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CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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May 10, 2005

OVERNIGHT COURIER 5/10/05

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned, on behalf of a client, submits this petition in quadruplicate under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("the FDC Act"), 21 U.S.C. § 355(j)(2)(C), and 21 C.F.R. §§ 10.20, 10.30, and 314.93 to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application (ANDA) may be submitted for Hydrocodone Bitartrate and Ibuprofen Tablets, in the following strength, 2.5 mg / 200 mg.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that a Hydrocodone Bitartrate and Ibuprofen Tablet combination drug product, in the following strength 2.5 mg / 200 mg, is suitable for submission in an ANDA. The reference-listed drug product upon which this petition is based is Vicoprofen[®] (Hydrocodone Bitartrate and Ibuprofen) Tablets, NDA 20-716 (7.5 mg / 200 mg) manufactured by Abbott Laboratories Pharmaceutical Products. Therefore, this petition requests a change in the strength of the narcotic component of the reference-listed drug product from 7.5 mg / 200 mg of hydrocodone bitartrate and ibuprofen to a strength of 2.5 mg / 200 mg of hydrocodone bitartrate and ibuprofen per tablet.

B. Statement of Grounds

Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act provides for the submission of an ANDA for a new drug that differs in strength from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application. This petition requests a change in the strength of the narcotic component of the reference-listed drug product from 7.5 mg / 200 mg of hydrocodone bitartrate and ibuprofen per tablet, to include a strength of 2.5 mg / 200 mg of hydrocodone bitartrate and ibuprofen per tablet. The listing of reference drug product upon which this petition is based, Vicoprofen[®] (Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg / 200 mg), appears in the electronic 24th edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book"). (See Attachment A)

2005P.0180

CP1

According to the approved labeling of the referenced-listed drug product, the usual dosage of Vicoprofen[®] is: "One tablet every four to six hours as needed for pain. The total daily dose should not exceed 5 tablets." The approved package insert for Vicoprofen[®] Tablets, is included in Attachment B. In addition, the RLD labeling states: "The lowest effective dose or the longest dosing interval should be sought for each patient, especially in the elderly. After observing the initial response to therapy with Hydrocodone Bitartrate and Ibuprofen Tablets, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended." The dosage for the proposed product is "one tablet every four to six hours as needed for pain. The total daily dose should not exceed 5 tablets." This dosage is consistent with that stated in the approved labeling of the reference-listed drug product and will carry the same warnings as the RLD. The RLD labeling clearly indicates that patients, especially the elderly, should be carefully titrated to the appropriate dose. The proposed product can be used to assist the prescriber in attaining that objective.

In addition, the Agency has approved an ANDA suitability petition (Docket 02-0270/CP1) that requested a change in strength of the narcotic component of the Vicoprofen[®] product from 7.5 mg to 5 mg, and ultimately approved ANDA of this strength, thus supporting this request to include a hydrocodone bitartrate and ibuprofen product containing a lower strength of hydrocodone bitartrate with a fixed 200 mg of ibuprofen (see Attachment C). Also, the FDA has approved numerous combination products containing 2.5 mg of hydrocodone bitartrate as a safe and effective dose of this narcotic in combination with other non-narcotic analgesics, such as acetaminophen, further attesting to the fact that the proposed product will contain a safe and effective dose of the designated narcotic component. The labeling of the proposed drug product, as stated above, will be consistent with the labeling of the reference-listed drug product and will propose a maximum of 5 tablets per day, which would provide hydrocodone bitartrate at a total daily dose within that recommended for other FDA-approved products containing this component.

In summary, the strength changes proposed for the narcotic component (hydrocodone bitartrate) from that of the reference-listed drug (i.e., from 7.5 mg to 2.5 mg) is consistent with, and provides a safe and effective dose of each of the proposed product's components, which have been previously approved by the FDA in other drug products. The proposed change in strength of the narcotic component, therefore, should not affect the safety or efficacy of the proposed combination product. The indication and uses remain unchanged, and the proposed dosing is consistent with dosing recommendations in the labeling of the approved reference-listed drug product and the dosing for the narcotic component of other FDA-approved products containing this ingredient. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness.

The proposed labeling for Hydrocodone Bitartrate and Ibuprofen Tablets, 2.5 mg / 200 mg per tablet is included as Attachment D. Labeling for the proposed product will be consistent with the approved labeling for Vicoprofen[®] (hydrocodone bitartrate and ibuprofen) Tablets, 7.5 mg / 200 mg.

For the aforementioned reasons, the undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for Hydrocodone Bitartrate and Ibuprofen Tablets, 2.5 mg / 200 mg.

C. Environmental Impact

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact Statement

According to 21 C.F.R. § 10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,



Robert W. Pollock
Vice President
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RWP/pk

cc: Emily Thakur (Office of Generic Drugs)

Attachments:

- A. Electronic 24th edition of the Approved Drug Products with Therapeutic Equivalence Evaluations
- B. Approved package insert for Vicoprofen[®] Tablets
- C. FDA Approval Letter for ANDA Suitability Petition (Docket 02-0270/CP1)
- D. Proposed labeling for Hydrocodone Bitartrate and Ibuprofen Tablets

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT A

Search results from the "OB_Rx" table for query on "020716."

