs of Abuse**

Pentazocine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, profound sedation, coma or death may result.

**Patients Receiving Narcotics**

Pentazocine is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving pentazocine.

**Acute CNS Manifestations**

Patients receiving therapeutic doses of pentazocine and naloxone tablets have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted, it should be done with caution since these acute CNS manifestations may recur.
PRECAUTIONS

Drug Abuse and Dependence

Pentazocine and naloxone tablets are a Schedule IV controlled substance. Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of a drug for non-medical purposes, often in combination with other psychoactive substances. Addiction is a disease of repeated drug abuse. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physicians 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 addiction and is characterized by misuse of the drug for non-medical purposes, and often in combination with other psychoactive substances.

There have been some reports of dependence and of withdrawal symptoms with pentazocine and naloxone tablets. Patients with a history of drug dependence should be under close supervision while receiving pentazocine and naloxone tablets. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of pentazocine and naloxone tablets during pregnancy. There have been reports of development of addiction and physical dependence in patients receiving parenteral pentazocine. People with a history of drug abuse or alcohol abuse may have a higher chance of becoming addicted to opioid medicines.

Abrupt dose cessation or rapid dose reduction following the extended use of parenteral pentazocine has resulted in withdrawal symptoms such as abdominal cramps, nausea, vomiting, elevated temperature, chills, rhinorrhea, restlessness, anxiety, or lacrimation. In general opioid therapy should not be abruptly discontinued. When the patient no longer requires treatment with pentazocine and naloxone tablets, the drug should be tapered gradually to prevent signs and symptoms of withdrawal in patients who have been receiving opioids for an extended period of time and might have become physically dependent.

In prescribing pentazocine and naloxone tablets for chronic use, the physician should take under consideration that proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to identify and decrease misuse and abuse of opioid drugs.

The amount of naloxone present in pentazocine and naloxone tablets (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

CNS Effect

Caution should be used when pentazocine and naloxone tablets is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of pentazocine though no cause and effect relationship has been established.
Porphyria

Particular caution should be exercised in administering pentazocine to patients with porphyria since it may provoke an acute attack in susceptible individuals.

Cardiovascular Disease

Pentazocine can elevate blood pressure, possibly through the release of endogenous catecholamines. Particular caution should be exercised in conditions where alterations in vascular resistance and blood pressure might be particularly undesirable, such as in the acute phase of myocardial infarction.

Pentazocine and naloxone tablets should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Impaired Renal or Hepatic Function

Decreased metabolism of pentazocine by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that pentazocine causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

Other

Caution should also be observed when administering pentazocine and naloxone tablets in patients with hypothyroidism, adrenocortical insufficiency, prostate hypertrophy, inflammatory or obstructive bowel disease, acute abdominal syndromes of unknown etiology, cholecystitis, pancreatitis, or acute alcohol intoxication and delirium tremens.

Biliary Surgery

Narcotic drug products are generally considered to elevate biliary tract pressure for varying periods following their administration. Some evidence suggests that pentazocine may differ from other marketed narcotics in this respect (i.e., it causes little or no elevation in biliary tract pressures). The clinical significance of these findings, however, is not yet known.

Information for Patients

Addiction, Abuse, and Misuse
Inform patients that the use of pentazocine and naloxone tablets, 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 pentazocine and naloxone tablets with others and to take steps to protect pentazocine and naloxone tablets 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 pentazocine and naloxone tablets 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 pentazocine and naloxone tablets securely and to dispose of unused pentazocine and naloxone tablets by consulting their pharmacist for proper disposal instructions.

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if pentazocine and naloxone tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to
use these concomitantly unless supervised by a healthcare provider [see WARNINGS and PRECAUTIONS; Drug Interactions].

Serotonin Syndrome
Inform patients that pentazocine and naloxone tablets 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 pentazocine and naloxone tablets 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].

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of pentazocine and naloxone tablets 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 pentazocine and naloxone tablets can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [see PRECAUTIONS; Pregnancy].

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 PRECAUTIONS; Nursing Mothers].

Disposal of Unused Pentazocine and Naloxone Tablets
Advise patients to consult their pharmacist for proper disposal instructions.

Patients receiving pentazocine and naloxone tablets should be given the following instructions by the physician:
- Patients should be advised that pentazocine and naloxone tablets are a narcotic pain reliever, and should be taken only as directed.
- The dose of pentazocine and naloxone tablets should not be adjusted without consulting with a physician or other healthcare professional.
- Patients should be advised that pentazocine and naloxone tablets may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on pentazocine and naloxone tablets or patients whose dose has been adjusted should refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- If patients have been receiving treatment with pentazocine and naloxone tablets for more than a few weeks and cessation of therapy is indicated, they should be counseled on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. The physician should provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Patients should be advised that pentazocine and naloxone tablets are a potential drug of abuse. They should protect it from theft. It should never be given to anyone other than the individual for whom it was prescribed.
- As with other opioids, patients taking pentazocine and naloxone tablets should be advised of the
potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.

