CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-642

Name: Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg and 7.5 mg/200 mg.

Sponsor: Interpharm, Inc.

Approval Date: March 18, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

APPROVAL LETTER

ANDA 76-642

MAR 18 2004

SciRegs
Attention: C. Jeanne Taborsky
U.S. Agent for: INTERPHARM, Inc.
6333 Summercrest Drive
Columbia, MD 21045

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 16, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg and 7.5 mg/200 mg.

Reference is made to your amendments dated March 26, April 11, April 21, August 22, September 27, October 6, November 11, November 13, and November 24, 2003; and February 5, March 2, March 5, and March 9, 2004.) We acknowledge receipt of your correspondence dated April 21, and July 5, 2003; and January 9, January 27, and March 2, 2004, addressing the patent issues noted below. Reference is also made to the ANDA Suitability Petition submitted under Section 505(j)(2)(C) of the Act and approved on September 25, 2002. This approved petition permitted you to submit an ANDA for a drug product that differs in strength from that of the reference listed drug product (RLD). Specifically, you have provided for Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg in this application. The reference listed drug product, Vicoprofen Tablets 7.5 mg/200 mg, of Abbott Laboratories, is not marketed in the strength you have proposed.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that both strengths of the drug product are safe and effective for use as recommended in the submitted labeling. However, final approval of your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg is blocked at this time by another

applicant's eligibility for 180-day generic drug exclusivity for this drug product as noted in further detail below. **Therefore, final approval is granted for your Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg.** Please note that your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg is regarded as tentatively approved, and will be eligible for final approval upon the expiration of the other applicant's 180-day generic drug exclusivity.

The Division of Bioequivalence has determined that your Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg, can be expected to have the same therapeutic effect as that of an equivalent dose of the reference listed drug product (RLD) upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product referenced in your application (RLD), Vicoprofen Tablets, 7.5 mg/200 mg, of Abbott Laboratories, Pharmaceutical Products Division, is subject to multiple periods of patent protection. The following United States patents and their expiration dates currently appear in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

Patent Number	Expiration Date
4,587,252 (the '252 patent)	December 18, 2004
6,348,216 (the '216 patent)	June 10, 2017
6,599,531 (the '531 patent)	June 10, 2017

Your application contains paragraph IV certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg and 7.5 mg/200 mg under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against INTERPHARM Inc. (Interpharm) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This infringement action must have been brought against

Interpharm prior to the expiration of forty-five (45) days from the date the notice Interpharm provided under paragraph (2)(B)(i) was received by the patent and NDA holder(s). You have informed the agency that Interpharm complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement of the '252, '216, or '531 patents was brought against Interpharm within the statutory forty-five day period.

Under Section 506(A) of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change can be made.

Post-marketing requirements for this ANDA for Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of your Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns for the 5 mg/200 mg tablet strength. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Please note that our decision to grant tentative approval to your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg is based upon information currently available to the Agency; (i.e., data in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

As noted previously, we are unable to grant final approval to your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg at this time. Your ANDA contains a paragraph IV certification to the '531 patent, and provides for approval of the same drug product, 7.5 mg/200 mg, as Andrx Pharmaceuticals LLC's ANDA 76-604 that was approved by this Office on December 31, 2003. Andrx's ANDA also contained a paragraph IV certification to the '531 patent, and was received prior to the receipt of your ANDA. Under this circumstance, Andrx is eligible for 180 days of generic drug exclusivity with regard to the '531 patent for the 7.5 mg/200 mg strength of this drug product. The Act provides that final approval of your ANDA providing for the 7.5 mg/200 mg strength of the drug product shall be made effective one hundred and eighty (180) days after the date that Andrx begins first commerical marketing of their drug product. Once it is known, the expiration date for Andrx's exclusivity will be placed on the Agency's "Orange Book" InterNet site. For additional information, we refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1988).

In order to reactivate this application to provide for final approval of the 7.5 mg/200 mg strength, you must submit a "Supplemental Application - Expedited Review Requested". This supplemental application should be submitted for prior approval approximately 90 days prior to the date you believe that your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg will be eligible for final approval. The supplement should include a detailed explanation of why and when you believe final approval should be granted. It should also include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This supplemental application should be submitted even if no changes have been made to the application since the date of this tentative approval. Significant changes, as well as an update of the status of the manufacturing and testing facilities' compliance with cGMPs are subject to Agency review before final approval of the supplemental application will be granted. We request that you categorize the changes as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the supplemental application requested above, the Agency may request at any time prior to the date of final approval that you submit an additional document containing the requested information. Failure to submit either or, if requested, both documents may result in the rescission of the tentative approval status of your application for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg, or may result in a delay in the issuance of the final approval letter.

Please note that under Section 505 of the Act, your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg, may not be marketed without final agency approval. The introduction or delivery for introduction into interstate commerce of your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg, before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg will not be deemed approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting an amendment providing for the final approval of your Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg, please contact Simon Eng, R.Ph., Project Manager, at (301) 827-5848.

Sincerely yours,

Gary Buehler 3/18/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-642
Division File
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HFD-610/R. West
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HFD-205
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HFD-623/R.D'Costa/ 3/11/04
HFD-623/A.Mueller/
HFD-617/S.Eng/ 3/11/04
HFD-613/J.Barlow/ 3/11/04
HFD-613/J.Grace/ 3/12/04

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F/T by

APPROVAL

An explanation for exclusivity and the date needs to be added for the 7.5mg/20mg strength (FA) i.e. Andrx
3/18/04

Robert West
3/18/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

LABELING

Hydrocodone Bitartrate and Ibuprofen Tablets

CIII

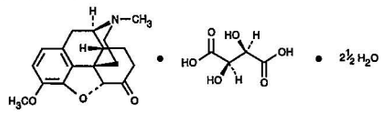
Rx only

APPROVAL

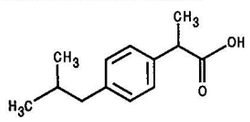
MAR 17 2004

DESCRIPTION

Hydrocodone bitartrate and ibuprofen tablets are supplied in a fixed combination tablet form for oral administration. Hydrocodone bitartrate and ibuprofen tablets combine 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 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its chemical formula is: $C_{18}H_{21}NO_3{\cdot}C_4H_6O_6{\cdot}2½\ H_2O$, 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:



Hydrocodone bitartrate and ibuprofen tablets are available in 7.5 mg / 200 mg and 5 mg / 200 mg strengths. They contain the following inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polydextrose, pregelatinized starch, 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 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 hydrocodone bitartrate and ibuprofen tablet, 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 tablets 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 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-α and 6-β-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'-(2hydroxy-2-methyl-propyl) phenyl propionic acid and (+)-2-4'-(2carboxypropyl) 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 tablets 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 post surgical pain (abdominal, gynecological, orthopedic), 940 patients were studied at doses of one or two tablets. Hydrocodone bitartrate and ibuprofen produced greater efficiency 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 are not indicated for the treatment of such conditions as osteoarthritis or rheumatoid arthritis.

CONTRAINDICATIONS

Hydrocodone bitartrate and ibuprofen tablets 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, uticaria, or allergic-type reactions after taking aspirin or the 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 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 been 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 are 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 are 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 dysfunctions, 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 have been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosous 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, 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 7.5 mg and ibuprofen 200 mg tablets 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.

Anticholingerics: The concurrent use of anticholingerics with hydrocodone preparations may produce paralytic ileus.

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

CNS Depressants: Patients receiving other opioids, antihistamines, antipsychotics, antianxiety 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 are 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 duration of maternal opioid use oral 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 are not recommended during labor and delivery.

Nursing Mothers
It is not known whether hydrocodone bitartrate and ibuprofen are 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 ≥ 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 increase 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 with 600 mg 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 (12%), 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, Glyosuria; 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 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 in the treatment of acute pain.

OVERDOSAGE
Following an acute overdosage, toxicity may result for 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, cyanis) 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 measure 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 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 tablets is one 7.5 mg / 200 mg tablet every 4 to 6 hours, as necessary. Dosage should not exceed five 7.5 mg / 200 mg 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 of 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, 7.5 mg / 200 mg are available as: White film-coated, round, biconvex tablets, debossed with "IP" over "145" on one side and plain on the other side.
Bottles of 24 - NDC #53746-145-24
Bottles of 100 - NDC #53746-145-01
Bottles of 500 - NDC #53746-145-05
Bottles of 1000 - NDC #53746-145-10

Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg / 200 mg are available as: White film-coated, oval shaped, bisected tablets, debossed with "IP/146" on one side and plain on the other side.
Bottles of 24 - NDC #53746-146-24
Bottles of 100 - NDC #53746-146-01
Bottles of 500 - NDC #53746-146-05
Bottles of 1000 - NDC #53746-146-10

Storage: Store at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF). [See USP Controlled Room Temperature.]
Dispense in a tight, light-resistant container.

Manufactured By:
INTERPHARM, INC.
Hauppauge, NY 11788

MG #18590

Revised: August 2003

NDC 53746-146-10

INTERPHARM

III

HYDROCODONE BITARTRATE 5 mg
AND
IBUPROFEN 200 mg
TABLETS

Rx only

APPROVAL
MAR 17 2004

1000 TABLETS

Rev. 5/03

Each tablet contains:
Hydrocodone bitartrate, USP . . . . . 5 mg
Ibuprofen, USP . . . . . 200 mg

USUAL DOSAGE: See package insert.

Dispense in light-resistant container as defined in the USP.

Storage: Store at 25°C (77°F); excursions permitted to controlled room temperature 15°-30°C (59°-86°F).

Manufactured By: **INTERPHARM, INC.**
Hauppauge, NY 11788

Lot No.:

Exp.:

3 53746-146-10 6

NDC 53746-146-05

HYDROCODONE BITARTRATE 5 mg AND IBUPROFEN 200 mg TABLETS

APPROVAL MAR 17 2004

Rx only

500 TABLETS

Rev. 5/03

Each tablet contains:
Hydrocodone bitartrate, USP . . . . 5 mg
Ibuprofen, USP . . . . . 200 mg

USUAL DOSAGE: See package insert.

Dispense in light-resistant container as defined in the USP.

Storage: Store at 25°C (77°F); excursions permitted to controlled room temperature 15°-30°C (59°-86°F).

Manufactured By: **INTERPHARM, INC.**
Hauppauge, NY 11788

Lot No.:

Exp.:

N 3 53746-146-05 2

NDC 53746-146-01

HYDROCODONE BITARTRATE 5 mg
AND
IBUPROFEN 200 mg
TABLETS

APPROVAL
MAR 17 2004

Rx only

100 TABLETS

Rev. 5/03

Each tablet contains:
Hydrocodone bitartrate, USP .... 5 mg
Ibuprofen, USP ..... 200 mg

USUAL DOSAGE: See package insert.

Dispense in light-resistant container as defined in the USP.

Storage: Store at 25°C (77°F); excursions permitted to controlled room temperature 15°-30°C (59°-86°F).

Manufactured By: **INTERPHARM, INC.**
Hauppauge, NY 11788

Lot No.:

Exp.:

3 53746-146-01 4

NDC 53746-146-24

HYDROCODONE BITARTRATE 5 mg
AND
IBUPROFEN APPROVAL 200 mg
TABLETS

Rx only
24 TABLETS

MAR 17 2004

Rev. 5/03

Each tablet contains:
Hydrocodone bitartrate, USP .... 5 mg
Ibuprofen, USP ..... 200 mg

USUAL DOSAGE: See package insert.

Dispense in light-resistant container as defined in the USP.

Storage: Store at 25°C (77°F); excursions permitted to controlled room temperature 15°-30°C (59°-86°F).