Active Ingredient: HYDROCODONE BITARTRATE; IBUPROFEN
Dosage Form;Route: TABLET; ORAL
Proprietary Name: VICOPROFEN
Applicant: ABBOTT
Strength: 7.5MG;200MG
Application Number: 020716
Product Number: 001
Approval Date: Sep 23, 1997
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code: **AB**
Patent and Exclusivity Info for this product: [View](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through March, 2005

Patent and Generic Drug Product Data Last Updated: May 09, 2005

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT B

This information is intended for U.S. residents only.

VICOPROFEN®

(hydrocodone bitartrate and ibuprofen tablets)
7.5mg/200mg



Rx only

- **DESCRIPTION**
- **CLINICAL PHARMACOLOGY**
- **CLINICAL STUDIES**
- **INDICATIONS AND USAGE**
- **CONTRAINDICATIONS**
- **WARNINGS**
- **PRECAUTIONS**
- **ADVERSE REACTIONS**
- **DRUG ABUSE AND DEPENDENCE**
- **OVERDOSAGE**
- **DOSAGE AND ADMINISTRATION**
- **HOW SUPPLIED**

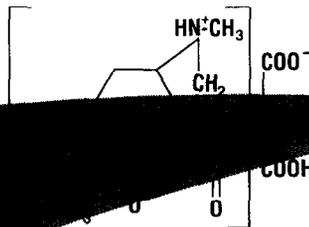
DESCRIPTION

Each VICOPROFEN® tablet contains:

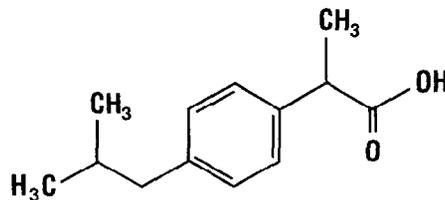
Hydrocodone Bitartrate, USP 7.5 mg
Ibuprofen, USP 200 mg

VICOPROFEN is supplied in a fixed-dose combination tablet form for oral administration. VICOPROFEN combines the opioid analgesic agent, hydrocodone bitartrate, and the nonsteroidal anti-inflammatory agent, ibuprofen.

Hydrocodone bitartrate is a semisynthetic and centrally acting opioid analgesic. Its chemical name is: 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one (1:1) hydrate (2:5). Its chemical formula is: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2H_2O$, and its molecular weight is 494.50. Its structural formula is:



Ibuprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Its chemical name is: (±)-2-(β -isobutylphenyl)propanoic acid. Its chemical formula is: $C_{13}H_{18}O_2$, and the molecular weight is: 206.29. Its structural formula is:



Inactive ingredients in VICOPROFEN tablets include: colloidal silicon dioxide, corn starch, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyso-bate 80, and titanium dioxide.

▲ CLINICAL PHARMACOLOGY

Hydrocodone component: Hydrocodone is a semisynthetic opioid 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 opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding.

Ibuprofen component: Ibuprofen is a non-steroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is a peripherally acting analgesic. Ibuprofen does not have any known effects on opiate receptors.

Pharmacokinetics:

Absorption: After oral dosing with the VICOPROFEN tablet, a peak hydrocodone plasma level of 27 ng/mL is achieved at 1.7 hours, and a peak ibuprofen plasma level of 30 mg/mL is achieved at 1.8 hours. The effect of food on the absorption of either component from the VICOPROFEN tablet has not been established.

Distribution: Ibuprofen is highly protein-bound (99%) like most other non-steroidal anti-inflammatory agents. Although the extent of protein binding of hydrocodone in human plasma has not been definitely determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar extent (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Metabolism: Hydrocodone exhibits a complex pattern of metabolism including *O*-demethylation, *N*-demethylation, and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxy metabolites. Oxycodone, a potent opioid, is formed from the *O*-demethylation of hydrocodone and contributes to the total analgesic activity of hydrocodone. The *O*- and *N*-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4.

Ibuprofen is present in this product as a racemate. After oral absorption it undergoes interconversion in the plasma from the R-isomer to the S-isomer. Both the R- and S- isomers are converted to two primary metabolites, (+)-2-4'-(2-hydroxy-2-methyl-propyl) phenyl propionic acid and (+)-2-4'-(2-carboxypropyl) phenyl propionic acid, both of which are excreted in the plasma at low levels relative to the parent.

Elimination: Hydrocodone and its metabolites are eliminated primarily in the kidneys with a mean plasma half-life of 4.5 hours. Ibuprofen is excreted in the urine, 50% to 60% as unchanged drug and approximately 15% as metabolites. The plasma half-life is 2.2 hours.

Special Populations: No significant pharmacokinetic differences based on age have been demonstrated. The pharmacokinetics of hydrocodone and ibuprofen from VICOPROFEN has not been established in children.

