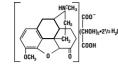


Hydrocodone bitartrate and acetaminophen is

supplied in tablet form for oral administration. Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



 $C_{18}H_{21}NO_3.C_4H_6O_6.2\%H_2O$ 

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



 $C_8H_9NO_2$ 

M.W. 151.16

Each VICODIN ES Tablet contains:

Each VICUDIN ES lablet contains:
Hydrocodone Bitartrate
7.5 mg
Acetaminophen
In addition each tablet contains the following inactive
ingredients: Colloidal silicon dioxide, pregelatinized
starch, magnesium stearate, croscarmellose sodium, povidone, and stearic acid.
Meets USP Dissolution Test 2.
CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other process of the contract of the opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalmic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen are negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid shalling herathing.

effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-\(\alpha\)- and 6-\(\alpha\)- hydroxy- metabolites. See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates, and unchanged drug. See most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information. INDICATIONS AND USAGE

VICODIN ES Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

WARNINGS

MARNINGS
Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of nacrotics and their capacity to elevate cerebrospinal fluid pressure may be

markedly exaggerated in the presence of head injury. markedly exaggerated in the presence of nead injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions, which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of

narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions. Misuse, Abuse, and Diversion of Opioids: VICODIN ES contains hydrocodone, an opioid agonist, and is a Schedule III controlled substance. Opioid agonists have the actential for heir abused on the control of the patients and the control of the control o

Schedule III controlled substance. Opioid agonists have the potential for being abused and are sought by abusers and people with addiction disorders, and are subject to diversion.

VICODIN ES can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing VICODIN ES in situations where the physician or pharmacist is concerned about an increased risk of misues, abuse or diversion (see DRUG ABUSE AND DEPENDENCE).

General:

Special Risk Patients: As with any narcotic analgesic agent, VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN ES Tablets are used postoperatively and

when VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease

Information for Patients: Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided. Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the

amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests. Drug Interactions: Patients receiving other narcotic

analgesics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN ES Tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic

antidepressants with hydrocodone preparations may increase the effect of either the antidepressant of Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary

S-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of
Fertility: No adequate studies have been conducted in
animals to determine whether hydrocodone or
acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include

irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawals.

withdrawai.

Labor and Delivery: As with all narcotics, administration of VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher departs are used. higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions

in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in the pediatric reniaric use: Saley and enectiveness in the pediatric population have not been established.

Geriatric Use: Clinical studies of VICODIN ES® (hydrocodone bitartrate 7.5 mg and acetaminophen 750 mg) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported

03-5541-R3-Revised November, 2006 Temperature). Dispense in a tight, light-resistant container as defined in the USP. A Schedule © Controlled Drug Substance.

source of 100-NDC #0074-1973-14

Borliles of 100-NDC #0074-1973-54

Borliles of 500-NDC #0074-1973-12.

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room 16°-30°C (50°-86°F).

DUSAGE AND ADMINISTRATION

Disages favour be adjusted according to the severify of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of uninward effects is dose related. The usual adult dosage is one tablet severy four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.

White, oval-shaped, faceted edged tablet bisected on one side and imprinted with "VICODIN ES" on the other side.

The toxic dose for adults for acetaminophen is 10 g. **DOSAGE AND ADMINISTRATION** administration methylene blue by slow intravenous

A may is given parenterally. Since the duration of action of bydrocodone may exceed that of the healt occore, by advanced on the antiagonist should be kept under confinuous surveillance and repeated doses of the antiagonist should not be administered as needed to maintain adequate respiration. A narcolic antagonist should not be administered in the absence of clinically significant of the action of the approximate of actions of the action of the action of the action action help predict action more thours following be obtained, since levels four or more hours following ingestion help predict actsiminophen levels should be daintaistered as await acetaminophen assay results before initiality and repeated at 24-hour intervals. The predict actsiminophen before initiality and repeated at 24-hour intervals. Metheroneoglobnemia over 30% achould be cheated initially, and repeated at 24-hour intervals. Wether actions of a calculation of the predict action of a calculation of the predict action of the predict and the predict action of the predict and action of the predict action of the predict

hypoglycemic comas, and thrombocytopenia may also occurs serous adverse effect. Hensi tubular herotosis occurs, and thrombocytopenia may also occur.

Early symptome following a potentially hepatotoxic hepates. Clinicial and aboratory evidence of hepatic protection of the apparent until 48 to hepatic toxicity may not be apparent until 48 to the adverse of less than 10 grams and acetalian that a familiar beat familiar series of less than 10 grams and the acetalian that a familiar beat than 15 grams.