Manufactured By: **INTERPHARM, INC.**
Hauppauge, NY 11788

Lot No.:

Exp.:

3 53746-146-24 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-642
Date of Submission: January 16, 2003 **AND** March 26, 2003
Applicant's Name: INTERPHARM, Inc.
Established Name: Hydrocodone Bitartrate and Ibuprofen Tablets, **5 mg/200 mg** and 7.5 mg/200 mg

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LABELING COMMENTS

1. **CONTAINER – Bottles of 24, 100, 500 and 1000 tablets**
   a. Front Panel: Revise to read as follows –

HYDROCODONE BITARTRATE xx mg
AND
IBUPROFEN xx mg
TABLETS

Rx only
xx Tablets

   b. We encourage the use of boxing, contrasting colors or other means to differentiate between your two proposed tablet strengths.

2. **PACKAGE INSERT**
   See attached mocked-up copy of package insert labeling for requested revisions

Please revise your labels and labeling, as instructed, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attached: Copy of mocked-up package insert labeling

Following this page, 10 pages are withheld in full under (b)(4).
Copy of mocked-up package insert labeling (draft).

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?.		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	**X**		
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD? **Yes, Only because new strength introduced in suitability petition.**		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

Note: that the 5 mg/200 mg strength tablet was submitted as a suitability petition and approved on September 25, 2002 by the Agency. This was NOT actually withdrawn and the labels and labeling should be considered and reviewed as per Jeanne Taborsky as my conversation on 4/9/03. Note that this 5 mg/200 mg tablet will be scored providing a possible additional available strength to the application.

1. The model labeling the review was based on was for Vicoprofen® which was approved on; September 23, 1997; revised 9/97. This is the most recently approved labeling for the RLD.

2. Patent/ Exclusivities:

NDA 20-716

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

4587252 6348216	12/18/04 6/10/17	U-55	Treatment of Pain	Paragraph IV Paragraph III	None None

Exclusivity Data– NDA 20-716

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Keep bottles tightly closed and store below 77°F(25°C); excursions permitted to 15 to 30C(59 – 86F).[See USP Controlled Room Temperature]. Dispense in tight, light-resistant container.
   ANDA: Store at 25°C (77°F); excursions permitted to controlled room temperature 15 to 30°C(59 – 86°F).

4. Product Line:
   The innovator markets their 7.5 mg/200 mg strength tablet product in bottles containing 100 and 500 tablets and unit dose packages of 100.

   The applicant proposes to market their 7.5 mg/200 mg strength tablet product in bottles containing 24, 100, 500 and 1000 tablets. Also, Interpharm, Inc. is proposing a 5 mg/200 mg strength tablet in bottles of 24, 100, 500 and 1000 count bottles as of the SUITABILITY PETITION approved 9/25/02

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2372 Vol. B. 1.2.

6. All manufacturing will be performed by Interpharm, Inc. See pages (2452, Vol. B. 1.2.)

7. Container/Closure:
   This product will be packaged in white HDPE bottles. The 100 count and 1000 count bottles will **utilize non-CRC** cap. **(see pg 6337 in vol. B. 1.2)**

8. The tablet imprintings have been accurately described in the HOW SUPPLIED section. (see pg. 2940 in Vol, B 1.3 **but have NOT been described accurately in the CFFDF in volume B. 2.2 page 0503. Listed as having bisect in the HOW SUPPLIED section and no bisect mentioned in the CFFDF. NOTE that the RLD does NOT market a 5 mg/200 mg strength tablet. A suitability petition was granted in 9/25/02 by the Agency.**

9. **Note that the DOSAGE AND ADMINISTRATION section was ONLY designed to dose the 7.5 mg/200 mg tablet.**

Date of Review: 4/8/03 Date of Submission: 1/16/03 and 3/26/03

Primary Reviewer: Jim Barlow Date: 4/9/03

Team Leader: John Grace Date: 4/10/2003

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cc:

ANDA: 76-642
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
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Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-642
Date of Submission: August 22, 2003
Applicant's Name: INTERPHARM, Inc.
Established Name: Hydrocodone Bitartrate and Ibuprofen Tablets, **5 mg/200 mg** and 7.5 mg/200 mg

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Approval Summary

1. **Do you have 12 Final Printed Labels and Labeling?** Yes

2. **CONTAINER – Bottles of 24, 100, 500 and 1000 tablets**
   Satisfactory in **final print** as of the August 22, 2003 submission.
   (See blue volume 3.1)

3. **PACKAGE INSERT**
   Satisfactory in **final print** as of the August 22, 2003 submission.
   (See blue volume 3.1)

4. **Revisions needed post-approval;** None

5. **Patent Data:**
   NDA 20-716

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4587252	12/18/04	U-55	Treatment of Pain	Paragraph IV	None
6348216	6/10/17			Paragraph IV	None
6599531	6/10/17			Paragraph IV	None

Exclusivity Data:

NDA 20-716

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Vicoprofen®
NDA Number: N 20-716
NDA Drug Name: Vicoprofen®
NDA Firm: Knoll Pharmaceutical Company; N 20-716; Approved September 23, 1997.
Date of Approval of NDA Insert; NDA 20-716; Approved Sept. 23, 1997
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug,

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	

Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?.		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	**X**		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? Been addressed by firm as of 4/21/03 submission		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			

Is the scoring configuration different than the RLD? **Yes, Only because new strength introduced in suitability petition.**		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

Note: that the 5 mg/200 mg strength tablet was submitted as a suitability petition and approved on September 25, 2002 by the Agency. This was NOT actually withdrawn and the labels and labeling should be considered and reviewed as per Jeanne Taborsky as my conversation on 4/9/03. Note that this 5 mg/200 mg tablet will be scored providing a possible additional available strength to the application.

1. The model labeling the review was based on was for Vicoprofen® which was approved on; September 23, 1997; revised 9/97. This is the most recently approved labeling for the RLD.

2. Patent/ Exclusivities: Note that as of 1/9/04 patent revisions were made. Interpharm paragraphed IV'd every patent

NDA 20-716

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4587252	12/18/04	U-55	Treatment of Pain	Paragraph IV	None
6348216	6/10/17			Paragraph IV	None
6599531	6/10/17			Paragraph IV	None

Exclusivity Data:

NDA 20-716

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Keep bottles tightly closed and store below 77°F(25°C); excursions permitted to 15 to 30C(59 – 86F).[See USP Controlled Room Temperature]. Dispense in tight, light-resistant container.
   ANDA: Store at 25°C (77°F); excursions permitted to controlled room temperature 15 to 30°C(59 – 86°F).
4. Product Line:
   The innovator markets their 7.5 mg/200 mg strength tablet product in bottles containing 100 and 500 tablets and unit dose packages of 100.

   The applicant proposes to market their 7.5 mg/200 mg strength tablet product in bottles containing 24, 100, 500 and 1000 tablets. Also, Interpharm, Inc. is proposing a 5 mg/200 mg strength tablet in bottles of 24, 100, 500 and 1000 count bottles as of the SUITABILITY PETITION approved 9/25/02

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2372 Vol. B. 1.2.

6. All manufacturing will be performed by Interpharm, Inc. See pages (2452, Vol. B. 1.2.)

7. Container/Closure:
   This product will be packaged in white HDPE bottles. The 24 & 100 count bottles will utilize a CRC-closure and the 500 & 1000 count bottles will **utilize non-CRC** closures. **(see pg 2813 in vol. B. 1.3)**

8. The tablet imprintings have been accurately described in the HOW SUPPLIED section. (see pg. 2940 in Vol, B 1.3 but have NOT been described accurately in the CFFDF in volume B. 2.2 page 0503. Listed as having bisect in the HOW SUPPLIED section and no bisect mentioned in the CFFDF. NOTE that the RLD does NOT market a 5 mg/200 mg strength tablet. A suitability petition was granted in 9/25/02 by the Agency. **(Note as of 4/21/03 submission. This discrepancy has been resolved. See page 000085 in red jacket volume 3.1. The 5 mg/200 mg tablet IS SCORED)**

9. **Note that the DOSAGE AND ADMINISTRATION section was ONLY designed to dose the 7.5 mg/200 mg tablet.**

Date of Review: 9/30/03 Date of Submission: 8/22/03

Primary Reviewer: Jim Barlow Date: 3/11/04

Team Leader: John Grace Date: 3/11/04

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cc:

ANDA: 76-642
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\INTERPH\LTRS&REV\76642ap.s.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

CHEMISTRY REVIEWS

ANDA 76-642

Hydrocodone Bitartrate/Ibuprofen Tablets
7.5mg/200mg

Interpharm, Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-642

2. REVIEW #: 1

3. REVIEW DATE: 05/10/03

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	01/16/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Interpharm, Inc.
Address:	Attn: Nilkanth J. Patel 75 Adams Avenue, Hauppauge, NY 11788. 631-952-0214 ext. 106 Fax: 631-952-9587
Representative:	C. Jeanne Taborsky (Agent)
Telephone:	410-309-3145 Fax: 410-309-6145

8. DRUG PRODUCT NAME/CODE/TYPE:
   Hydrocodone Bitartrate/Ibuprofen Tablets

9. LEGAL BASIS FOR SUBMISSION: FFD & CA
   Paragraph IV Certification: Interpharm certifies that in its opinion and to the best of its knowledge, US patent #6,348,216 expiring June 10, 2017, which claims the reference listed drug will not be infringed upon by the manufacture, use or sale of Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg.
   The basis for submission is the approved listed drug Abbott's VICOPROFEN® (Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg) the subject of NDA #20716.
   Paragraph III Certification: With respect to Interpharm's drug product, Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg, the firm certifies that U.S. Patent #4,587,252 will expire December 18, 2004 and does not intend to market the drug product before December 18, 2004, the date the exclusivity expires (Section III of the application).

10. PHARMACOL. CATEGORY: Opioid Analgesic, Antitussive, Anti-inflammatory

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 7.5mg/200mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

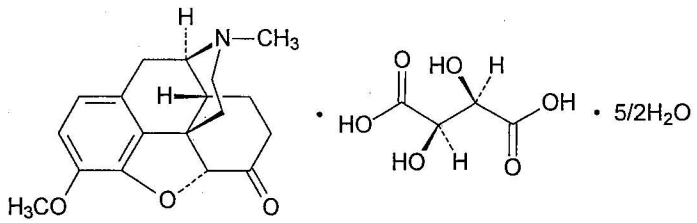
    _____SPOTS product – Form Completed

    _X____Not a SPOTS product

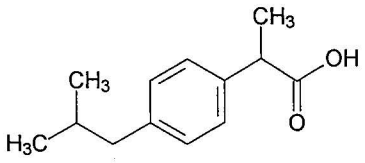
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

    Generic Name: Hydrocodone Bitartrate

Chemical Name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5α)-, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)
Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$
Molecular weight: 494.5
CAS registry number(s): 34195-34-1, 6190-38-1
Antitussive



Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Formula: $C_{13}H_{18}O_2$
Molecular weight: 206.29
CAS registry number(s): 15687-21-1, 58560-75-1
Anti-inflammatory



17. RELATED/SUPPORTING DOCUMENTS: None

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	9/09/02	Reviewed by A. Basak
	II			1	Inadequate	05/27/03	Reviewed by RD'Costa
	II			3	Adequate	04/21/03	Reviewed by S. Dhanesar
	IV			3	Adequate	06/06/03	Reviewed by C. Bertha
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III						
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: Not Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Inadequate	5/8/03	J. Barlow
Bioequivalence	Pending		
EA	Categorical Exclusion Requested	05/23/03	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-642

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in areas of manufacturing and controls and is therefore recommended for "not-approvable".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a combination of two drug substances, Hydrocodone Bitartrate and Ibuprofen. Hydrocodone Bitartrate is a white to creamy crystalline powder where as Ibuprofen is a white to off-white crystalline powder. Both the drug substances are synthesized by a multi-step chemical synthesis. The drug substance and its impurities have been characterized using the standard analytical techniques of IR, NMR, MS, HPLC, etc. They are formulated with known compendium excipients to form the drug product.