- Patients should be advised of the most common adverse events that may occur while taking pentazocine and naloxone tablets: constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, and sweating.

**Drug Interactions**

**CYP3A4**

**Inhibitor**
The concomitant use of pentazocine and naloxone tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), can increase the plasma concentration of pentazocine and naloxone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of pentazocine and naloxone tablets and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of pentazocine and naloxone tablets is achieved [see WARNINGS].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the pentazocine and naloxone plasma concentration will decrease [see CLINICAL PHARMACOLOGY], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to pentazocine and naloxone tablets.

If concomitant use is necessary, consider dosage reduction of pentazocine and naloxone tablets 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 pentazocine and naloxone tablet dosage until stable drug effects are achieved [see DOSAGE AND ADMINISTRATION]. Monitor for signs of opioid withdrawal.

**Inducer**
The concomitant use of pentazocine and naloxone tablets and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of pentazocine and naloxone tablets [see CLINICAL PHARMACOLOGY], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to pentazocine and naloxone tablets [see WARNINGS].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the pentazocine and naloxone tablets plasma concentration will increase [see CLINICAL PHARMACOLOGY], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the pentazocine and naloxone tablets dosage until stable drug effects are achieved [see DOSAGE AND ADMINISTRATION]. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider pentazocine and naloxone tablet dosage reduction and monitor for signs of respiratory depression.

**Benzodiazepines and other Central Nervous System (CNS) Depressants**
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increases the risk of 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 (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome. [see PRECAUTIONS; Information for Patients].

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue pentazocine and naloxone tablets if serotonin syndrome is suspected.

Opioid Agonist Analgesics
Pentazocine and naloxone tablets can antagonize the effects of a pure opioid agonist analgesic and/or may precipitate withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOIs)
Concomitant use of monoamine oxidase inhibitors (MAOIs) with pentazocine and naloxone tablets may cause CNS excitation and hypertension through their respective effects on catecholamines. Caution should therefore be observed in administering pentazocine and naloxone tablets to patients who are currently receiving MAOIs or who have received them within the preceding 14 days.

Anticholinergics
Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Tobacco
Smoking tobacco could enhance the metabolic clearance rate of pentazocine reducing the clinical effectiveness of a standard dose of pentazocine.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals to test for carcinogenesis have been performed with the components of pentazocine and naloxone tablets.

Studies to evaluate the mutagenic potential of the components of pentazocine and naloxone tablets have not been conducted.

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
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 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. Pentazocine and naloxone tablets are not recommended for use in
pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including pentazocine and naloxone tablets, 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**

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for pentazocine and naloxone tablets and any potential adverse effects on the breastfed infant from pentazocine and naloxone tablets or from the underlying maternal condition.

Infants exposed to pentazocine and naloxone 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.

**Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

**Geriatric Use**

Elderly patients (aged 65 years or older) may have increased sensitivity to pentazocine and naloxone tablets. 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 pentazocine and naloxone tablets slowly in geriatric patients [see WARNINGS].

**ADVERSE REACTIONS**

**Cardiovascular** - Hypertension, hypotension, circulatory depression, tachycardia, syncope.

**Respiratory** - Rarely, respiratory depression.

**Acute CNS Manifestations** - Hallucinations (usually visual), disorientation, and confusion.

**Other CNS Effects** - Grand mal convulsions, increase in intracranial pressure, dizziness, lightheadedness, hallucinations, sedation, euphoria, headache, confusion, disorientation; infrequently weakness, disturbed dreams, insomnia, syncope, and depression; and rarely tremor, irritability, excitement, tinnitus.

**Autonomic** - Sweating; infrequently flushing; and rarely chills.

**Gastrointestinal** - Nausea, vomiting, constipation, diarrhea, anorexia, dry mouth, biliary tract spasm, and rarely abdominal distress.

**Allergic** - Edema of the face; anaphylactic shock; dermatitis, including pruritus; flushed skin, including plethora; infrequently rash, and rarely urticaria.

**Ophthalmic** - Visual blurring and focusing difficulty, miosis.

**Hematologic** - Depression of white blood cells (especially granulocytes), with rare cases of agranulocytosis, which is usually reversible, moderate transient eosinophilia.

**Dependence and Withdrawal Symptoms** - (See WARNINGS, PRECAUTIONS, and DRUG ABUSE AND DEPENDENCE Sections).
Other - Urinary retention, paresthesia, serious skin reactions, including erythema multiforme, Stevens-Johnson syndrome toxic epidermal necrolysis, and alterations in rate or strength of uterine contractions during labor.

Postmarketing Experience
- serotonin syndrome
- adrenal insufficiency

Androgen deficiency
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms of hypogonadism, such as impotence, erectile dysfunction, or amenorrhea. The causal role of opioids in the 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Pentazocine and naloxone tablets contain pentazocine, a Schedule IV controlled substance.