Renal Impairment: The effect of renal insufficiency on the pharmacokinetics of the VICOPROFEN has not been determined.

▲ CLINICAL STUDIES

In single-dose studies of post surgical pain (abdominal, gynecological, orthopedic), 90% of patients were studied at doses of one or two tablets. VICOPROFEN produced analgesia similar to that of the individual components given at the same dose. No advantage was observed in the use of VICOPROFEN over the individual components.

▲ INDICATIONS

VICOPROFEN is indicated for the short-term (generally less than 10 days) management of acute pain. VICOPROFEN is not indicated for the management of chronic pain such conditions as osteoarthritis or rheumatoid arthritis.

▲ CONTRAINDICATIONS

VICOPROFEN should not be administered to patients who previously have exhibited hypersensitivity to hydrocodone or ibuprofen. VICOPROFEN should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Pre-existing Asthma).

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

▲ WARNINGS

Abuse and Dependence: Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic and physical dependence as well as tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution as other narcotic drugs (see DRUG ABUSE AND DEPENDENCE).

Respiratory Depression: At high doses or in opioid-sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers. 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 opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation: Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper GI problems, such as dyspepsia, are common and may occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI events and what steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated and is not routinely recommended. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Even short term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a past history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the risk of an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a history of peptic ulcer disease or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold risk of developing a GI bleed than patients not exhibiting either of these risk factors. In addition to a past history of ulcer disease, pharmacological studies have identified other risk factors for co-therapies or co-morbid conditions that may increase the risk for GI events, such as: treatment with oral corticosteroids, concurrent treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health.

Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without a history of hypersensitivity to VICOPROFEN. VICOPROFEN should not be given to patients with the aspirin triad. The triad typically consists of asthma, nasal polyps, or patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm with aspirin or other NSAIDs. Fatal reactions to NSAIDs have been reported in such patients (see CONTRAINDICATIONS - PRECAUTIONS - Pre-existing Asthma). Emergency help should be sought when anaphylactoid reaction occurs.

Advanced Renal Disease: In patients with advanced renal disease, VICOPROFEN is not recommended. If NSAID therapy, however, is considered necessary, the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy: As with other NSAID products, VICOPROFEN should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

▲ PRECAUTIONS

General Precautions

Special Risk Patients: As with any opioid analgesic agent, VICOPROFEN 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 opioids, caution should be exercised when VICOPROFEN is used postoperatively and in patients with pulmonary disease.

Effect on Diagnostic Signs: The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Hepatic Effects: As with other NSAIDs, ibuprofen has been reported to cause borderline elevations of one or more liver enzymes, this may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or

may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with VICOPROFEN. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), VICOPROFEN should be discontinued.

Renal Effects: Caution should be used when initiating treatment with VICOPROFEN in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VICOPROFEN. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS - Advanced Renal Disease).

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Ibuprofen metabolites are eliminated primarily by renal excretion. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Patients with significantly impaired renal function should be more closely monitored.

Hematological Effects: Ibuprofen, like other NSAIDs, may inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Clinical studies have shown no prolong bleeding time in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, VICOPROFEN should be used with caution in persons with intrinsic or acquired bleeding disorders and those on anticoagulant therapy.

Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, GI loss, or an incompletely described effect upon hemopoiesis.

Fluid Retention and Edema: Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation, hypertension, or heart failure.

Pre-existing Asthma: Patients with aspirin sensitivity have aspirin-sensitive asthma. The occurrence of asthma in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which may be fatal. Since cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VICOPROFEN should be used with caution in patients with this form of aspirin sensitivity and should be avoided in patients with pre-existing asthma.

Aseptic Meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in patients receiving ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and other autoimmune diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of aseptic meningitis develop in a patient on VICOPROFEN, the possibility of its being related to the drug should be considered.

Information for Patients

VICOPROFEN® (ibuprofen 200 mg), like other opioid-containing analgesics, may impair mental and/or physical 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.

VICOPROFEN may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and not more frequently than prescribed.

VICOPROFEN, like other drugs containing ibuprofen, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Patients should be instructed to report any signs and symptoms of gastrointestinal bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Laboratory Tests

A decrease in hemoglobin may occur during VICOPROFEN therapy, and elevations of liver enzymes may be seen in a small percentage of patients during VICOPROFEN therapy (see PRECAUTIONS - Hematological Effects and PRECAUTIONS - Hepatic Effects).

In patients with severe hepatic or renal disease, effects of therapy should be monitored with liver and/or renal function tests.

Drug Interactions

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction

should be given consideration in patients taking VICOPROFEN concomitantly with ACE-inhibitors.

Anticholinergics: The concurrent use of anticholinergics with hydrocodone preparations may produce paralytic ileus.

Antidepressants: The use of MAO inhibitors or tricyclic antidepressants with VICOPROFEN may increase the effect of either the antidepressant or hydrocodone.

Aspirin: As with other products containing NSAIDs, concomitant administration of VICOPROFEN and aspirin is not generally recommended because of the potential of increased adverse effects.