The drug product is based on the innovator drug Abbott's VICOPROFEN® (Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg) the subject of NDA #20716. The drug is supplied in a fixed combination tablet form for oral administration. Hydrocodone Bitartrate and Ibuprofen combine the opioid analgesic agent, Hydrocodone Bitartrate, with the non-steroidal anti-inflammatory (NSAID) agent, Ibuprofen. Hydrocodone Bitartrate is a semi-synthetic and centrally acting opioid analgesic and Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. The drug product is formulated through a (b) (4) and packaged into various configurations.

B. Description of How the Drug Product is Intended to be Used

The recommended daily dose is one tablet every 4 to 6 hours and should not exceed 5 tablets in a 24 hours period.

C. Basis for Approvability or Not-Approval Recommendation

The "not-approvable" recommendation for chemistry is based on the following issues:

- There are issues in the drug substance, manufacturing process, finished drug product controls for release and stability that need to be resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: RD'Costa, Ph.D. /05/26/03
ChemistryTeamLeaderName/Date: AMueller, Ph.D. /05/26/03 for G Bykadi 7-9-03
ProjectManagerName/Date: C.Kiester, PM /05/26/03 7/9/03
F/T by:

C. CC Block

Following this page, 13 pages are withheld in full (b)(4).
Chemistry Review #1.

12. (b) (4)

13.

14.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide current room temperature stability data.

2. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval.

3. The labeling information that you have provided has been reviewed and found to be deficient. These deficiencies have been communicated to you under a separate cover.

4. The bioequivalence information that you have provided is currently under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

5. Since an official monograph in the USP does not cover this drug product, the analytical methods must be validated by a FDA field laboratory. Samples for the methods validation will be requested by the FDA at the appropriate time.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-642
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/RD'Costa, Ph.D./06/20/03
HFD-623/Amueller, Ph.D./06/20/03
HFD-617/C. Kiester, PM/07/03/03
F/T by/ade/7/9/03
V:\FIRMSAM\INTERPH\LTRS&REV\76642N01.R01.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-642

Hydrocodone Bitartrate/Ibuprofen Tablets
7.5mg/200mg and 5mg/200mg

Interpharm, Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-642

2. REVIEW #: 2

3. REVIEW DATE: 09/22/03

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	01/16/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	03/08/04
Telephone Amendment	03/05/04
Minor Amendment	02/05/04
Telephone Amendment	11/24/03
Gratuitous Minor Amendment	11/11/03
Gratuitous Minor Amendment	10/06/03
Minor Amendment	09/27/03
Gratuitous Amendment	03/12/03

7. NAME & ADDRESS OF APPLICANT:

Name: Interpharm, Inc.

Chemistry Review Data Sheet

Address: Attn: Nilkanth J. Patel
75 Adams Avenue,
Hauppauge, NY 11788.
631-952-0214 ext. 106
Fax: 631-952-9587

Representative: C. Jeanne Taborsky (Agent)

Telephone: 410-309-3145
Fax: 410-309-6145

8. DRUG PRODUCT NAME/CODE/TYPE:
Hydrocodone Bitartrate/Ibuprofen Tablets

9. LEGAL BASIS FOR SUBMISSION: FFD & CA
Paragraph IV Certification: Interpharm certifies that in its opinion and to the best of its knowledge, US patent #6,348,216 expiring June 10, 2017, which claims the reference listed drug will not be infringed upon by the manufacture, use or sale of Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg.
The basis for submission is the approved listed drug Abbott's VICOPROFEN® (Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg) the subject of NDA #20716.

Interpharm submitted a gratuitous amendment dated March 12, 2003, for a lower strength of Hydrocodone Bitartrate/Ibuprofen Tablets, 5mg/200mg. This is based on a suitability petition filed on July 12, 2002, approved on September 25, 2002 and the Telephone Amendment dated on March 10, 2003. Also, the firm submitted a gratuitous amendment dated November 11, 2003 for a packaging change followed by a telephone amendment dated November 24, 2003. This is followed by a Minor Amendment and Telephone Amendments dated February 05, 2004, March 05 and March 09,, 2004, respectively.

Paragraph III Certification: With respect to Interpharm's drug product, Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg, the firm certified that U.S. Patent #4,587,252 will expire December 18, 2004. The firm does not intend to market the drug product before December 18, 2004, the date the exclusivity expires (Section III of the application).

10. PHARMACOL. CATEGORY: Opioid Analgesic, Antitussive, Anti-inflammatory

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 7.5mg/200mg and 5mg/200mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

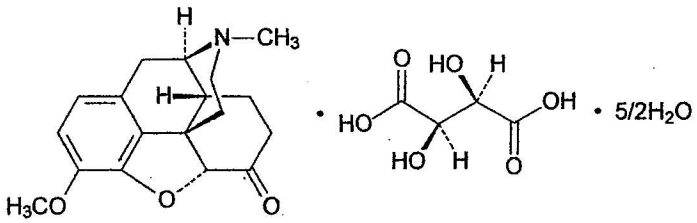
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

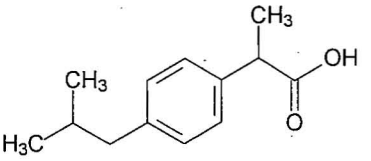
__X____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Generic Name: Hydrocodone Bitartrate
Chemical Name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5□)-, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)
Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$
Molecular weight: 494.5
CAS registry number(s): 34195-34-1, 6190-38-1
Antitussive



Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Formula: $C_{13}H_{18}O_2$
Molecular weight: 206.29
CAS registry number(s): 15687-21-1, 58560-75-1
Anti-inflammatory



17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	01/06/04	Reviewed by RD'Costa
	II			1	Adequate	11/17/03	Reviewed by RD'Costa
	II			3	Adequate	04/21/03	Reviewed by S. Dhanesar
	IV			3	Adequate	06/06/03	Reviewed by C. Bertha
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: **Approvable**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	07/29/03	J. D. Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	10/30/03	J. Barlow
Bioequivalence	Acceptable	12/23/03	Z. Wahba
EA	Categorical Exclusion Requested (Acceptable)	05/23/03	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-642

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The chemistry section is adequate in areas of manufacturing and controls and is therefore deemed "approvable".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments:

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a combination of two drug substances, Hydrocodone Bitartrate and Ibuprofen. Hydrocodone Bitartrate is a white to creamy crystalline powder where as Ibuprofen is a white to off-white crystalline powder. Both the drug substances are synthesized by a multi-step chemical synthesis. The drug substance and its impurities have been characterized using the standard analytical techniques of IR, NMR, MS, HPLC, etc. They are formulated with known compendium excipients to form the drug product.

The drug product is based on the innovator drug Abbott's VICOPROFEN® (Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg and 5mg/200mg) the subject of NDA #20716. The drug is supplied in a fixed combination tablet form for oral administration. Hydrocodone Bitartrate and Ibuprofen combine the opioid analgesic agent, Hydrocodone Bitartrate, with the non-steroidal anti-inflammatory (NSAID) agent, Ibuprofen. Hydrocodone Bitartrate is a semi-synthetic and centrally acting opioid analgesic and Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. The drug product is formulated through a (b) (4)) and packaged into various packaging configurations.

B. Description of How the Drug Product is Intended to be Used:

The recommended daily dose is one tablet every 4 to 6 hours and should not exceed 5 tablets in a 24 hours period.

C. Basis for Approvability or Not-Approval Recommendation:

The chemistry section is adequate in areas of manufacturing and controls and is therefore deemed "approvable".

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: RD'Costa, Ph.D. /03/09/04
ChemistryTeamLeaderName/Date: AMueller, Ph.D. /03/09/04
ProjectManagerName/Date: C.Kiester/S. Eng, PM /03/09/04
V:\FIRMSAM\INTERPH\LTRS&REV\76642.REV2.doc
F/T by:

C. CC Block

ANDA 76-642
ANDA DUP
DIV FILE
Field Copy

Following this page, 9 pages are withheld in full (b)(4).
Chemistry Review #2.

(b) (4)

[redacted]

30. **MICROBIOLOGY:** **N/A**

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS:** N/A

32. **LABELING:** **Acceptable as of October 30, 2003, J. Barlow.**

33. **ESTABLISHMENT INSPECTION:** **Acceptable as of July 29, 2003, J. D. Ambrogio, HFD-322.**

34. **BIOEQUIVALENCE:** **Acceptable as of December 23, 2003, Z. Wahba, Division of Bioequivalence.**

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** **Satisfactory in Review #1.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-712

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-642
Drug Product Name	Hydrocodone Bitartrate and Ibuprofen tablets
Strength	7.5 mg/200 mg and 5 mg/200 mg
Applicant Name	Interpharm Inc.
Address	Hauppauge, NY
Submission Date(s)	01/16/03
Amendment Date(s)	~~04/11/03~~ (for a new strength, 5 mg/200 mg) 3/24/03
Reviewer	Zakaria Z. Wahba
First Generic	The 7.5 mg/200 mg strength is not first generic. The 5 mg/200 mg strength is first generic.
File Location	V:\firmsam\Interpharm\ltrs&rev\76642n0103.doc

I. Executive Summary

This submission consisted of two bioequivalence (BE) studies under fasting and non-fasting conditions, and dissolution data for the 7.5 mg/200 mg and 5 mg/200 mg strengths. The BE study under fasting condition is a single dose two-way crossover design in normal males and females (n=24). The BE study under non-fasting conditions is a single dose two-way crossover design in normal males and females (n=17).

Statistical analyses of the plasma concentration data for hydrocodone bitartrate and ibuprofen for both studies demonstrate bioequivalence.

For the fasting BE study, hydrocodone results are (point estimate, 90% CI): $LAUC_t$ of 0.95, 91.32-98.51%; $LAUC_i$ of 0.95, 91.02-98.44% and LCmax of 1.01, 93.98-108.27%. For the ibuprofen results are (point estimate, 90% CI): $LAUC_t$ of 0.98, 93.93-102.74%; $LAUC_i$ of 0.98, 94.20-101.61% and LCmax of 0.95, 84.96-107.18%.

For the nonfasting BE study, hydrocodone results are (point estimate, 90% CI): $LAUC_t$ of 0.98, 95.12-101.64%; $LAUC_i$ of 0.98, 95.20-101.90% and LCmax of 0.95, 90.37-100.13%. For the ibuprofen results are (point estimate, 90% CI): $LAUC_t$ of 1.00, 96.17-104.59%; $LAUC_i$ of 1.00, 96.63-103.51% and LCmax of 0.83, 75.43-90.84%. The ratios of the geometric means are within the acceptable 0.8-1.25 range for AUCt, AUCi and Cmax for ibuprofen. The fed study meets the FDA acceptance criteria in place at the time that the study was initiated on August 03, 2002.

