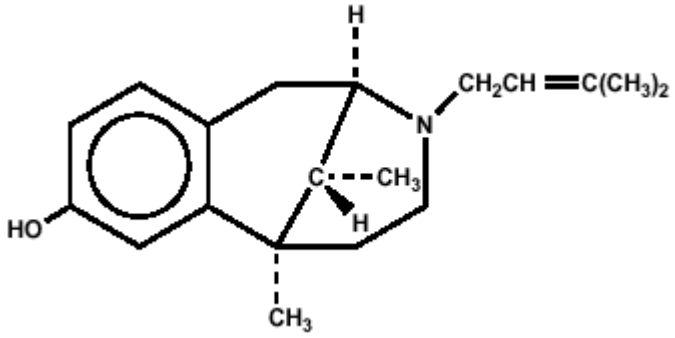
CIV

TALACEN®
Pentazocine hydrochloride, USP, and acetaminophen, USP

DESCRIPTION

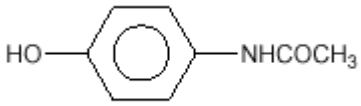
TALACEN is a combination of pentazocine hydrochloride, USP, equivalent to 25 mg base and acetaminophen, USP, 650 mg.

Pentazocine is a member of the benzazocine series (also known as the benzomorphan series). Chemically, pentazocine 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, a white, crystalline substance soluble in acidic aqueous solutions, and has the following structural formula:



$C_{19}H_{27}NO$ HCl M.W. 321.88

Chemically, acetaminophen is Acetamide, N-(4-hydroxyphenyl)-, and has the following structural formula:



$C_8H_9NO_2$ M.W. 151.16

Pentazocine is an analgesic and acetaminophen is an analgesic and antipyretic.
Inactive Ingredients: Colloidal Silicon Dioxide, FD&C Blue #1, Gelatin, Microcrystalline Cellulose, Potassium Sorbate, Pregelatinized Starch, Sodium Lauryl Sulfate, Sodium Metabisulfite, Sodium Starch Glycolate, Stearic Acid.

CLINICAL PHARMACOLOGY

Pentazocine is a Schedule IV opioid analgesic with agonist/antagonist action which when administered orally is approximately equivalent on a mg for mg basis in analgesic effect to codeine.

Acetaminophen is an analgesic and antipyretic.

Pentazocine weakly antagonizes the analgesic effects of morphine, meperidine, and phenazocine; 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 with pentazocine 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. Plasma levels closely correspond to 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).

The action of pentazocine is terminated for the most part by biotransformation in the liver with some free pentazocine excreted 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 fetal circulation.

Onset of significant analgesic and antipyretic activity of acetaminophen when administered orally occurs within 30 minutes and is maximal at approximately 2 1/2 hours. The pharmacological mode of action of acetaminophen is unknown at this time.

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. In 24 normal volunteers the time to mean peak plasma concentration was 1 hour (range 0.25 to 3 hours) after oral administration and the mean plasma elimination half-life was 2.8 hours (range 2 to 4 hours).

The effect of pentazocine on acetaminophen plasma protein binding or vice versa has not been established. For acetaminophen there is little or no plasma protein binding at normal therapeutic doses. When toxic doses of acetaminophen are ingested and drug plasma levels exceed 90 mcg/mL, plasma binding may vary from 8% to 43%.

Acetaminophen is conjugated in the liver with glucuronic acid and to a lesser extent with sulfuric acid. Approximately 80% of acetaminophen is excreted in the urine after conjugation and about 3% is excreted unchanged. The drug is also conjugated to a lesser extent with cysteine and additionally metabolized by hydroxylation.

If TALACEN is taken every 4 hours over an extended period of time, accumulation of pentazocine and to a lesser extent, acetaminophen, may occur.

INDICATIONS AND USAGE

TALACEN is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TALACEN is contraindicated in patients who are hypersensitive to either pentazocine or acetaminophen.

TALACEN is contraindicated in patients with sulfite allergy.