CNS Depressants: Patients receiving other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICOPROFEN may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Furosemide: Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with VICOPROFEN the patient should be observed closely for signs of renal failure (see PRECAUTIONS - Renal Effects), as well as diuretic efficacy.

Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when VICOPROFEN and lithium are administered concurrently, patients should be observed for signs of lithium toxicity.

Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen may enhance the toxicity of methotrexate. Caution should be used when VICOPROFEN is administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on platelet aggregation are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

The carcinogenic and mutagenic potential of VICOPROFEN has not been investigated. The ability of VICOPROFEN to impair fertility has not been assessed.

Pregnancy: Pregnancy Category C

Teratogenic Effects: VICOPROFEN, administered to rats at 100 mg/kg (5.72 and 11.44 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, resulted in an increase in the number of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with more nonossified metatarsals (one or more minor abnormalities). VICOPROFEN, administered to rats at 166 mg/kg (10.0 and 1.66 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, did not result in any reproductive effects. There are no adequate and well-controlled studies in pregnant women. VICOPROFEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), their use during pregnancy (particularly late pregnancy) should be avoided. Babies born to mothers who have been taking NSAIDs regularly prior to delivery will be physically dependent. Withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, and nasal congestion, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery

As with other drugs, the use of VICOPROFEN during labor and delivery is not recommended. An increased incidence of dystocia and delayed parturition occurred in rats. Administration of VICOPROFEN is not recommended during labor and delivery.

Nursing Mothers

It is not known if VICOPROFEN is excreted in human milk. In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate the presence of VICOPROFEN in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, VICOPROFEN is not recommended for use in nursing mothers.

Pediatric Use

The safety and effectiveness of VICOPROFEN in pediatric patients below the age of 16 have not been established.

Geriatric Use

In controlled clinical trials there was no difference in tolerability between patients < 65 years of age and those ≥ 65, apart from an increased tendency of the elderly to develop constipation. However, because the elderly may be more sensitive to the renal and gastrointestinal effects of nonsteroidal anti-inflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution and reduced dosages should be used when treating the elderly with VICOPROFEN.

▲ ADVERSE REACTIONS

VICOPROFEN was administered to approximately 300 pain patients in a safety study that employed dosages and a duration of treatment sufficient to encompass the recommended usage (see DOSAGE AND ADMINISTRATION). Adverse event rates generally increased with increasing daily dose. The event rates reported below are from approximately 150 patients who were in a group that received one tablet of VICOPROFEN an average of three to four times daily. The overall incidence rates of adverse experiences in the trials were fairly similar for this patient group and those who received the comparison treatment, acetaminophen 600 mg with codeine 60 mg.

The following lists adverse events that occurred with an incidence of 1% or greater in clinical trials of VICOPROFEN, without regard to the causal relationship of the events to the drug. To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

name of adverse event = less than 3%

*adverse events marked with an asterisk * = 3% to 9%*

adverse event rates over 9% are in parentheses.

Body as a Whole: Abdominal pain*; Asthenia*; Fever; Headache (27%); Infection*; Pain.

Cardiovascular: Palpitations; Vasodilation.

Central Nervous System: Anxiety*; Confusion; Dizziness (16%); Hypertonia; Insomnia*; Nervousness*; Paresthesia. Somnolence (22%); Thinking abnormalities.

Digestive: Anorexia; Constipation (22%); Diarrhea*; Dyspepsia (12%); Flatulence*; Gastritis; Melena; Mouth ulcers; Nausea (21%); Thirst; Vomiting*.

Metabolic and Nutritional Disorders: Edema.

Respiratory: Dyspnea; Hiccups; Pharyngitis.

Skin and Appendages: Pruritus*; Sweating*.

Special Senses: Tinnitus.

Urogenital: Urinary frequency.

Incidence less than 1%

Body as a Whole: Allergic reaction.

Cardiovascular: Arrhythmia; Hypotension; Tachycardia.

Central Nervous System: Agitation; Anxiety; Dreams; Decreased libido; Dizziness; Euphoria; Mood changes; Neuralgia; Slurred speech; Tremor; Vertigo.

Digestive: Chalky stool; "Clenching teeth"; Dysphagia; Esophageal spasm; Esophagitis; Constipation; Liver enzyme elevation.

Metabolic and Nutritional: Weight decrease.

Musculoskeletal: Arthralgia; Myalgia.

Respiratory: Asthma; Bronchitis; Dyspnea; Increased cough; Pulmonary congestion; Pharyngitis; Sinusitis.

Skin and Appendages: Rash; Urticaria.

Special Senses: Altered vision; Bad taste; Dry eyes.

Urogenital: Cystitis; Glycosuria.

▲ DRUG ABUSE AND DEPENDENCE

Controlled Substance: VICOPROFEN Tablets are a Schedule III controlled substance.

Abuse: Psychic dependence, tolerance, and addiction may develop upon repeated administration of opioids; therefore, VICOPROFEN Tablets should be administered with the same degree of caution appropriate to use of other oral narcotic medications.