The application has been found incomplete due to deficiencies related to analytical method validation (details are given in the deficiency section).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg
Reference Product	Vicoprofen® Tablets, 7.5 mg/200 mg
RLD Manufacturer	Abbott
NDA No.	20-716
RLD Approval Date	September 23, 1997
Indication	Treatment of pain

B. PK/PD Information

Food Effect	The effect of food on the absorption of either component from the VICOPROFEN tablet has not been established.
Tmax	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 mcg/mL is achieved at 1.8 hours.
Metabolism	By *O* -demethylation, *N* -demethylation, and 6-keto reduction
Excretion	Hydrocodone and its metabolites are eliminated primarily in the kidneys
Half-life	Hydrocodone : 4.5 hours; ibuprofen: 2.2 hours
Relevant OGD or DBE History	There is only one generic drug approved for Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg (ANDA 76-023 by Teva, approved date: 04/11/03). Only hydrocodone and ibuprofen plasma levels were measured for bioequivlence evaluation.
Agency Guidance	According to the general BA/BE guidance, only parent drug levels in plasma should be measured.
Drug Specific Issues (if any)	The 5 mg/200 mg strength is a new strength and is a subject of the amendment dated 04/16/03. The new strength is based on a suitability petition Docket No. 02P-0270/CPI approved on September 25, 2002.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	2
Steady-state	No	
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation (p 202-250, vol. C1.2)

Information on pages 190-		
Analyte name	Ibuprofen	Hydrocodone
Internal Standard	(b) (4)	
Method description	LC/MS/MS	HPLC
QC range	2.5, 15.0, and 75.o mcg/mL	0.11, 0.33, 11.0, and 93.5 ng/mL
Standard curve range	1.00 to 100 mcg/mL	0.110 to 110 ng/mL
Limit of quantitation	1.00 mcg/mL	0.11 ng/mL
Average recovery of Drug (%)	Not given	57.63
Average Recovery of Int. Std (%)	Not given	44.23
Intraday precision range (%CV)	2.62 to 4.06	0.62 to 12.77
Intraday accuracy range (%)	98.5 to 101	88 to 110
Interday precision range (%CV)	Not given	1.18 to 13.66
Interday accuracy range (%)	Not given	100.30 to 101.82
Bench-top stability (hrs)	24	24
Stock stability (days)	Not given	Not given
Processed stability (hrs)	Not given	24
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	69 days (p 1382, vol. C1.5) and 56 days (p 191, vol. C1.2)	70 days (p 1382, vol. C1.5) and 55 days (p 191, vol. C1.2)
Dilution integrity	Not given	Not given
Specificity	Yes	Yes
SOPs submitted	Not given	Not given
Bioanalytical method is acceptable	See deficiency section	See deficiency section
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	#207-04-11710
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover study, under fasting conditions.
No. of subjects enrolled	26
No. of subjects completing	24
No. of subjects analyzed	24
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 21 Female: 5
Test product	Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg
Reference product	Vicoprofen® Tablets, 7.5 mg/200 mg
Strength tested	7.5 mg/200 mg tablet
Dose	1 X 7.5 mg/200 mg tablet with 240 mL of water

Summary of Statistical Analysis Hydrocodone Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t (ng.hr/mL)	0.95	91.32-98.51
AUC∞ (ng.hr/mL)	0.95	91.02-98.44
Cmax (ng/mL)	1.01	93.98-108.27
Summary of Statistical Analysis Ibuprofen Additional Information in Appendix, Table 9 and Table 10		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t (mcg.hr/mL)	0.98	93.93-102.74
AUC∞ (mcg.hr/mL)	0.98	94.20-101.61
Cmax (mcg/mL)	0.95	84.96-107.18

Reanalysis of Study Samples Additional information in Appendix, Table 5								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
No reassayed samples were reported								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on Fasting Study: The 90% confidence intervals for log-transformed AUCt, AUCi, and CMAX (for both hydrocodone bitartrate and ibuprofen) are within the acceptable range of 80-125%. The reviewer's calculations are similar to those submitted by the firm. However, the study is incomplete due to deficiencies in the analytical method validation.

2. Single-dose Fed Bioequivalence Study

Study No.	207-05-11711
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover study under fed conditions.
No. of subjects enrolled	18
No. of subjects completing	17
No. of subjects analyzed	17
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 13 Female: 5
Test product	Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg
Reference product	Vicoprofen® Tablets, 7.5 mg/200 mg
Strength tested	7.5 mg/200 mg tablet
Dose	1 X 7.5 mg/200 mg tablet with 240 mL of water

Summary of Statistical Analysis Hydrocodone Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t (ng.hr/mL)	0.98	95.12-101.64
AUC∞ (ng.hr/mL)	0.98	95.20-101.90
Cmax (ng/mL)	0.95	90.37-100.13
Summary of Statistical Analysis Ibuprofen Additional Information in Appendix, Table 9 and Table 10		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t (mcg.hr/mL)	1.00	96.17-104.59
AUC∞ (mcg.hr/mL)	1.00	96.63-103.51
Cmax (mcg/mL)	0.83	75.43-90.84

For the test product, the ratios of the geometric means for AUCt, AUCi, and CMAX (for both hydrocodone bitartrate and ibuprofen) are within the acceptable range of 0.8-1.25. The reviewer's calculations are similar to those submitted by the firm. It is noted that the study was initiated on 08/11/02, which was before the issuance of the CDER Guidance "Food-Effect Bioavaliability and Fed Bioequivalence Studies" (December 2002). The fed study meets the FDA acceptance criteria in place at the time it was initiated. The criteria were that the ratio of AUC and Cmax geometric means for hydrocodone bitartrate and ibuprofen should fall within the interval of 80 to 125%. However, the study is incomplete due to the deficiencies cited in the deficiency section.

Reanalysis of Study Samples								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
No reassayed samples were reported								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on fed study:

F. Formulation

Location in appendix	Section B, Page 30
Inactive ingredients within IIG Limits (yes or no)	**Yes**
If no, list ingredients outside of limits	**-**
If a tablet, is the product scored? (yes or no)	**No**
If yes, which strengths are scored?	**-**
Is scoring of RLD the same as test? (yes or no)	**No**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	**-**

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA (per ANDA 76-023 Amendment, dated 3/7/01 and DBE review date 2/9/01)
Medium	Phosphate Buffer, pH 7.2
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
Firm's proposed specifications	-
FDA-recommended specifications	NLT (b) (4) (Q) of the labeled amount of both hydrocodone and ibuprofen in the dosage form is dissolved in 15 minutes.
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Rapidly dissolving
Method is acceptable (yes or no)	Yes

Note: The dissolution data for the hydrocodone bitartrate and ibuprofen tablets, 5 mg/200 mg, are incomplete. The firm provided the dissolution data for ibuprofen only. The firm is requested to submit the dissolution data for hydrocodone for its 5 mg/200 mg strength. See the deficiency section.

H. Waiver Request(s)

Strengths for which waivers requested	5 mg/200 mg
Regulation cited	The new strength is based on a suitability petition Docket No. 02P-0270/CPI approved on September 25, 2002.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	No (incomplete)
Waiver granted (yes or no)	No

I. Deficiency Comments

1. The provided long-term stability data of hydrocodone bitartrate and ibuprofen in frozen study samples (pages #191, and 1382) were not sufficient to cover the entire length of the sample storage period (from first blood sample was drawn to the last plasma sample analyzed). The firm should submit data to support the long-term stability of hydrocodone bitartrate and ibuprofen in frozen study samples for a period at least covers the entire length of the biostudy.

2. The submitted information on assay methodology description and validation was not adequate. The following raw data for pre-study validation on ibuprofen are requested: 1) inter-day quality control (QC) samples; 2) recovery of the drug and internal standard; 3) Stock stability data, for how long (hours/days), and identify temperature; 4) In-process stability, for how long (hours); and Dilution integrity.

   For hydrocodone bitartrate, only data on stock stability and dilution integrity are requested.

   For each item, the mean value for each sample set, range (minimum and maximum), precision (%CV), accuracy (%) accuracy, and number of samples, should be provided.

3. The standard operation procedure (SOP) for describing the analytical method and data (sample acceptance and rejection criteria) for the studies under fasting and fed conditions was not provided in the submission. The SOP number, date of SOP approved, and SOP title should be also included.

4. The submitted dissolution testing data on the 5 mg/200 mg strength are incomplete. The firm submitted the dissolution data for ibuprofen only. Dissolution data on hydrocodone bitartrate (5 mg/200 mg strength) are requested.

J. Recommendations

1. The two single-dose bioequivalence study, under fasting (#207-04-11710), and non-fasting conditions (#207-04-11711), conducted by Interpharm, Inc., on its Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg, lot #E04402, comparing it to Abbott's Vicoprofen® Tablets, 7.5 mg/200 mg, lot #02PROF1017, has been found to be incomplete by the Division of Bioequivalence for the reasons given in deficiency comment section.

2. Dissolution data submitted by Interpharm are incomplete. The firm should submit dissolution data for the Hydrocodone Bitartrate component for the 5 mg/200 mg strength.

3. The waiver of bioequivalence requirements for the 5 mg/200 mg strength was not granted at this time due to the reasons given in deficiency comment.

The firm should be informed of the deficiency comment and recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED GJPSINGH
FT INITIALED GJPSINGH Date: 10-9-03

Concur: Barbara M. Davit Date: 10/9/03
for
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information (pages 148-217 , volume C1.2)	
Study Number	Project #207-04-11710, protocol #11710A
Study Title	A comparative bioavailability study of 7.5 mg/200 mg Hydrocodone Bitartrate and Ibuprofen Tablets versus 7.5 mg/200 mg Vicoprofen® Tablets under fasting conditions.
Clinical Site	PharmacoKinetic Laboratories, Inc. Baltimore, MD 21201
Principal Investigator	Ronald Goldwater, M.D.
Study/Dosing Dates	Period I: August 03, 2002 Period II: August 10, 2002 (p 174, vol. C1.2)
Analytical Site	PharmacoKinetic Laboratories, Inc. Baltimore, MD 21201
Analytical Director	(b) (6) , Ph.D.
Analysis Dates	11/04/02 to 11/14/02 (p 190, vol. C1.2)
Storage Period (no. of days from first sample to final analysis)	101 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Hydrocodone Bitartrate and Ibuprofen Tablets	Vicoprofen® Tablets
Manufacturer	Interpharm	Abbott Laboratories
Batch/Lot No.	E04402	02PROF1017
Manufacture Date	5/8/02 (p 3061, vol. A1.9)	N/A
Expiration Date	N/A	March 2004
Strength	7.5 mg/200 mg	7.5 mg/200 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4) tablets	N/A
Production Batch Size	(b) (4) tablets	N/A
Potency	Ibuprofen = 101.5% Hydrocodone = 103.6% (p 2371, vol. C1.7))	Ibuprofen = 101.0% Hydrocodone = 102.0% (p 2371, vol. C1.7))
Content Uniformity	Ibuprofen = 98.7-105.5% Hydrocodone = 98.9-108.76%	Ibuprofen = 99.8-103.1% Hydrocodone = 100.7-104.7%
Formulation	See Appendix Section B	
Dose Administered	1 X 7.5 mg/200 mg tablet with 240 mL of water	1 X 7.5 mg/200 mg tablet with 240 mL of water
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	-
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5. 3, 4, 5, 6, 8, 10, 12 and 24 hours.
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C.
IRB Approval	Yes on 08/01/02 (p 173, vol. C1.2)
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours before dosing and for 5 hours after dosing.
Length of Confinement	10 hours predose until 24 hours postdose.
Safety Monitoring	Vital signs (blood pressure and heart rate) measured prior to dosing and 4 and 12 hours postdose.

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	19
Mean	30.23	Mean	165.73	18-40	85	Male	81	Afr. Amer.	73
SD	9.59	SD	19.34	41-64	15	Female	19	Hispanic	4
Range	19-49	Range	126-199	65-75	0			Asian	4
				>75	0			Others	0

Study Results

Table 1 Dropout Information (p 159, vol. C1.2)

Subject No	21	22
Reason	Voluntarily withdrew for personal reasons	Failed to return to the facility to complete Period II
Period	After completing Period I	After completing Period I
Replacement	No	No

Was there a difference in side effects for the test versus the reference? No

Table 2 Study Adverse Events

Adverse Events	# in Test Group	# in Reference Group
Total:	21	20

Comments: The adverse events occurred with similar frequency for both treatments. No serious adverse events were reported (for more details see page 738, vol. C1.3).