WARNINGS

Hypersensitivity/anaphylaxis

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

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 emergent medical attention. Instruct patients to discontinue TALACEN immediately and seek medical care if they experience these symptoms. Do not prescribe TALACEN for patients with acetaminophen allergy.

Drug Dependence

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

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, TALACEN 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.

Respiratory Depression
Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. Use TALACEN with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. Alternative non-opioid analgesics should be considered, and TALACEN should be employed only under careful medical supervision at the lowest effective dose in such patients.

Acute CNS Manifestations

Patients receiving therapeutic doses of TALACEN 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 reinstituted, it should be done with caution since these acute CNS manifestations may recur.

PRECAUTIONS
Drug Abuse and Dependence
TALACEN 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 TALACEN. 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 TALACEN, 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 TALACEN 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.

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 TALACEN is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of pentazocine although 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.

TALACEN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Impaired Renal or Hepatic Function

Decreased metabolism of the drug 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.

Since acetaminophen is metabolized by the liver, the question of the safety of its use in the presence of liver disease should be considered.

Other

Caution should also be observed when administering TALACEN 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.
Patients receiving TALACEN should be given the following instructions by the physician:

- Patients should be advised that TALACEN is a narcotic pain reliever, and should be taken only as directed.
- The dose of TALACEN should not be adjusted without consulting with a physician or other healthcare professional.
- Patients should be advised that TALACEN 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 TALACEN or patients whose dose has been adjusted should refrain from any potentially dangerous activity until it is established that they are not adversely affected.

- TALACEN will add to the effect of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO]inhibitors).
- Patients should not combine TALACEN with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Women of childbearing potential who become or are planning to become pregnant should consult a physician prior to initiating or continuing therapy with TALACEN.
- Safe use in pregnancy has not been established. Prolonged use of opioid analgesics during pregnancy may cause neonatal physical dependence, and neonatal withdrawal may occur.
- If patients have been receiving treatment with TALACEN 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 TALACEN is 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.
- Patients should be instructed to keep TALACEN in a secure place out of the reach of children. When TALACEN is no longer needed, please consult your pharmacist for proper disposal instructions.
- As with other opioids, patients taking TALACEN 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 TALACEN: constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, and sweating.

Drug Interactions.

CNS Depressants

Other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use morphine sulfate with caution and in reduced dosages in patients taking these agents.

Opioid Agonist Analgesics

TALACEN 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 TALACEN may cause CNS excitation and hypertension through their respective effects on catecholamines. Caution should

therefore be observed in administering TALACEN 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

Carcinogenesis, mutagenesis, and impairment of fertility studies have not been done with this combination product.

Studies to evaluate the mutagenic potential of the components of TALACEN have not been conducted.

Pentazocine, when administered orally or parenterally, had no adverse effect on either the reproductive capabilities or the course of pregnancy in rabbits and rats. Embryotoxic effects on the fetuses were not shown.

The daily administration of 4 mg/kg to 20 mg/kg pentazocine subcutaneously to female rats during a 14 day pre-mating period and until the 13th day of pregnancy did not have any adverse effects on the fertility rate.

Pregnancy
Teratogenic Effects
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. TALACEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal studies with the combination of pentazocine and acetaminophen have not been completed.

In a published report, a single dose of pentazocine administered to pregnant hamsters on gestation day 8 increased the incidence of exencephaly and cranioschisis at a dose of 196 mg/kg, SC (0.2-times the maximum daily human dose of pentazocine via 6 caplets on a mg/m^2 basis).

Nonteratogenic Effects

There has been no experience in this regard with the combination pentazocine and acetaminophen. However, there have been rare reports of possible abstinence syndromes in

newborns after prolonged use of pentazocine during pregnancy. Frequent use of acetaminophen (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant which may persist into childhood.

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. TALACEN should be used with caution in women delivering premature infants. The effect of TALACEN 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 TALACEN, on the later growth, development, and functional maturation of the child are unknown at the present time.

