BOXED WARNING

Refractory Atelectasis
Atelectasis has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen along with ethanol doses exceeding 4000 mg/day per week, and often involve more than one acetaminophen-containing product.

DESCRIPTION

NORCOD (hydrocodone bitartrate and acetaminophen) is supplied in two forms: tablets and oral solution.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as white, crystalline powder. It is an opium alkaloid, specifically 7,8-dihydroxy-17,3-dimethoxy-17,3-dihydroxy-2,3,14,14-tetrahydro-5H-dibenzo[a,d]cycloheptene-5,10-dione, and has the following structural formula:

\[
\text{C}_{17}\text{H}_{21}\text{NO}_4 \\text{CH}_3
d\text{H}_2\text{O}
\]

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

\[
\text{C}_8\text{H}_9\text{NO}_2
\]

Each NORCOD 50/5 mg tablet contains:

Hydrocodone Bitartrate……………….. 5 mg
Acetaminophen……………….. 50 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The color of the tablets is derived from corn, sucrose, and FD&C Yellow #6.

Each NORCOD 50/300 mg tablet contains:

Hydrocodone Bitartrate……………….. 5 mg
Acetaminophen……………….. 300 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Each NORCOD 100/300 mg tablet contains:

Hydrocodone Bitartrate……………….. 10 mg
Acetaminophen……………….. 300 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Each NORCOD 200/250 mg tablet contains:

Hydrocodone Bitartrate……………….. 20 mg
Acetaminophen……………….. 250 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

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 opiates is not known, although it is believed to involve the release of norepinephrine in the central nervous system. In addition, hydrocodone may produce drowsiness, changes in mood and motor claudication. The analgesic action of acetaminophen involves peripheral influences, but the specific mechanisms is as yet undefined. Antitussive activity is mediated through hypothalamic-test regulating centers. Atelectasis inhibits prostaglandin synthesis. These effects of acetaminophen have negligible 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 10 mg oral dose of hydrocodone administered to five adult males, the mean peak concentration was 28.8 ± 5.7 μg/mL. Maximal serum levels were achieved within 4.3 ± 0.9 hours; the half-life was determined to be 3.4 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism involving a 3-dehydrogenation, 2-demethylation and 6-hydroxylation of the compound 4- and 9-hydroxyhydrocodone. See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastro-intestinal tract and is distributed throughout most body tissues. The plasma half-life is 1-2 hours, but may be increased by liver damage and following overdose. 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 OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

NORCOD is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

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

PATIENTS known to be hypersensitive to other opioids may experience cross-sensitivity to hydrocodone.

WARNINGS

Hepatotoxicity: Atelectasis has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen along with ethanol doses exceeding 4000 mg/day per week, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver diseases and in individuals who ingested alcohol while taking acetaminophen. Restrict patients to look for Aminophyllin or APAP on package labels and ne ascites, more than 1 product that exceeds 4000 mg/day per week, or to more than one acetaminophen-containing product. Restrict patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen in any 24 hours even if they feel well.

Serious skin reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of SJS and TEN and should discontinue treatment at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/Anaphylaxis: There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and neck, and urticaria. Cardiac arrest should be considered when NODOR is taken in patients with a history of hypersensitivity.

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

Heart Rate and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be exaggerated in the presence of intracranial lesions or a pre-existing increased intracranial pressure. Furthermore, narcotics produce some degree of respiratory depression which may obscure the clinical course of patients with head injuries. In Acute Asthmatic Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute asthmatic conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, use 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 and in patients receiving monoamine oxidase inhibitors. The possibility of respiratory depression should be kept in mind. Cough Suppression: Hydrocodone suppresses the cough reflex; as with all opioids, use with caution in patients requiring cough suppression (e.g., tuberculosis).

Doseage and Administration: NORCOD tablets 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 renal function tests.

Drug Interactions: Patients receiving other narcotics, tranquilizers, antidepressants, antihistamines, or other CNS depressants (including alcohol) concurrently with NORCOD 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 or the narcotic.

Drug/Laboratory Test Interactions: Aminophyllin: NORCOD may produce false-positive test results for urinary 5-Hydroxytryptamine.
overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment:
A single or multiple drug overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered.