Dependence: Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although a mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order 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. However, psychic dependence is unlikely to develop when VICOPROFEN Tablets are used for a short time for the treatment of acute pain.

▲ OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone and/or ibuprofen

Signs and Symptoms:

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

Ibuprofen component: Symptoms include gastrointestinal irritation with erosion and hemorrhage or perforation, kidney damage, liver damage, heart damage, hemolytic anemia, agranulocytosis, thrombocytopenia, aplastic anemia, and meningitis. Other symptoms may include headache, dizziness, tinnitus, confusion, blurred vision, mental disturbances, skin rash, stomatitis, edema, reduced retinal sensitivity, corneal deposits, and hyperkalemia.

Treatment:

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose or undue sensitivity to opioids, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered intravenously with simultaneous efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist may be administered as needed to maintain adequate respiration. Supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. In cases where consciousness is impaired it may be necessary to perform gastric lavage. If gastric lavage is performed, little drug will likely be recovered if more than an hour has elapsed since ingestion. Ibuprofen is acidic and is excreted in the urine; therefore, it may be beneficial to administer a diuretic to increase diuresis. In addition to supportive measures the use of oral activated charcoal may help to reduce the absorption and intestinal reabsorption of ibuprofen. Dialysis is not likely to be effective for removal of ibuprofen because it is very highly bound to plasma proteins.

▲ DOSAGE AND ADMINISTRATION

For the short-term (generally less than 10 days) management of acute pain, the recommended dose of VICOPROFEN is one tablet every 4 to 6 hours, as necessary. The total daily dose should not exceed 5 tablets in 24 hours. It should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of side effects is dose related.

The lowest effective dose or the longest dosing interval should be sought for each patient, especially in the elderly. After observing the initial response to therapy with VICOPROFEN, the dose and frequency should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended.

▲ HOW SUPPLIED

VICOPROFEN® tablets are available in the following strengths and packaging:
White film-coated round tablets, 5 mg hydrocodone bitartrate and 200 mg ibuprofen, scored on one side and plain on the other side

Bottles of 100-NDC 0010-0100-01

Bottles of 500-NDC 0010-0100-02

Hospital Unit Dose

(4x25 tablets)-NDC 0010-0100-03

Storage: Store at controlled room temperature (20°-25° F); excursions permitted to 15°-30°C (59°-86° F). [See USP Controlled Room Temperature].

Dispense in child-resistant, light-resistant container.

A Schedule C Narcotic.

©Abbott

Revised: August, 2001

Ref.: 03-5136

ATTACHMENT C



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

HF
SEP 25 2002

SciRegs Consulting
Attention: C. Jeanne Taborsky
6333 Summercrest Drive
Columbia, MD 21045

Docket No.02P-0270/CP1

Dear Ms. Taborsky:

This is in response to your petition filed on June 13, 2002, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug product: Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg. The listed drug product to which you refer in your petition is Vicoprofen® (hydrocodone bitartrate and ibuprofen) Tablets, 7.5 mg/200 mg, approved under NDA 20-716 held by Abbott.

Your request involves a change in strength of the hydrocodone bitartrate component from that of the listed drug product (i.e., from 7.5 mg to 5 mg). The change you request is the type of change that is authorized under the Federal Food, Drug, and Cosmetic Act (Act).

We have reviewed your petition under Section 505(j)(2)(C) of the Act and have determined that it is approved. This letter represents the Food and Drug Administration's (FDA) determination that an ANDA may be submitted for the above-referenced drug product.

Under Section 505(j)(2)(C)(i) of the Act, the FDA must approve a petition seeking a strength that differs from the strength of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The FDA finds that the change in strength for the specific proposed drug product does not pose questions of safety or effectiveness because the uses and route of administration of the proposed drug product are the same as that of the listed drug product. In addition, a 5 mg dose of hydrocodone bitartrate has been previously approved as safe and effective by the FDA when combined with other non-narcotic analgesics such as acetaminophen and aspirin. The FDA concludes, therefore, that investigations are not necessary in this instance. Also, if shown to meet bioavailability requirements, the proposed drug product can be expected to have the same therapeutic effect as the listed reference drug product.

02P-0270

PAV/I

02P-0270/CP1
SciRegs Consulting

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug product does not mean that the FDA has determined that an ANDA will be approved for the drug product. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the FDA.

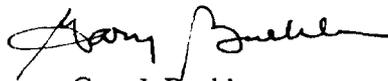
For your information, the listed drug product to which you refer is covered by a period of patent protection which appears in the Approved Drug Products With Therapeutic Equivalence Evaluations, 22nd Edition, published by the FDA. The existence of such a patent will require a certification upon submission of an ANDA for your proposed drug product and may also affect the approval date of any ANDA.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug product will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you submit your protocol for this drug product to the Office of Generic Drugs, Division of Bioequivalence prior to the submission of your ANDA. During the review of your application, the FDA may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,



Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT D

Hydrocodone Bitartrate and Ibuprofen Tablets

2.5 mg/200 mg

Rx only

DESCRIPTION

Each hydrocodone bitartrate and ibuprofen tablet contains.

