

TALWIN[®] Nx C_{IV}
pentazocine and naloxone
hydrochlorides, USP

Analgesic for Oral Use
Only

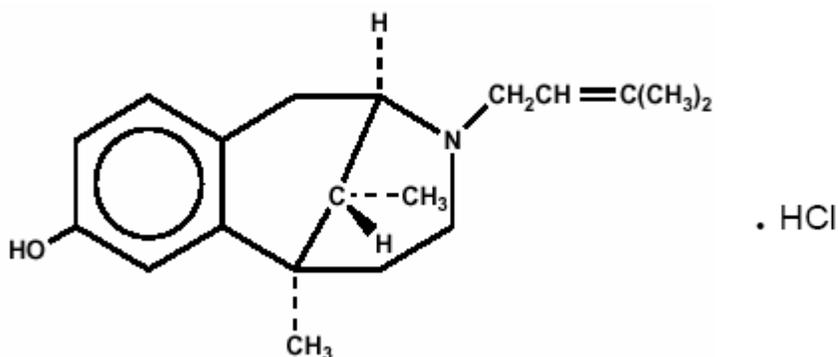
TALWIN[®] Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN[®] Nx by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

DESCRIPTION

TALWIN Nx (pentazocine and naloxone hydrochlorides, USP) contains 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.

TALWIN Nx is an analgesic for oral administration.

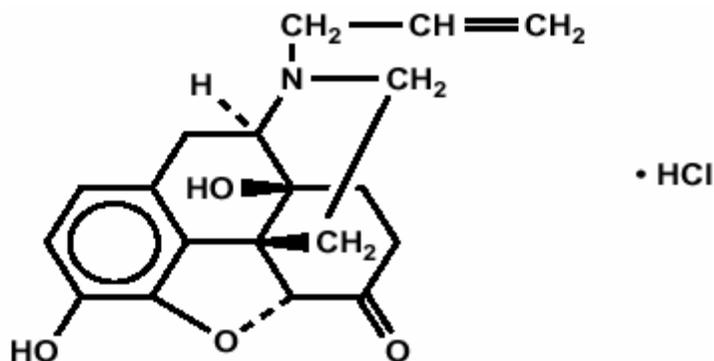
Chemically, pentazocine hydrochloride is (2*R**,6*R**,11*R**)-1,2, 3, 4, 5, 6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride, a white, crystalline substance soluble in acidic aqueous solutions, and has the following structural formula:



C₁₉H₂₇NO·HCl

M.W. 321.88

Chemically, naloxone hydrochloride 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:



$C_{19}H_{21}NO_4 \cdot HCl$

M.W.=363.84

Inactive Ingredients: Colloidal Silicon Dioxide, Dibasic Calcium Phosphate, D&C Yellow #10, FD&C Yellow #6, Magnesium Stearate, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Starch.

CLINICAL PHARMACOLOGY

Pentazocine is a potent analgesic which when administered orally in a 50 mg dose appears equivalent in analgesic effect to 60 mg (1 grain) of codeine. Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually three hours or longer. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain. 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.

Pentazocine is well absorbed from the gastrointestinal tract. Concentrations in plasma coincide closely with the onset, duration, and intensity of analgesia; peak values occur 1 to 3 hours after oral administration. The half-life in plasma is 2 to 3 hours.

Pentazocine is metabolized in the liver and excreted primarily in the urine. 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 effective antagonist to pentazocine and a pure antagonist to narcotic analgesics.

TALWIN Nx is a potent analgesic when administered orally. However, the presence of naloxone in TALWIN Nx will 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

TALWIN[®] Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN[®] Nx by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

TALWIN Nx (pentazocine and naloxone hydrochlorides, USP) is indicated for the relief of moderate to severe pain.

TALWIN Nx is indicated for oral use only.

CONTRAINDICATIONS

TALWIN Nx should not be administered to patients who are hypersensitive to either pentazocine or naloxone.

TALWIN[®] Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN[®] Nx by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

WARNINGS

Drug Dependence. Pentazocine can cause a physical and psychological dependence. (See DRUG ABUSE AND DEPENDENCE.)

Head Injury and Increased Intracranial Pressure. As in the case of other potent analgesics, the potential of pentazocine for elevating cerebrospinal fluid pressure may be attributed to CO₂ retention due to the respiratory depressant effects of the drug. These effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, pentazocine can produce effects which may obscure the clinical course of patients with head injuries. In such patients, pentazocine must be used with extreme caution and only if its use is deemed essential.

Usage with Alcohol. Due to the potential for increased CNS depressant effects, alcohol should be used with caution in patients who are currently receiving pentazocine.

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.

Certain Respiratory Conditions. Although respiratory depression has rarely been reported after oral administration of pentazocine, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma, and other obstructive respiratory conditions, or cyanosis.

Acute CNS Manifestations. Patients receiving therapeutic doses of pentazocine 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 reinstated, it should be done with caution since these acute CNS manifestations may recur.