For hydrocodone overdose, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration. Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

**DOSAGE AND ADMINISTRATION**

DOSAGE should be adjusted according to the severity 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 untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

**HOW SUPPLIED**

NORCO® 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/325 mg) contain hydrocodone bitartrate 5 mg and acetaminophen 325 mg. They are supplied as white with orange specks, capsule-shaped, bisected tablets, debossed WATSON on one side and 913 on the other side, in bottles of 100 tablets, NDC 52544-913-01, in bottles of 500 tablets, NDC 52544-913-05, and in hospital unit-dose cartons of 100 tablets (25 tablets x 4 cards), NDC 52544-913-48.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

A Schedule II Narcotic.

**Manufactured by:** Mikart, Inc. Atlanta, GA 30318

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

Rev. 08/2014
Code 667C00
INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the management of moderate to moderately severe pain.

DESCRIPTION

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-(6-chloro-1,3-benzodioxolo-5-yl)-1-methyl-7-ethoxymethyl-1H-tetrahydropyridine dihydrobromide. It has the following structural formula:

\[
\text{C}_17\text{H}_{19}\text{NO}_3 \cdot \text{H}_2\text{CO} \cdot \text{H}_2\text{O} \quad \text{MW = 494.49}
\]

Each tablet contains:

- Hydrocodone Bitartrate .......................... 5 mg
- Acetaminophen ................................. 325 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres which are composed of starch derived from corn, sucrose, and FD&C Yellow #6.

OVERDOSAGE

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:

\[
\text{C}_8\text{H}_{11}\text{NO}_2 \quad \text{MW = 151.16}
\]

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to take more than the recommended dose.

Serious skin reactions: Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/anaphylaxis: There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs may include angioedema, swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention.

Improper administration of hydrocodone bitartrate and acetaminophen tablets, USP immediately and seeking medical care if they experience these symptoms. Do not prescribe Hydrocodone Bitartrate and Acetaminophen Tablets, USP for patients with acetaminophen allergy.

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

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to lower the threshold of intracranial lesions may be exaggerated in patients with head injury, brain tumors, or other intracranial lesions.

Information for Patients/Caregivers:

Do not take Hydrocodone Bitartrate and Acetaminophen Tablets, USP if you are allergic to any of its ingredients.

If you develop signs of allergy such as a rash or difficulty breathing stop taking Hydrocodone Bitartrate and Acetaminophen Tablets, USP and contact your healthcare provider immediately.

If you are allergic to any of its ingredients.

If you are allergic to any of its ingredients.

Drug Interactions: Monitor patients for respiratory depression when hydrocodone bitartrate and acetaminophen tablets are used concomitantly with other respiratory depressants including opioid analgesics, sedative-hypnotics, alcohol, or other CNS depressants (including alcohol).

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate and well-controlled studies of hydrocodone and/or acetaminophen have been conducted in pregnant women. In animals, hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nongeriatric Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs in neonates include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, and vomiting. The intensity of the Neonatal abstinence syndrome may vary with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: There are no adequate and well-controlled studies of hydrocodone and acetaminophen administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if 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 pediatric patients have not been established.

Geriatric Use: Clinical studies of hydrocodone bitartrate 5 mg and acetaminophen 500 mg 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

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

Central Nervous System:

Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychological mood changes.

Gastrointestinal System:

Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System:

Urinary spasm, spasms of vesical sphincter and urinary retention have been reported with opiates.

Respiratory Depression:

Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center (see OVERDOSAGE).

Special Senses:

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

Dermatological:

Skin rash, pruritus. The following adverse drug events may be borne in patients treated with hydrocodone: allergic reactions, rash, thrombocytopenia, agranulocytosis. Potential effects of high dosage are listed in the OVERDOSAGE section.

Drug Abuse and Dependence:

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule II controlled substance.

Abuse and Dependence: Psychotic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinical significance only in the minority of patients who may alter several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increased dosages are required to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdose, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose of hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence or unconsciousness, cold and
clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment:
A single or multiple drug overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered.

For hydrocodone overdose, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

DOSAGE AND ADMINISTRATION
Dosage should be adjusted according to the severity 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 untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

HOW SUPPLIED
Hydrocodone Bitartrate and Acetaminophen Tablets USP, contain hydrocodone bitartrate 5 mg and acetaminophen 325 mg. They are supplied as white with orange specks, capsule-shaped, bisected tablets, debossed WATSON on one side and 3202 on the other side, in bottles of 100 and 500.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

A Schedule CII Narcotic.

Manufactured by:
Mikart, Inc.
Atlanta, GA 30318

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

Rev. 08/2014 Code 667D00