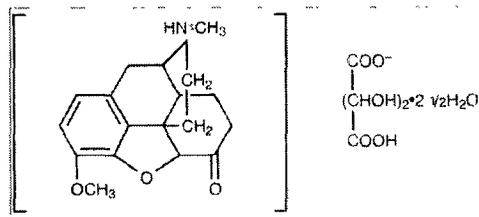
Hydrocodone Bitartrate, USP 2.5 mg

Ibuprofen, USP 200 mg

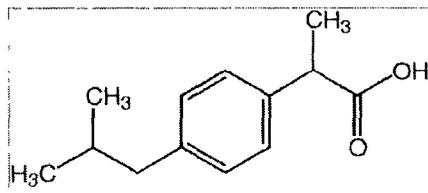
Hydrocodone bitartrate and ibuprofen is supplied in a fixed combination tablet form for oral administration. Hydrocodone bitartrate and ibuprofen combines the opioid analgesic agent, hydrocodone bitartrate, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen.

Hydrocodone bitartrate is a semisynthetic and centrally acting opioid analgesic. Its chemical name is 4,5 (alpha)-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2.5). Its chemical formula is:

$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2 \frac{1}{2} H_2O$, and the molecular weight is 494.50. Its structural formula is:



Ibuprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Its chemical name is: (±)-2-(*p*-isobutylphenyl) propionic acid. Its chemical formula is $C_{13}H_{18}O_2$, and the molecular weight is: 206.29. Its structural formula is:



Inactive ingredients in hydrocodone bitartrate and ibuprofen tablets include. This information will be provided when the application is submitted.

CLINICAL PHARMACOLOGY

Hydrocodone component: Hydrocodone is a semisynthetic opioid 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 opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding.

Ibuprofen component: Ibuprofen is a non-steroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is a peripherally acting analgesic. Ibuprofen does not have any known effects on opiate receptors.

Pharmacokinetics:

Absorption: After oral dosing with hydrocodone bitartrate and ibuprofen tablets, a peak hydrocodone plasma level of 27 ng/mL is achieved at 1.7 hours, and a peak ibuprofen plasma level of 30 mcg/mL is achieved at 1.8 hours. The effect of food on the absorption of either component from the hydrocodone bitartrate and ibuprofen tablet has not been established.

Distribution: Ibuprofen is highly protein-bound (99%) like most other non-steroidal anti-inflammatory agents. Although the extent of protein binding of hydrocodone in human plasma has not been definitely determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Metabolism: Hydrocodone exhibits a complex pattern of metabolism, including *O*-demethylation, *N*-demethylation, and 6-keto reduction to the corresponding 6-(alpha)- and 6-(beta)-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the *O*-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The *O*- and *N*-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Ibuprofen is present in this product as a racemate, and following absorption it undergoes interconversion in the plasma from the R-isomer to the S-isomer. Both the R- and S- isomers are metabolized to two primary metabolites: (+)-2-(4-(2-hydroxy-2-methyl-propyl) phenyl) propionic acid and (+)-2-(4-(2-carboxypropyl) phenyl) propionic acid, both of which circulate in the plasma at low levels relative to the parent.

Elimination: Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours. Ibuprofen is excreted in the urine, 50% to 60% as metabolites and approximately 15% as unchanged drug and conjugate. The plasma half-life is 2.2 hours.

Special Populations: No significant pharmacokinetic differences based on age or gender have been demonstrated. The pharmacokinetics of hydrocodone and ibuprofen from hydrocodone bitartrate and ibuprofen has not been evaluated in children.

Renal Impairment: The effect of renal insufficiency on the pharmacokinetics of the hydrocodone bitartrate and ibuprofen dosage form has not been determined.

CLINICAL STUDIES

In single-dose studies of hydrocodone bitartrate and ibuprofen tablets in post surgical pain (abdominal, gynecological, orthopedic), 940 patients were studied at doses of one or two tablets. Hydrocodone bitartrate and ibuprofen produced greater efficacy than placebo and each of its individual components given at the same dose. No advantage was demonstrated for the two-tablet dose.

INDICATIONS AND USAGE

Hydrocodone bitartrate and ibuprofen tablets are indicated for the short-term (generally less than 10 days) management of acute pain. Hydrocodone bitartrate and ibuprofen is not indicated for the treatment of such conditions as osteoarthritis or rheumatoid arthritis.

CONTRAINDICATIONS

Hydrocodone bitartrate and ibuprofen should not be administered to patients who previously have exhibited hypersensitivity to hydrocodone or ibuprofen. Hydrocodone bitartrate and ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Pre-existing Asthma).

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

WARNINGS

Abuse and Dependence: Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic and physical dependence as well as tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution as other narcotic drugs (see DRUG ABUSE AND DEPENDENCE).