Was there a difference in protocol deviations for the test versus the reference? No

Table 3 Protocol Deviations

Type	**Subject #s (Test)**	**Subject #s (Reference)**
Delay to draw blood (most of samples between 2-6 minutes, only one sample was 10 minutes delay).	33	37

Comments: The PK analysis was based on actual sample times. The deviations are unlikely to impact the outcome of the study.

Table 4 Assay Validation – Within Study (p 196, vol. C1.2)

	Ibuprofen	Hydrocodone
QC Conc.	2.50, 15.0, and 75.0 mcg/mL	0.33, 11.0, and 93.5 ng/mL
Inter day Precision (%CV)	1.48 - 2.45	2.45 - 7.16
Inter day Accuracy (%)	99.87 - 100.00	1.21 - 3.64
Cal. Standards Conc.	1.00 - 100 mcg/mL	0.110 - 110 ng/mL
Inter day Precision (%CV)	1.16 - 3.45	1.09 - 3.59
Inter day Accuracy (%)	98.20 - 101%	99.09 - 103.94%
Linearity Range (range of R^2 values)	0.9953 - 1.00	0.9973 - 0.9998

Chromatograms: Any interfering peaks? No

Table 5 SOP's dealing with analytical repeats of study samples

The SOP was not provided in the submission (see the deficiency comment section).

Comments on Within-Study Validation: Incomplete due the deficiencies cited in the deficiency section.

Conclusion: Analytical method is incomplete due the deficiencies cited in the deficiency section.

Table 6 Arithmetic Mean Pharmacokinetic Parameters (Hydrocodone)

Mean plasma concentrations are presented in Table 13 and Figure 1

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	109.21	28.05	116.55	34.89	0.94
AUCT	106.25	26.13	113.01	32.00	0.94
CMAX	17.34	5.23	17.14	5.25	1.01
KE	0.16	0.02	0.16	0.02	1.01
THALF	4.42	0.60	4.46	0.66	0.99
TMAX	1.17	0.44	1.59	0.77	0.74

MEAN1=Test, MEAN2=Reference
UNIT: AUC=NG.HR/ML CMAX=NG/ML, KE=hrs^{-1}, THALF=hrs, TMAX=hrs

Table 7 Least Square Geometric Means and 90% Confidence Intervals (Hydrocodone)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	105.91	111.88	0.95	91.02	98.44
LAUCT	103.27	108.87	0.95	91.32	98.51

LCMAX	16.59	16.45	1.01	93.98	108.27

Table 8 Additional Study Information (Hydrocodone)

Root mean square error, AUC_{0-t}	0.0764270	
Root mean square error, AUC_{∞}	0.0790017	
Root mean square error, C_{max}	0.1428592	
mean ratio AUC_{0-t}/AUC_{∞}	T = 0.98	R = 0.97
Range of values, ratio AUC_{0-t}/AUC_{∞}	T = 0.93-0.99	R = 0.91-0.99

Comments - Hydrocodone: (on pharmacokinetic analysis)

- k_{el} and AUC_{∞} were determined for how many subjects. All subjects
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as T_{max}: None
  c. first measurable drug concentration as C_{max}: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? None
- Are the 90% confidence intervals for AUC_{0-t}, AUC_{∞}, C_{max} within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Table 9 Arithmetic Mean Pharmacokinetic Parameters (Ibuprofen)

Mean plasma concentrations are presented in Table 14 and Figure 2

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	74.94	18.27	77.04	17.03	0.97
AUCT	70.00	16.94	71.29	16.22	0.98
CMAX	16.96	3.22	18.35	5.88	0.92
KE	0.32	0.06	0.33	0.05	0.96
THALF	2.29	0.50	2.17	0.37	1.06
TMAX	1.79	1.21	1.68	1.38	1.07

MEAN1=Test, MEAN2=Reference
UNIT: AUC=MCG.HR/ML CMAX=MCG/ML, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 10 Least Square Geometric Means and 90% Confidence Intervals (Ibuprofen)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12

PARAMETER					
LAUCI	73.13	74.74	0.98	94.20	101.61
LAUCT	68.30	69.52	0.98	93.93	102.74
LCMAX	16.67	17.47	0.95	84.96	107.18

Table 11 Additional Study Information (Ibuprofen)

Root mean square error, AUC_{0-t}	0.0904394	
Root mean square error, AUC_{∞}	0.0729832	
Root mean square error, C_{max}	0.2343497	
mean ratio AUC_{0-t}/AUC_{∞}	T = 0.93	R = 0.94
Range of values, ratio AUC_{0-t}/AUC_{∞}	T = 0.88-0.96	R = 0.88-0.96

Comments - Ibuprofen: (on pharmacokinetic analysis)

- k_{el} and AUC_{∞} were determined for how many subjects. All subjects except one (subject #8, reference treatment, period-2).
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as T_{max}: None
  c. first measurable drug concentration as C_{max}: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? None
- Are the 90% confidence intervals for AUC_{0-t}, AUC_{∞}, C_{max} within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Conclusion: The single-dose fasting bioequivalence study is incomplete due to the deficiency comments #1-3 cited above.

Table 12 Mean Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Hydrocodone

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	1.72	2.57	0.90	1.51	1.90
0.5	10.03	7.38	6.69	5.85	1.50
0.75	14.19	6.02	12.49	7.34	1.14
1	15.64	4.89	14.45	7.36	1.08
1.33	14.89	3.62	14.72	4.87	1.01
1.67	14.47	3.18	15.04	3.95	0.96
2	13.84	2.77	14.75	3.67	0.94
2.5	12.24	2.89	13.42	2.80	0.91
3	12.07	2.91	12.98	2.95	0.93
4	9.92	2.37	10.61	2.62	0.93
5	8.38	2.05	9.26	2.40	0.90
6	6.80	1.70	7.39	2.05	0.92
8	4.90	1.38	5.51	1.75	0.89
10	3.54	1.12	4.03	1.61	0.88
12	2.37	0.83	2.62	1.16	0.90
24	0.43	0.28	0.50	0.37	0.86

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Hydrocodone

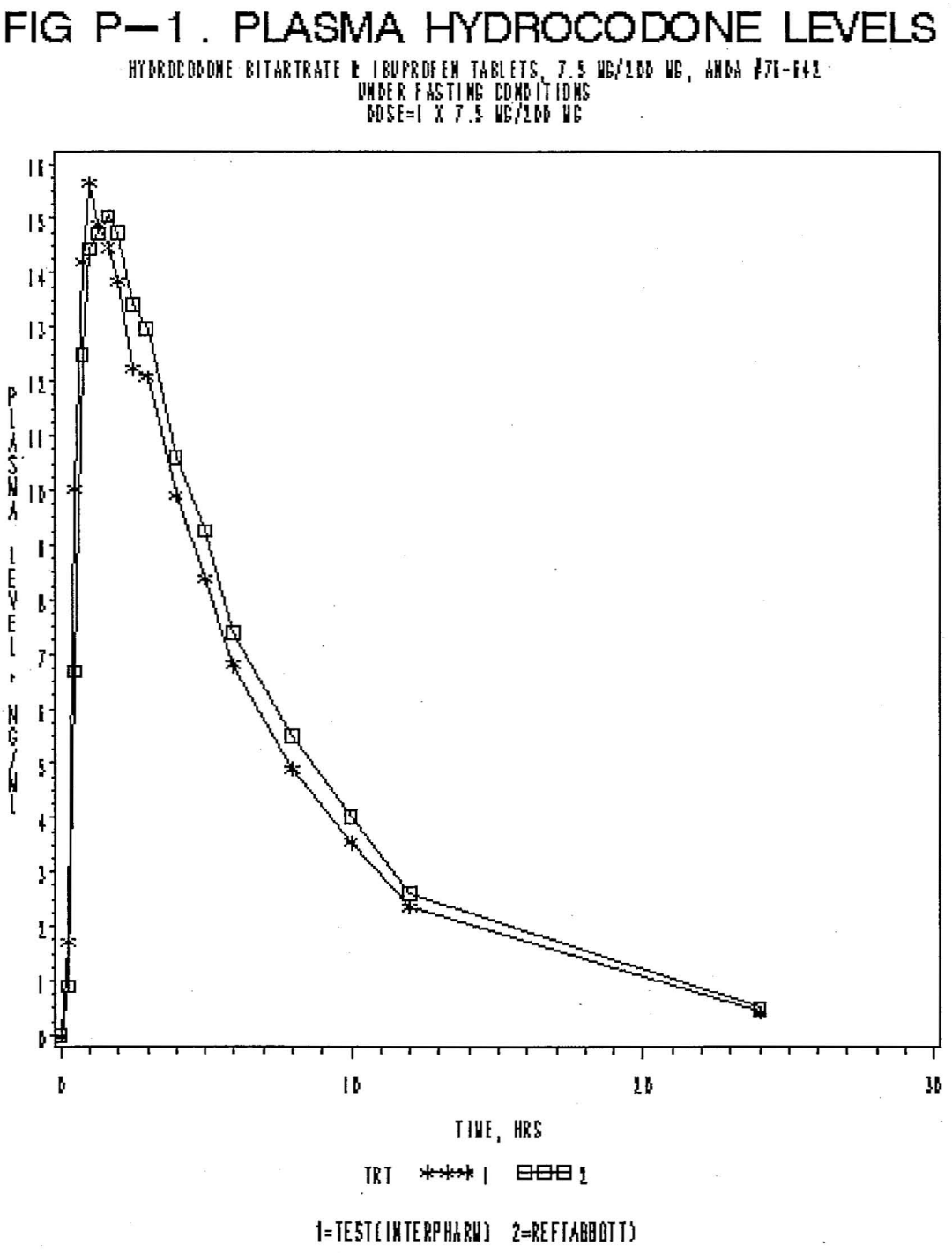


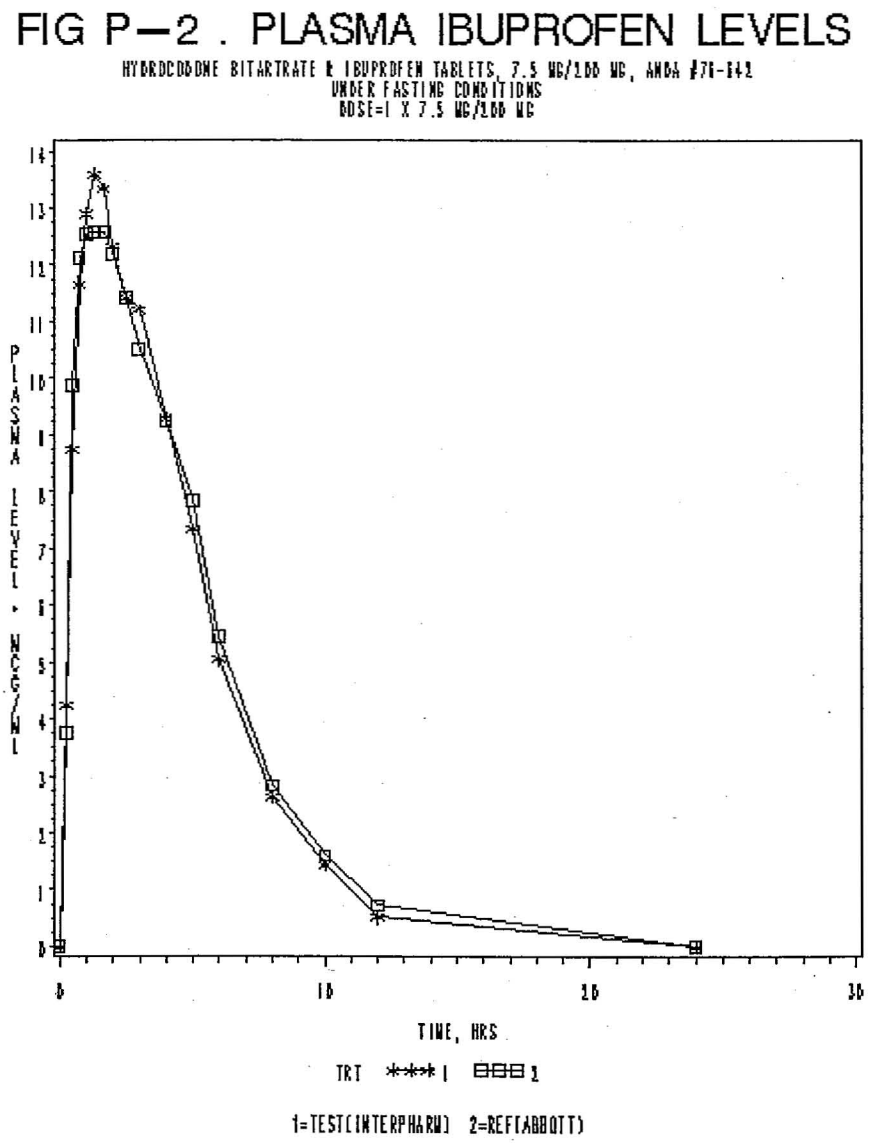
Table 14 Mean Plasma Concentrations (mcg/mL), Single-Dose Fasting Bioequivalence Study