PRECAUTIONS

CNS Effect. Caution should be used when pentazocine 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.

As with all drugs, pentazocine 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.

In prescribing pentazocine for long-term use, the physician should take precautions to avoid increases in dose by the patient.

Other. Caution should also be observed when administering pentazocine 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. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. Pentazocine may cause physical and psychological dependence when taken alone and may have additive CNS depressant properties when taken in combination with alcohol or other CNS depressants.

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

Agents with CNS depressant properties including phenothiazine, tricyclic antidepressants, and ethyl alcohol can enhance the central nervous system depressant effects of pentazocine (See WARNINGS).

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

Pentazocine can antagonize the effects of opiate agonists such as diamorphine, morphine, and heroin and is itself antagonized by naloxone.

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

Pregnancy Category C. In animal reproduction studies (rodents), teratogenic effects were reported only at doses high enough to cause maternal toxicity. The safe use of

pentazocine in pregnant women (other than during labor) has not been established. TALWIN Nx should be given to pregnant women only if clearly needed.

Labor and Delivery. Patients receiving pentazocine during labor have experienced no adverse effects other than those that occur with commonly used analgesics. However, pentazocine can cross the placental barrier and cause central nervous system depression in the newborn and, if used regularly throughout pregnancy, may lead to symptoms of withdrawal in the newborn. TALWIN Nx should be used with caution in women delivering premature infants. The effect of TALWIN Nx on the mother and fetus, the duration of labor or delivery, the possibility that forceps delivery or other intervention or resuscitation of the newborn may be necessary, or the effect of TALWIN Nx on the later growth, development, and functional maturation of the child are unknown at the present time.

Nursing Mothers. Pentazocine is excreted in human milk. Caution should be exercised when TALWIN Nx is administered to a nursing woman.

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

Geriatric Use. Controlled clinical studies of TALWIN NX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses or effectiveness in analgesic activity between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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.

ADVERSE REACTIONS

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

Respiratory. Rarely, respiratory depression.

Acute CNS Manifestations. Patients receiving therapeutic doses of pentazocine 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 closely observed and vital signs checked. If the drug is reinstated it should be done with caution since these acute CNS manifestations may recur.

Other CNS Effects. Grand mal convulsions, increase in intracranial pressure, dizziness, lightheadedness, hallucinations, sedation, euphoria, headache, confusion, disorientation; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, 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. Headache, chills, insomnia, weakness, 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance. TALWIN Nx is 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 orally administered pentazocine. Patients with a history of drug dependence should be under close supervision while receiving pentazocine orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of pentazocine 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 Talwin Nx, 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 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 TALWIN Nx (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.

TALWIN Nx contains an opioid antagonist, naloxone (0.5 mg). Naloxone is inactive when administered orally at this dose, and its inclusion in TALWIN Nx is intended to curb a form of misuse of oral pentazocine. Parenterally, naloxone is an active narcotic antagonist. Thus, TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation TALWIN® 50 (pentazocine hydrochloride tablets, USP). However, it is still subject to patient misuse and abuse by the oral route.

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OVERDOSAGE

Manifestations. The symptoms and clinical signs of pentazocine overdose may resemble those of morphine or other opioids. They may include somnolence, respiratory depression, hypotension, hypertension, tachycardia, hallucinations, or seizures. Circulatory failure and deepening coma may occur in more severe cases, particularly in patients who have also ingested other CNS depressants such as alcohol, sedative/hypnotics, or antihistamines.

Treatment. Adequate measures to maintain ventilation and general circulatory support should be employed. Assisted or controlled ventilation, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Consideration should be given to gastric lavage and gastric aspiration. For respiratory depression due to overdose or unusual sensitivity to pentazocine, parenteral naloxone is a specific and effective antagonist. Initial doses of 0.4 to 2.0 mg of naloxone are recommended, repeated at 2-3 minute intervals, if needed, up to a total of 10 mg. Anti-convulsant therapy may be necessary.

DOSAGE AND ADMINISTRATION

Adults. 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.

When anti-inflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with this product.

Pediatric Patients. Since clinical experience in pediatric patients under 12 years of age is limited, administration of this product in this age group is not recommended.

Duration of Therapy. Patients with chronic pain who receive TALWIN Nx orally for prolonged periods have only rarely been reported to experience withdrawal symptoms when administration was abruptly discontinued (see WARNINGS). Tolerance to the analgesic effect of pentazocine has also been reported only rarely. However, there is no long-term experience with the oral administration of TALWIN Nx.

HOW SUPPLIED

Talwin Nx (pentazocine and naloxone hydrochlorides, USP) is available as yellow, scored, oblong tablets, debossed with a “W” surrounded by a box on one side and “T51” on the other. Each tablet contains pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base.

Bottles of 100 (NDC 0024-1951-04).

Store at 25° C (77° F); excursions permitted between 15° - 30° C (59° F to 86° F).

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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