Treatment: A single or multiple overdose with a familiar series and acetalminophen is a potentially lethal hydrocodone and acetalminophen to principle overdose with hydrocodone and acetalminophen to a potentially lethal cardiorespiratory function and measures to reduce drug absorption. Vomiting sind acetalmine to reduce cardiorespiratory of metalmine and acetalmine and acetal the activated charcies (I tropeated doses are used, the activated charcies (I tropeated doses are used, the activated charcies (I tropeated doses are used, the culted endo-tracheal lube accompanie doses are used, the culted and and acetal ace

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially faish hepatic nerousles is the most serious adverse effect. Renal tubular necrosis, most expensic coma, and thrombocytopenia may also process.

progressing to sulpor or come, skeletal muscle brogressing to sulpor or come, skeletal muscle bradycards and hypotension. In severe overdosage, amay occur.

Acetamore and death sulpores or cardiac arrest and death may occur. from hydrocodone or scelaminophen.

Signs and Symptoms:

Hydrocodone is Serious overdose with hydrocodone is characterized by respiratory rate and/or tidal volume, Cheyne-Stokes respiratory rate and/or tidal volume, Cheyne-Stokes respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme sommolence respiration, cyanosis), extreme sommolence more transfer.

Following an acute overdosage, toxicity may result OVERDOSAGE help to limit abuse of opioid drugs. dispensing and storage are appropriate measures that

treating physician(s). "Jootor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. But begins to the physical dependence and tolerance. Physical dependence and tolerance. Physical dependence and tolerance. Physical dependence and tolerance. Physical dimensions only after several weeks of confinued dimensions only after several weeks of opioid describing a mild degree of physical dependence may develop after a few days of opioid dependence in which increasingly large doses are required in order to produce the same degree of an experience of the same degree of an englesia. It may be develop after a few days of opioid dependence may develop after a few days of opioid and an experience of the same degree of development of tolerance varies among a physicians should be aware that abuse of opioid sea of opioid and an experience of true addiction and is content in ombination with other psychoactive development of misuses of normedical use. Record-keeping of the passers of the product of the patient of duentity. Tolerance in information, including quantity of the patient of the patient of the patient of the patient of duentity duentity. Tolerance in an expension of the patient of duentity and section of the patient o additional prescriptions is common among drug refusal to undergo appropriate examination, testing or referred, repeated "loss" of prescriptions, fampering with prescriptions and reluctance to provide prior medical records or contact information for other freating physician(s). "Doctor apopping" to obtain additional resecribinos are contact and additional resecriptions are prescriptions. emergency calls or visits near the end of office hours, compulsive use, continued use despite harm, and craving, Drug addiction is a treatable disease ullisting a multidisciplinary approach, but relapse is common. "Brug seeking" behavior is very common in addicts and the seeking a feet seeking a feet seeking a promeror in common and common in addicts and the seeking a feet seeking a feet seeking a promeror of the seeking a page of the seeking a pag

more of the following: impaired control over drug use, Addiction is a primary, chronic, neurobiologic sease, with genetic, psychosocial, and environmental ctors influencing its development and manifestations. Is characterized by behaviors that include one or so that include one or so that the statement and the properties of the propert subject to criminal diversion.

other opioids, used in analgesia can be abused and are Misuse, Abuse, and Diversion of Opioids: VICODIN ES contains hydrocodone, an opioid agonist, and is a Schedule III controlled substance, VICODIN ES, and **ВВИС АВИЗЕ АИВ ВЕРЕИВЕИСЕ** 

The following adverse drug events may be borne in mind as potential effects of acetaminophen; allergic reactions, each, ihromboytopenia, agranulocytosis. Potential effects of high dosage are listed in the Potential effects of high dosage are listed in the manner and account of the properties of the

Special Senses: Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.

Dermatologieal: Skin rash, pruritus. directly on the brain stem respiratory center. (see

broduce dose-related respiratory depression by acting VICODIN ES Tablets may produce constipation.

Mepulvaint System: Urteteral spasm, spasm of ported with opiates.

Mespirationy Depression: Hydrocodone bitaritatie may produce and urinary refention have been reported with opiates.

Other adverse reactions includes.

Central Nervous System: Drowsiness, mental couding, lethacy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Castonintestinal System: Prolonged administration of MCROINES. Tablets may produce administration of Tablets may produce administration of Tablets.

alleviated if the patient lies down. The most frequently reported adverse reactions include: lightheadedness, alzsiness, sedation, nauses and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be allevisted if the natient lies drawn

ADVERSE REACTIONS

Hydrocodone may cause confusion and over-sedation in the elderty; elderty patients generally should be started on low doses of hydrocodone bitartrate and acetaminophen tablets and observed closely.

greater in patients with impaired renal function due to accumulation of the parent compound and/or more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monifor renal function. Hydrocompound and or provide the taken in force or the provider of the provider of the provider of the provider of the parent of the

disease or other drug therapy.

Hydrocodone and the major metabolites of acetaminophen are known to be substantially excreted by the kidney. Thus the risk of toxic reactions may be 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 scradies function, and of concomitant listease or other drug therapy.