Ibuprofen

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	4.23	3.35	3.77	3.93	1.12
0.5	8.72	4.57	9.89	8.11	0.88
0.75	11.65	5.24	12.13	7.38	0.96
1	12.90	5.63	12.55	7.02	1.03
1.33	13.60	4.96	12.59	6.20	1.08
1.67	13.34	4.47	12.59	5.48	1.06
2	12.34	4.11	12.21	4.91	1.01
2.5	11.41	3.57	11.43	3.58	1.00
3	11.20	3.37	10.51	3.09	1.07
4	9.28	3.48	9.23	4.07	1.01
5	7.33	2.71	7.85	3.51	0.93
6	5.04	2.03	5.45	2.40	0.93
8	2.64	1.13	2.83	1.37	0.93
10	1.43	1.11	1.60	1.45	0.89
12	0.51	0.79	0.73	0.98	0.69
24	0.00	0.00	0.00	0.00	.

Figure 2 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Ibuprofen



2. Single-dose Fed Bioequivalence Study

Study Information (page 1341- , volume C1.5)	
Study Number	Project #207-04-11711, protocol #11711A
Study Title	A comparative bioavailability study of 7.5 mg/200 mg Hydrocodone Bitartrate and Ibuprofen Tablets versus 7.5 mg/200 mg Vicoprofen® Tablets under fed conditions.
Clinical Site	PharmacoKinetic Laboratories, Inc. Baltimore, MD 21201
Principal Investigator	Ronald Goldwater, M.D.
Study/Dosing Dates	Period I: August 11, 2002 Period II: August 18, 2002 (p 1367, vol. C1.5)
Analytical Site	PharmacoKinetic Laboratories, Inc. Baltimore, MD 21201
Analytical Director	(b) (6) , Ph.D.
Analysis Dates	11/15/02 to 11/26/02 (p 1380, vol. C1.5)
Storage Period (no. of days from first sample to final analysis)	105 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Hydrocodone Bitartrate and Ibuprofen Tablets	Vicoprofen® Tablets
Manufacturer	Interpharm	Abbott Laboratories
Batch/Lot No.	E04402	02PROF1017
Manufacture Date	5/8/02 (p 3061, vol. A1.9)	N/A
Expiration Date	N/A	March 2004
Strength	7.5 mg/200 mg	7.5 mg/200 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4) tablets	N/A
Production Batch Size	(b) (4) tablets	N/A
Potency	Ibuprofen = 101.5% Hydrocodone = 103.6% (p 2371, vol. C1.7))	Ibuprofen = 101.0% Hydrocodone = 102.0% (p 2371, vol. C1.7))
Content Uniformity	Ibuprofen = 98.7-105.5% Hydrocodone = 98.9-108.76%	Ibuprofen = 99.8-103.1% Hydrocodone = 100.7-104.7%
Formulation	See Appendix Section B	
Dose Administered	1 X 7.5 mg/200 mg tablet with 240 mL water	1 X 7.5 mg/200 mg tablet with 240 mL water
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	-
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5. 3, 4, 5, 6, 8, 10, 12 and 24 hours.
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C.
IRB Approval	Yes on 08/01/02 (p 173, vol. C1.2)
Informed Consent	Yes
Subjects Demographics	See Table 15
Length of Fasting	At least 10 hours prior to serving a standard breakfast. The subjects were served breakfast 35 minutes prior to dosing.
Length of Confinement	10 hours predose until 24 hours postdose.
Safety Monitoring	Vital signs (blood pressure and heart rate) measured prior to dosing and 4 and 12 hours postdose.

Table 15 Demographics of Study Subjects (p 1371, vol. C1.5)

Age		**Weight**		**Age Groups**		**Gender**		**Race**	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0			Caucasian	22
Mean	40.22	Mean	151.39	18-40	30	Male	72	Afr. Amer.	72
SD	12.59	SD	20.32	41-64	70	Female	28	Hispanic	0
Range	18-53	Range	109-185	65-75	0			Asian	6
				>75	0			Others	0

Study Results

Table 16 Dropout Information (p 1352, vol. C1.5)

Subject No	10
Reason	The subject was withdrawn by the principle investigator due to an adverse event (diarrhea and abdominal discomfort).
Period	After Period-1
Replacement	No

Was there a difference in side effects for the test versus the reference? No

Table 17 Study Adverse Events

Adverse Events	# in Test Group	# in Reference Group
Total:	3	4

Comments: The adverse events occurred with similar frequency for both treatments. No serious adverse events were reported (for more details see page 1835, vol. C1.6).

Was there a difference in protocol deviations for the test versus the reference? No

Table 18 Proposed Deviations

Type	**Subject #s (Test)**	**Subject #s (Reference)**
Delay to draw blood (most of samples between 1-7 minutes, only one sample was 13 minutes delay).	36	35

Comments: The PK analysis was based on actual sample times. The deviations are unlikely to impact the outcome of the study.

Table 19 Assay Validation – Within Study (p 1386-1389, vol. C1.5)

	Ibuprofen	Hydrocodone
QC Conc.	2.50, 15.0, and 75.0 mcg/mL	0.33, 11.0, and 93.5 ng/mL
Inter day Precision (%CV)	1.26 - 1.68	1.92 - 7.18
Inter day Accuracy (%)	99.20 - 100.00	98.79 - 103.10
Cal. Standards Conc.	1.00 - 100 mcg/mL	0.110 - 110 ng/mL
Inter day Precision (%CV)	0.84 - 3.47	1.72 - 8.11
Inter day Accuracy (%)	98.60 - 101.00	97.88 - 101.82
Linearity Range (range of R^2 values)	0.9955 - 1.00	0.9953 - 0.9995

Chromatograms: Any interfering peaks? No

Table 20 SOP's dealing with analytical repeats

The SOP was not provided in the submission (see the deficiency comment section).

Comments on Within-Study Validation: Incomplete due the deficiencies cited in the deficiency section.

Table 21 Arithmetic Mean Pharmacokinetic Parameters (Hydrocodone)

Mean plasma concentrations are presented in Table 27 and Figure 3

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	151.88	37.45	152.12	28.63	1.00
AUCT	145.59	33.05	146.25	25.16	1.00
CMAX	19.51	2.82	20.56	3.47	0.95
KE	0.15	0.02	0.15	0.02	1.00
THALF	4.84	0.92	4.79	0.79	1.01
TMAX	2.35	0.75	2.39	1.24	0.98

MEAN1=Test, MEAN2=Reference
UNIT: AUC=NG.HR/ML CMAX=NG/ML, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 22 Geometric Means and 90% Confidence Intervals (Hydrocodone)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	147.94	150.21	0.98	95.20	101.90
LAUCT	142.27	144.69	0.98	95.12	101.64
LCMAX	19.29	20.28	0.95	90.37	100.13

Table 23 Additional Study Information

Root mean square error, AUC_{0-t}	0.0550989	
Root mean square error, AUC_{∞}	0.0565165	
Root mean square error, C_{max}	0.0851084	
mean ratio AUC_{0-t}/AUC_{∞}	T = 0.96	R = 0.96
Range of values, ratio AUC_{0-t}/AUC_{∞}	T = 0.89-0.98	R = 0.91-0.98

Comments - Hydrocodone: (on pharmacokinetic analysis)

- k_{el} and AUC_{∞} were determined for how many subjects. All subjects
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as T_{max}: None
  c. first measurable drug concentration as C_{max}: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? None

- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Table 24 Arithmetic Mean Pharmacokinetic Parameters (Ibuprofen)

Mean plasma concentrations are presented in Table 28 and Figure 4

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	65.33	15.62	65.81	17.15	0.99
AUCT	60.76	15.00	60.84	15.61	1.00
CMAX	13.67	3.06	16.73	4.42	0.82
KE	0.33	0.05	0.34	0.06	0.99
THALF	2.15	0.36	2.14	0.41	1.00
TMAX	2.92	1.76	2.07	1.14	1.41

MEAN1=Test, MEAN2=Reference
UNIT: AUC=MCG.HR/ML CMAX=MCG/ML, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 25 Least Square Geometric Means and 90% Confidence Intervals (Ibuprofen)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	63.86	63.86	1.00	96.63	103.51
LAUCT	59.21	59.04	1.00	96.17	104.59
LCMAX	13.40	16.19	0.83	75.43	90.84

Table 26 Additional Study Information (Ibuprofen)

Root mean square error, AUC0-t	0.0696602	
Root mean square error, AUC∞	0.0571127	
Root mean square error, Cmax	0.1542842	
mean ratio AUC0-t/AUC∞	T = 0.93	R = 0.94
Range of values, ratio AUC0-t/AUC∞	T = 0.83-0.96	R = 0.88-0.95

Comments - Ibuprofen: (on pharmacokinetic analysis)

- kel and AUC∞ were determined for how many subjects. All subjects
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None

c. first measurable drug concentration as C_{max}: None

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? Yes, period effect for LAUCt and LAUCi.
- Are the 90% confidence intervals for AUC_{0-t}, AUC_{∞}, C_{max} within the acceptable limits of 80-125%: LAUCt and AUCi values were within the acceptable range. Lcmax value was outside the acceptable range.
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Conclusion: The single-dose non-fasting bioequivalence study is acceptable. The ratios of the geometric means for AUCt, AUCi, and CMAX (for both hydrocodone bitartrate and ibuprofen) are within the acceptable range of 0.8-1.25. The reviewer's calculations are similar to those submitted by the firm. It is noted that the study was initiated on 08/11/02, which was before the issuance of the CDER Guidance "Food-Effect Bioavaliability and Fed Bioequivalence Studies" (December 2002). The fed study meets the FDA acceptance criteria in place at the time it was initiated. This was that the ratio of AUC and Cmax geometric means for hydrocodone bitartrate and ibuprofen fall within the interval of 80 to 125%. However, the study is incomplete due to the deficiencies (#1-3) cited in the deficiency section.