Respiratory Depression: At high doses or in opioid-sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers. 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 opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries

Acute Abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation: Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event of NSAID therapy, is symptomatic. Even short term therapy is not without risk

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmaco-epidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without known prior exposure to hydrocodone bitartrate and ibuprofen. Hydrocodone bitartrate and ibuprofen should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Fatal reactions to NSAIDs have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS - Pre-existing Asthma). Emergency help should be sought when anaphylactoid reaction occurs

Advanced Renal Disease: In cases with advanced kidney disease, treatment with hydrocodone bitartrate and ibuprofen is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects)

Pregnancy: As with other NSAID-containing products, hydrocodone bitartrate and ibuprofen should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General Precautions

Special Risk Patients: As with any opioid analgesic agent, hydrocodone bitartrate and ibuprofen 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 opioids, caution should be exercised when hydrocodone bitartrate and ibuprofen is used postoperatively and in patients with pulmonary disease.

Effect on Diagnostic Signs: The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions

Hepatic Effects: As with other NSAIDs, ibuprofen has been reported to cause borderline elevations of one or more liver enzymes, this may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with hydrocodone bitartrate and ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), hydrocodone bitartrate and ibuprofen should be discontinued

Renal Effects: Caution should be used when initiating treatment with hydrocodone bitartrate and ibuprofen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with hydrocodone bitartrate and ibuprofen. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS - Advanced Renal Disease).

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Ibuprofen metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Patients with significantly impaired renal function should be more closely monitored.

Hematological Effects: Ibuprofen, like other NSAIDs, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, hydrocodone bitartrate and ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis.

Fluid Retention and Edema: Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation, hypertension or heart failure.

Pre-existing Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which may be fatal. Since cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, hydrocodone bitartrate and ibuprofen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Aseptic Meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on hydrocodone bitartrate and ibuprofen, the possibility of its being related to ibuprofen should be considered.

Information for Patients

Hydrocodone bitartrate and ibuprofen (hydrocodone bitartrate 2.5 mg and ibuprofen 200 mg), like other opioid-containing analgesics, may impair 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 bitartrate and ibuprofen 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.

Hydrocodone bitartrate and ibuprofen, like other drugs containing ibuprofen, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Patients should be instructed to report any signs and symptoms of gastrointestinal bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Laboratory Tests

A decrease in hemoglobin may occur during hydrocodone bitartrate and ibuprofen therapy, and elevations of liver enzymes may be seen in a small percentage of patients during hydrocodone bitartrate and ibuprofen therapy (see PRECAUTIONS - Hematological Effects and PRECAUTIONS - Hepatic Effects).

In patients with severe hepatic or renal disease, effects of therapy should be monitored with liver and/or renal function tests.

Drug Interactions

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking hydrocodone bitartrate and ibuprofen concomitantly with ACE-inhibitors.

Anticholinergics: The concurrent use of anticholinergics with hydrocodone preparations may produce paralytic ileus.

Antidepressants: The use of MAO inhibitors or tricyclic antidepressants with hydrocodone bitartrate and ibuprofen may increase the effect of either the antidepressant or hydrocodone.

Aspirin: As with other products containing NSAIDs, concomitant administration of hydrocodone bitartrate and ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

CNS Depressants: Patients receiving other opioids, antihistamines, antipsychotics, anxiolytic agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and ibuprofen may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Furosemide: Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with hydrocodone bitartrate and ibuprofen the patient should be observed closely for signs of renal failure (see PRECAUTIONS - Renal Effects), as well as diuretic efficacy.

Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when hydrocodone bitartrate and ibuprofen and lithium are administered concurrently, patients should be observed for signs of lithium toxicity.

Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when hydrocodone bitartrate and ibuprofen is administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

The carcinogenic and mutagenic potential of hydrocodone bitartrate and ibuprofen has not been investigated. The ability of hydrocodone bitartrate and ibuprofen to impair fertility has not been assessed.

Pregnancy: Pregnancy Category C.

Teratogenic Effects: Hydrocodone bitartrate and ibuprofen, administered to rabbits at 95 mg/kg (5.72 and 1.9 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality). Hydrocodone bitartrate and ibuprofen, administered to rats at 166 mg/kg (10.0 and 1.66 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, did not result in any reproductive toxicity. There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and ibuprofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. 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 withdrawal.

Labor and Delivery

As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of hydrocodone bitartrate and ibuprofen is not recommended during labor and delivery.

Nursing Mothers

It is not known whether hydrocodone is excreted in human milk. In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, hydrocodone bitartrate and ibuprofen is not recommended for use in nursing mothers.

Pediatric Use

The safety and effectiveness of hydrocodone bitartrate and ibuprofen in pediatric patients below the age of 16 have not been established.

Geriatric Use

In controlled clinical trials there was no difference in tolerability between patients < 65 years of age and those \geq 65, apart from an increased tendency of the elderly to develop constipation. However, because the elderly may be more sensitive to the renal and gastrointestinal effects of nonsteroidal anti-inflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution and reduced dosages should be used when treating the elderly with hydrocodone bitartrate and ibuprofen.