Nursing Mothers

Pentazocine and acetaminophen are excreted in human milk. Caution should be exercised when TALACEN is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

Clinical studies of TALACEN 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 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

Clinical experience with TALACEN has been insufficient to define all possible adverse reactions with this combination. However, reactions reported after oral administration of pentazocine hydrochloride in 50 mg dosage include the following:

Cardiovascular: hypertension, hypotension, circulatory depression, tachycardia.

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.

Numerous clinical studies have shown that acetaminophen, when taken in recommended doses, is relatively free of adverse effects in most age groups, even in the presence of a variety of disease states.

A few cases of hypersensitivity to acetaminophen have been reported, as manifested by skin rashes, thrombocytopenic purpura, rarely hemolytic anemia and agranulocytosis. Occasional individuals respond to ordinary doses with nausea and vomiting and diarrhea.

OVERDOSAGE

Manifestations

For pentazocine alone in single doses above 60 mg there have been reports of the occurrence of nalorphine-like psychotomimetic effects such as anxiety, nightmares, strange thoughts, and hallucinations. Somnolence, marked respiratory depression associated with increased blood pressure and tachycardia have also resulted as have seizures, hypotension, dizziness, nausea, vomiting, lethargy, and paresthesias. The respiratory depression is antagonized by naloxone (see Treatment). 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.

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, a single dose of 10 g to 15 g (200 mg/kg to 250 mg/kg) of acetaminophen may cause hepatotoxicity. A dose of 25 g or more is potentially fatal. The potential seriousness of the intoxication may not be evident during the first two days of acute acetaminophen poisoning. During the first 24 hours, nausea, vomiting, anorexia, and abdominal pain occur. These may persist for a week or more. Liver injury may become evident the second day, initial signs being elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration, and prolongation of prothrombin time. Serum albumin concentration and alkaline phosphatase activity may remain normal. The hepatotoxicity may lead to encephalopathy, coma, and death. Transient azotemia is evident in a majority of patients and acute renal failure occurs in some.

There have been reports of glycosuria and impaired glucose tolerance, but hypoglycemia may also occur. Metabolic acidosis and metabolic alkalosis have been reported. Cerebral edema and non-specific myocardial depression have also been noted. Biopsy reveals centrolobular necrosis with sparing of the periportal area. The hepatic lesions are reversible over a period of weeks or months in nonfatal cases.

The severity of the liver injury can be determined by measurement of the plasma halftime of acetaminophen during the first day of acute poisoning. If the halftime exceeds 4 hours, hepatic necrosis is likely and if the halftime is greater than 12 hours, hepatic coma will probably occur. Only minimal liver damage has developed when the serum concentration was below 120 mcg/mL at 12 hours after ingestion of the drug. If serum bilirubin concentration is greater than 4 mg/100 mL during the first 5 days, encephalopathy may occur.

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 overdosage or unusual sensitivity to TALACEN, 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.

The toxic effects of acetaminophen may be prevented or minimized by antidotal therapy with N-acetylcysteine. In order to obtain the best possible results, N-acetylcysteine should be administered as soon as possible.

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. Induction of vomiting or gastric lavage, followed by oral administration of activated charcoal should be done in all cases.

If hemodialysis can be initiated within the first 12 hours, it is advocated for patients with a plasma acetaminophen concentration exceeding 120 mcg/mL at 4 hours after ingestion of the drug.

DOSAGE AND ADMINISTRATION

Adult

The usual adult dose is 1 caplet every 4 hours as needed for pain relief, up to a maximum of 6 caplets per day.

Discontinuation

Due to the potential for withdrawal symptoms associated with abrupt discontinuation, consideration should be given to tapering patients off TALACEN after prolonged periods of treatment with TALACEN (See PRECAUTIONS, Drug Abuse and Dependence).

HOW SUPPLIED

TALACEN is available for oral administration as a pale blue, scored caplet embossed with “Winthrop” on one side and “T37” on the other side.

Bottles of 100 (NDC 0024-1937-04).

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

Rx Only

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