Table 27 Mean Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Hydrocodone

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.68	2.27	0.23	0.69	2.91
0.5	2.15	3.33	2.78	5.52	0.77
0.75	4.52	4.87	6.67	7.76	0.68
1	8.48	6.84	10.19	8.25	0.83
1.33	13.00	5.67	12.33	8.56	1.05
1.67	15.65	4.73	14.09	6.74	1.11
2	16.29	3.66	15.49	5.51	1.05
2.5	17.56	3.07	17.00	4.48	1.03
3	17.81	3.29	16.33	3.80	1.09
4	15.29	3.53	15.13	2.63	1.01
5	12.95	3.25	13.14	3.67	0.99
6	10.65	2.87	10.73	3.59	0.99
8	7.55	2.14	7.71	2.62	0.98
10	5.47	1.74	5.70	1.85	0.96
12	3.95	1.45	4.13	1.45	0.96
24	0.82	0.54	0.79	0.46	1.03

Figure 3 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Hydrocodone

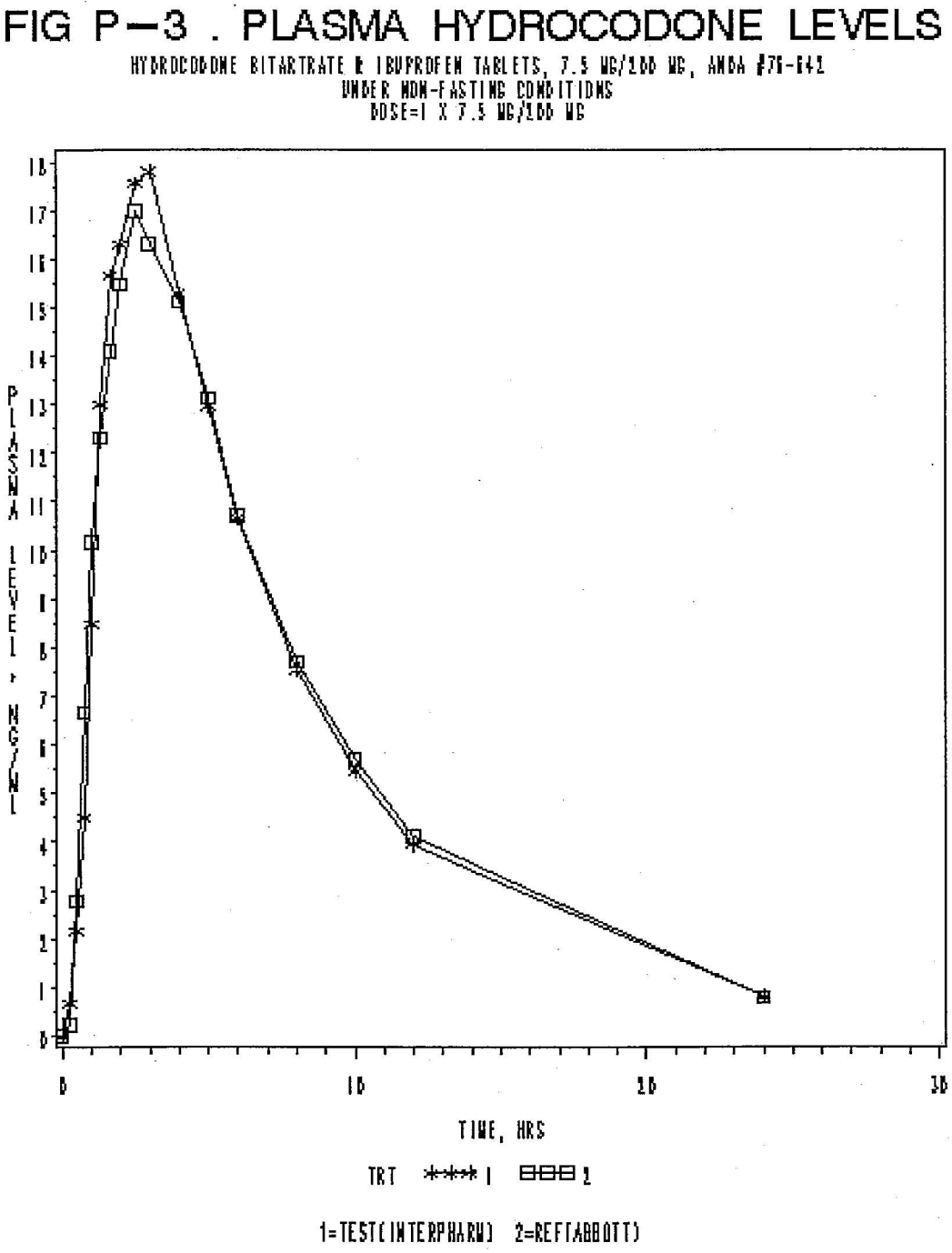


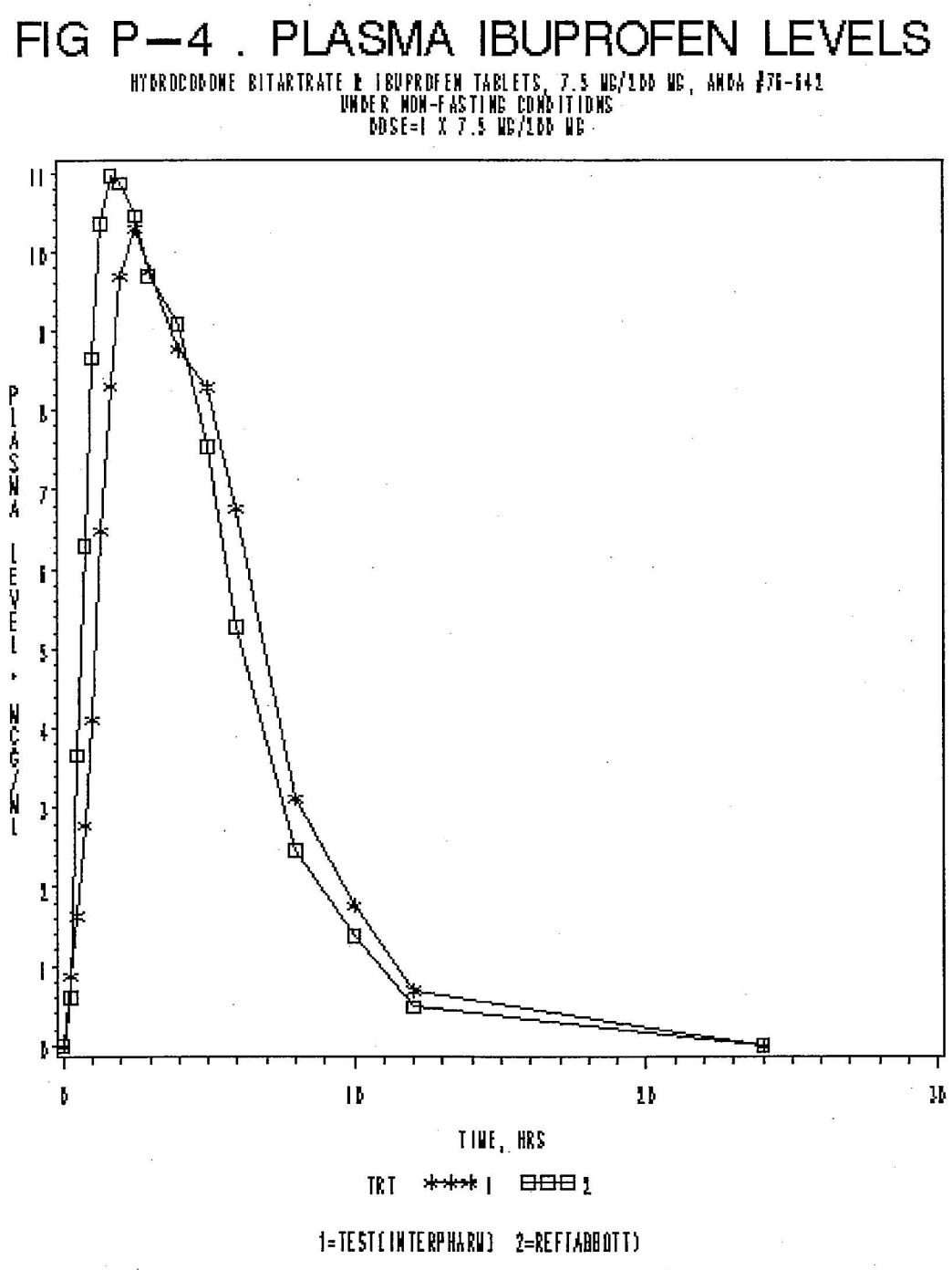
Table 28 Mean Plasma Concentrations (mcg/mL), Single-Dose Fed Bioequivalence Study

Ibuprofen

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.87	2.23	0.61	2.06	1.43
0.5	1.63	3.40	3.67	5.81	0.45
0.75	2.78	4.04	6.30	6.53	0.44
1	4.11	5.00	8.66	7.16	0.47
1.33	6.47	5.02	10.37	6.54	0.62
1.67	8.30	5.19	10.97	5.83	0.76
2	9.68	5.41	10.87	4.90	0.89
2.5	10.29	4.41	10.46	4.70	0.98
3	9.75	3.39	9.70	2.90	1.01
4	8.76	2.83	9.08	4.76	0.96
5	8.29	3.45	7.55	4.57	1.10
6	6.75	3.66	5.27	3.40	1.28
8	3.11	2.02	2.45	1.95	1.27
10	1.76	1.27	1.38	1.43	1.28
12	0.70	0.89	0.49	0.90	1.43
24	0.00	0.00	0.00	0.00	.

Figure 4 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Ibuprofen



B. Formulation Data

The composition of Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5mg/200mg, dosage form is as follows (Section VII, vol. 1.8, pages 2372-2376; and page 9, vol. C2.1):

INGREDIENTS USED FOR HYDROCODONE BITARTRATE/IBUPROFEN TABLETS	**7.5mg/200mg (mg per tablet)**	**5mg/200mg (mg per tablet)**
Hydrocodone Bitartrate (Active)	7.5	5
Ibuprofen (Active)	200	200
Colloidal Silicon Dioxide NF (b) (4)	(b) (4)	
Pregelatinized Starch NF		
Microcrystalline Cellulose NF		
Croscarmellose Sodium NF		
Magnesium Stearate NF		
(b) (4)		
Total	405.0	405.0

(b) (4)

The inactive ingredients are within acceptable range of the IIG.

C. Dissolution Data (p 2358-2366, vol.C1.7)

Table 1

Sampling Time (min)	**% dissolved Hydrocodone Bitartrate** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength:** 7.5 mg/200 mg **Lot No.** E04402			**% dissolved Hydrocodone Bitartrate** **Reference Product,** Vicoprofen® Tablets **Strength:** 7.5 mg/200 mg **Lot No.** 02PROF1017		
	Mean	**%CV**	**Range (%)**	**Mean**	**%CV**	**Range (%)**
15	100.9	2.5	97.20-106.18	100.7	3.5	95.03-103.91
30	102.4	3.9	95.91-107.57	100.8	3.0	95.92-104.27
45	101.2	2.8	96.23-108.06	101.1	2.5	96.13-104.19
60	101.8	2.6	97.34-106.99	101.1	2.5	96.49-104.01
90	101.7	1.1	99.04-103.59	102.2	1.2	100.60-104.14
Sampling Time (min)	**% dissolved Ibuprofen** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength:** 7.5 mg/200 mg **Lot No.** E04402			**% dissolved Ibuprofen** **Reference Product,** Vicoprofen® Tablets **Strength:** 7.5 mg/200 mg **Lot No.** 02PROF1017		
	Mean	**%CV**	**Range (%)**	**Mean**	**%CV**	**Range (%)**
15	98.3	1.5	94.26-99.98	98.7	3.4	91.61-101.92
30	98.7	2.0	94.30-100.67	98.5	3.0	92.42-101.69
45	99.1	2.1	94.05-101.08	98.9	3.0	92.20-101.92
60	99.4	1.6	95.37-101.01	98.8	2.9	92.39-102.11
90	100.3	1.1	97.67-101.53	99.7	1.8	96.90-102.00

D. Consult Reviews: N/A

Additional Attachments N/A

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-642 APPLICANT: Interpharm, Inc.