Abuse
Pentazocine and naloxone tablets contain pentazocine, a substance with a high potential for abuse similar to other opioids used in analgesia. Pentazocine and naloxone tablets 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.

Pentazocine and naloxone tablets, 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 Pentazocine and Naloxone Tablets

Pentazocine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

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.

Pentazocine and naloxone tablets should not be abruptly discontinued [see DOSAGE AND ADMINISTRATION]. If pentazocine and naloxone tablets are 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

Clinical Presentation

Acute overdose with pentazocine and naloxone tablets 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.

Treatment of Overdose

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

Because the duration of opioid reversal is expected to be less than the duration of action of pentazocine and naloxone in pentazocine and naloxone tablets, 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.

**DOSAGE AND ADMINISTRATION**

**Important Dosage and Administration Instructions**

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 to 72 hours of initiating therapy and following dosage increases with pentazocine and naloxone tablets and adjust the dosage accordingly [see **WARNINGS**].

**Initial Adult Dosage**

*Initiating Treatment with Pentazocine and Naloxone Tablets*

The usual initial adult dose is 1 tablet every three or four hours. This may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets.

*Conversion from Other Opioids to Pentazocine and Naloxone Tablets*

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 pentazocine and naloxone tablets. It is safer to underestimate a patient’s 24-hour pentazocine and naloxone tablet dosage than to overestimate the 24-hour pentazocine and naloxone tablet dosage and manage an adverse reaction due to overdose.

**Titration and Maintenance of Therapy**

Individually titrate pentazocine and naloxone tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving pentazocine and naloxone tablets 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 pentazocine and naloxone tablet 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 Pentazocine and Naloxone Tablets**

When a patient who has been taking pentazocine and naloxone tablets regularly and may be physically dependent no longer require therapy with pentazocine and naloxone tablets, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop pentazocine and naloxone tablets abruptly [see **WARNINGS, DRUG ABUSE AND DEPENDENCE**].

**HOW SUPPLIED**

Pentazocine and naloxone tablets USP are light green, scored, capsule shaped tablets debossed 395 to the left of the score, 50 over 0.5 to the right of the score and WATSON on the reverse side supplied in bottles of 100.

Bottles of 100…………………………………..NDC 0591-0395-01
Medication Guide

Pentazocine and Naloxone (pentazocine and naloxone)
Tablets, USP
CIV

Pentazocine and naloxone tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage moderate to severe pain, 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 pentazocine and naloxone tablets:

- Get emergency help right away if you take too many pentazocine and naloxone tablets (overdose). When you first start taking pentazocine and naloxone tablets, 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 pentazocine and naloxone tablets 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 pentazocine and naloxone tablets. They could die from taking them. Store pentazocine and naloxone tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away pentazocine and naloxone tablets are against the law.

Do not take pentazocine and naloxone tablets if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known hypersensitivity to pentazocine or naloxone.

Before taking pentazocine and naloxone tablets, tell your healthcare provider if you have a history of:
- head injury, seizures
- problems urinating
- 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 pentazocine and naloxone tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
• **breastfeeding.** Pentazocine and naloxone passes into breast milk and may harm your baby.
• taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking pentazocine and naloxone tablets with certain other medicines can cause serious side effects that could lead to death.

**When taking pentazocine and naloxone tablets:**
• Do not change your dose. Take pentazocine and naloxone tablets exactly as prescribed by your healthcare provider.
• Take your prescribed dose every 3 or 4 hours at the same time every day. 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 pentazocine and naloxone tablets regularly, do not stop taking pentazocine and naloxone tablets without talking to your healthcare provider.
• After you stop taking pentazocine and naloxone tablets, consult your pharmacist for proper disposal instructions.

**While taking pentazocine and naloxone tablets DO NOT:**
• Drive or operate heavy machinery, until you know how pentazocine and naloxone tablets affect you. Pentazocine and naloxone tablets 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 pentazocine and naloxone tablets may cause you to overdose and die.

**The possible side effects of pentazocine and naloxone tablets:**
• constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. 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.

These are not all the possible side effects of pentazocine and naloxone tablets. 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.**

For more information call Actavis at 1-800-272-5525.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

Manufactured by:
Watson Pharma Private Limited
Verna, Salcette Goa 403 722 INDIA

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: September 2016
224426-3

**Principal Display Panel**
PENTAZOCINE AND NALOXONE
pentazocine hydrochloride and naloxone hydrochloride tablet

Product Information

Product Type: HUMAN PRESCRIPTION DRUG
Route of Administration: ORAL

Active Ingredient/Active Moiety

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Inactive Ingredients

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## STARCH, CORN (UNII: O8232NY3SJ)

### SODIUM LAURYL SULFATE (UNII: 368GB5141J)

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### Labeler - Actavis Pharma, Inc. (119723554)

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Revised: 9/2016