ADVERSE REACTIONS

Hydrocodone bitartrate and ibuprofen was administered to approximately 300 pain patients in a safety study that employed dosages and a duration of treatment sufficient to encompass the recommended usage (see DOSAGE AND ADMINISTRATION). Adverse event rates generally increased with increasing daily dose. The event rates reported below are from approximately 150 patients who were in a group that received one tablet of hydrocodone bitartrate and ibuprofen, an average of three to four times daily. The overall incidence rates of adverse experiences in the trials were fairly similar for this patient group and those who received the comparison treatment, acetaminophen 600 mg with codeine 60 mg.

The following lists adverse events that occurred with an incidence of 1% or greater in clinical trials of hydrocodone bitartrate and ibuprofen, without regard to the causal relationship of the events to the drug. To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

name of adverse event = less than 3%

*adverse events marked with an asterisk * = 3% to 9%*

adverse event rates over 9% are in parentheses

Body as a Whole: Abdominal pain*, Asthenia*, Fever; Flu syndrome, Headache (27%), Infection*, Pain

Cardiovascular: Palpitations; Vasodilation

Central Nervous System: Anxiety*; Confusion, Dizziness (14%); Hypertonia, Insomnia*; Nervousness*, Paresthesia, Somnolence (22%), Thinking abnormalities

Digestive: Anorexia; Constipation (22%), Diarrhea*; Dry mouth*, Dyspepsia (12%); Flatulence*, Gastritis, Melena; Mouth ulcers; Nausea (21%), Thirst, Vomiting*.

Metabolic and Nutritional Disorders: Edema*.

Respiratory: Dyspnea, Hiccups; Pharyngitis, Rhinitis

Skin and Appendages: Pruritus*; Sweating*.

Special Senses: Tinnitus.

Urogenital: Urinary frequency

Incidence less than 1%

Body as a Whole: Allergic reaction.

Cardiovascular: Arrhythmia, Hypotension, Tachycardia.

Central Nervous System: Agitation; Abnormal dreams, Decreased libido, Depression, Euphoria; Mood changes, Neuralgia; Slurred speech, Tremor, Vertigo

Digestive: Chalky stool; "Clenching teeth"; Dysphagia, Esophageal spasm; Esophagitis, Gastroenteritis; Glossitis; Liver enzyme elevation

Metabolic and Nutritional: Weight decrease.

Musculoskeletal: Arthralgia, Myalgia

Respiratory: Asthma, Bronchitis, Hoarseness; Increased cough; Pulmonary congestion; Pneumonia; Shallow breathing; Sinusitis

Skin and Appendages: Rash; Urticaria.

Special Senses: Altered vision; Bad taste; Dry eyes

Urogenital: Cystitis; Glycosuria; Impotence, Urinary incontinence; Urinary retention.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone bitartrate and ibuprofen tablets are a Schedule III controlled substance

Abuse: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, hydrocodone bitartrate and ibuprofen tablets should be prescribed and administered with the same degree of caution appropriate to use of other oral narcotic medications.

Dependence: Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although a mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order 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. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and ibuprofen tablets are used for a short time for the treatment of acute pain.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone and/or ibuprofen.

Signs and Symptoms:

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

Ibuprofen component: Symptoms include gastrointestinal irritation with erosion and hemorrhage or perforation, kidney damage, liver damage, heart damage, hemolytic anemia, agranulocytosis, thrombocytopenia, aplastic anemia, and meningitis. Other symptoms may include headache, dizziness, tinnitus, confusion, blurred vision, mental disturbances, skin rash, stomatitis, edema, reduced retinal sensitivity, corneal deposits, and hyperkalemia.

Treatment:

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose or unusual sensitivity to opioids, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered intravenously with simultaneous efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. Supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. In cases where consciousness is impaired it may be inadvisable to perform gastric lavage. If gastric lavage is performed, little drug will likely be recovered if more than an hour has elapsed since ingestion. Ibuprofen is acidic and is excreted in the urine; therefore, it may be beneficial to administer alkali and induce diuresis. In addition to supportive measures the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen. Dialysis is not likely to be effective for removal of ibuprofen because it is very highly bound to plasma proteins.

DOSAGE AND ADMINISTRATION

For the short-term (generally less than 10 days) management of acute pain, the recommended dose of hydrocodone bitartrate and ibuprofen is one tablet every 4 to 6 hours, as necessary. Dosage should not exceed 5 tablets in a 24-hour period. 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 lowest effective dose or the longest dosing interval should be sought for each patient, especially in the elderly. After observing the initial response to therapy with hydrocodone bitartrate and ibuprofen, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended.

HOW SUPPLIED

Hydrocodone bitartrate and ibuprofen tablets 2.5mg/200mg are available as

[Color and shape TBD], [tablet imprint TBD]

[Package sizes TBD]

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

Dispense in a tight, light-resistant container.

A Schedule CIII Narcotic.

Revised. [Date TBD]

[Manufacturer TBD]