DRUG PRODUCT: Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 m and 5 mg/200 mg

The Division of Bioequivalence has completed its review of your submission(s)acknowledged on the cover sheet. The following deficiencies have been identified:

1. The submitted long-term stability data of hydrocodone bitartrate and ibuprofen in frozen study samples (pages #191, and 1382) were not sufficient to cover the entire length of the sample storage period (from first blood sample was drawn to the last plasma sample analyzed). Please submit data to support the long-term stability of hydrocodone bitartrate and ibuprofen in frozen study samples for a period at least covers the entire length of the biostudy.

2. The submitted information on assay methodology description and validation was not adequate. The following raw data for pre-study validation ibuprofen are requested: 1) inter-day quality control (QC) samples; 2) recovery of the drug and internal standard; 3) Stock stability data, for how long (hours/days), and identify temperature; 4) In-process stability, for how long (hours); and Dilution integrity.

   For hydrocodone bitartrate, only data on stock stability and dilution integrity are requested.

   For each item, the mean value for each sample set, range (minimum and maximum), precision (%CV), accuracy (%) accuracy, and number of samples, should be provided.

3. The standard operation procedure (SOP) for describing the analytical method and data (sample acceptance and rejection criteria) for the studies under fasting and fed conditions was not provided in the submission. The SOP number, date of SOP approved, and SOP title should be also included.

4. The submitted dissolution testing data on the 5 mg/200 mg strength are incomplete. Dissolution data for the hydrocodone bitartrate component of the 5 mg/200 mg strength are requested. The dissolution testing data should include the dissolution mean for each time point, the range (minimum and maximum), and the percentage of coefficient of variation (%CV)(in a side-by-side tabular format, if possible). The dissolution testing should be done on tablets from the same lot number that was used in the in vivo bioequivalence study.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-642
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba 10/7/03
HFD-658/ GJP Singh CDPS 10-8-03
HFD-650/ D. Conner BZD 10/9/03

v:\\firmsam\Interpharm\LTRS&REV\76642n0103.doc

BIOEQUIVALENCY – ACEPTAPLE Submission date: 01/16/03, 3/26/03

1. FASTING STUDY (STF) Strength: 7.5 mg/200 mg
Outcome: IC

Clinical Study Site: PharmacoKinetic Laboratories, Inc.
Analytical Site: PharmacoKinetic Laboratories, Inc.

2. FOOD STUDY (STP) Strength: 7.5 mg/200 mg
Outcome: IC

Clinical Study Site: PharmacoKinetic Laboratories, Inc.
Analytical Site: PharmacoKinetic Laboratories, Inc.

3. DISSOLUTION WAIVER (DIW) 3/26/03 Strength: 5 mg/200 mg
Outcome: IC

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

Outcome Decision: **Incomplete**
WINBIO COMMENTS: **Incomplete**

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-642
Drug Product Name	Hydrocodone Bitartrate and Ibuprofen tablets
Strength	7.5 mg/200 mg and 5 mg/200 mg
Applicant Name	Interpharm Inc.
Address	Hauppauge, NY
Submission Date(s)	01/16/03 (Original application), 03/26/03 (for a new strength, 5 mg/200 mg)
Amendment Date(s)	11/13/2003
Reviewer	Zakaria Z. Wahba
First Generic	The 7.5 mg/200 mg strength is not first generic. The 5 mg/200 mg strength is first generic.
File Location	V:\firmsam\Interph\ltrs&rev\76642a1103.doc

I. Executive Summary

This submission is an amendment containing the firm's responses to deficiencies in the original application. All responses are acceptable.

The original submission consisted of two bioequivalence (BE) studies (on 7.5 mg/200 mg) under fasting and non-fasting conditions, and dissolution data for the 7.5 mg/200 mg and 5 mg/200 mg strengths. The BE study under fasting condition was a single dose two-way crossover design in normal males and females (n=24). The BE study under non-fasting conditions was a single dose two-way crossover design in normal males and females (n=17).

Statistical analyses of the plasma concentration data for hydrocodone bitartrate and ibuprofen for both studies demonstrated bioequivalence. For the fasting BE study, hydrocodone results were (point estimate, 90% CI): $LAUC_t$ of 0.95, 91.32-98.51%; $LAUC_i$ of 0.95, 91.02-98.44% and LCmax of 1.01, 93.98-108.27%. For the ibuprofen results were (point estimate, 90% CI): $LAUC_t$ of 0.98, 93.93-102.74%; $LAUC_i$ of 0.98, 94.20-101.61% and LCmax of 0.95, 84.96-107.18%.

For the nonfasting BE study, hydrocodone results were (point estimate, 90% CI): $LAUC_t$ of 0.98, 95.12-101.64%; $LAUC_i$ of 0.98, 95.20-101.90% and LCmax of 0.95, 90.37-100.13%. For the ibuprofen results were (point estimate, 90% CI): $LAUC_t$ of 1.00, 96.17-104.59%; $LAUC_i$ of 1.00, 96.63-103.51% and LCmax of 0.83, **75.43-90.84%**. The ratios of the geometric means were within the acceptable 0.8-1.25 range for AUCt, AUCi and Cmax for ibuprofen. The fed study met the FDA acceptance criteria in place at the time that the study was initiated on August 03, 2002.

The firm has submitted acceptable dissolution data. The application is now acceptable with no deficiency.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg, and 5 mg/200 mg
Reference Product	Vicoprofen® Tablets, 7.5 mg/200 mg
RLD Manufacturer	Abbott
NDA No.	20-716
RLD Approval Date	September 23, 1997
Indication	Treatment of pain

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	N/A	
Single-dose fed	N/A	
Steady-state	N/A	
In vitro dissolution	N/A	
Waiver requests	No	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	1

C. Formulation

The formulation was previously submitted and reviewed (see the DBE review report dated 10/09/03 or "V:\firmsam\Interph\ltrs&rev\76642n0103.doc)

D. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA (per ANDA 76-023 Amendment, dated 3/7/01 and DBE review date 2/9/01)
Medium	Phosphate Buffer, pH 7.2
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
Firm's proposed specifications	-
FDA-recommended specifications	NLT (b) (4) (Q) of the labeled amount of both hydrocodone and ibuprofen in the dosage form is dissolved in 15 minutes.
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Rapidly dissolving
Method is acceptable (yes or no)	Yes

E. Waiver Request(s):

The formulation was presented in original review (ANDA 76-642, DBE review date: 11/09/03)

Strengths for which waivers requested	5 mg/200 mg Note: The 5 mg/200 mg strength is a new strength and is a subject of the amendment dated 04/16/03. The new strength is based on a suitability petition Docket No. 02P-0270/CPI approved on September 25, 2002.
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

F. Responses to Deficiency Comments Stated in the October 09, 2003 DBE Review:

FDA Deficiency Comment #1

The submitted long-term stability data of hydrocodone bitartrate and ibuprofen in frozen study samples (pages #191, and 1382) were not sufficient to cover the entire length of the sample storage period (from first blood sample was drawn to the last plasma sample analyzed). Please submit data to support the long-term stability of hydrocodone bitartrate and ibuprofen in frozen study samples for a period at least covers the entire length of the biostudy.

Firm's Response to Deficiency Comment #1

As requested, the firm provided long stability data for ibuprofen and hydrocodone in human plasma. The frozen storage stability data demonstrated that ibuprofen and hydrocodone are stable in plasma for 360 and 383 days, respectively.

DBE's Comment on Deficiency #1:

The firm's response is acceptable

FDA Deficiency Comment #2

The submitted information on assay methodology description and validation was not adequate. The following raw data for pre-study validation ibuprofen are requested: 1) inter-day quality control (QC) samples; 2) recovery of the drug and internal standard; 3) Stock stability data, for how long (hours/days), and identify temperature; 4) In-process stability, for how long (hours); and Dilution integrity.

For hydrocodone bitartrate, only data on stock stability and dilution integrity are requested.

For each item, the mean value for each sample set, range (minimum and maximum), precision (%CV), accuracy (%) accuracy, and number of samples, should be provided.

Firm's Response to Deficiency Comment #2

Information		
Analyte name	Ibuprofen	Hydrocodone
Average recovery of Drug (%)	89.00	57.63
Average Recovery of Int. Std (%)	78.70	44.23
Interday precision range (%CV)	0.91 to 1.24	1.18 to 13.66
Interday accuracy range (%)	99.73 to 100.67	100.30 to 101.82
Stock stability (days)	8 days	42 days
Processed stability (hrs)	24 hrs	24 hrs
Dilution integrity	None of the samples were diluted	None of the samples were diluted
Bioanalytical method is acceptable	Yes	Yes

DBE's Comment on Deficiency #2:

The firm's response is acceptable

FDA Deficiency Comment #3

The standard operation procedure (SOP) for describing the analytical method and data (sample acceptance and rejection criteria) for the studies under fasting and fed conditions was not provided in the submission. The SOP number, date of SOP approved, and SOP title should be also included.

Firm's Response to Deficiency Comment #3

The firm provided the requested SOPs (see the 11/13/03 Amendment, page 12-17, vol. A4.1).

SOP No.	Date of SOP	SOP Title
LAB.CHM.19.4	03/11/02	Standard Curve Acceptance Criteria
LAB.CHM.27.3	03/11/02	Quality Control Acceptance Criteria

DBE's Comment on Deficiency #3:

The firm's response is acceptable

FDA Deficiency Comment #4

The submitted dissolution testing data on the 5 mg/200 mg strength are incomplete. Dissolution data for the hydrocodone bitartrate component of the 5 mg/200 mg strength are requested.

Firm's Response to Deficiency Comment #4
(information on pages 2358, vol. C1.7; and the 11/13/03 Amendment, p 24-25)

Sampling Time (min)	**% dissolved Hydrocodone Bitartrate** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength: 7.5 mg/200 mg** **Lot No.** E04402 **(Bio-lot)**			**% dissolved Hydrocodone Bitartrate** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength: 5 mg/200 mg** **Lot No.** K05202		
	Mean	**%CV**	**Range (%)**	**Mean**	**%CV**	**Range (%)**
15	100.9	2.5	97.20-106.18	99.5	2.3	95.75-102.55
30	102.4	3.9	95.91-107.57	99.7	2.0	96.94-101.98
45	101.2	2.8	96.23-108.06	100.0	2.2	96.56-103.31
60	101.8	2.6	97.34-106.99	100.0	1.6	97.57-102.78
90	101.7	1.1	99.04-103.59	100.3	1.4	98.06-102.57
Sampling Time (min)	**% dissolved Ibuprofen** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength: 7.5 mg/200 mg** **Lot No.** E04402 **(Bio-lot)**			**% dissolved Ibuprofen** **Test Product,** Hydrocodone Bitartrate and Ibuprofen Tablets **Strength: 5 mg/200 mg** **Lot No.** K05202		
	Mean	**%CV**	**Range (%)**	**Mean**	**%CV**	**Range (%)**

15	98.3	1.5	94.26-99.98	98.7	1.8	98.87-101.78
30	98.7	2.0	94.30-100.67	100.2	2.6	97.10-107.28
45	99.1	2.1	94.05-101.08	98.6	2.3	94.65-102.47
60	99.4	1.6	95.37-101.01	98.3	1.4	95.95-100.82
90	100.3	1.1	97.67-101.53	98.3	1.1	96.43-99.84

Note: The 5 mg/200 mg strength is a new strength and is a subject of the amendment dated 04/16/03. The new strength is based on a suitability petition Docket No. 02P-0270/CPI approved on September 25, 2002.

DBE's Comment on Deficiency #4:

The firm's response is acceptable

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G. Recommendations

1. The two single-dose bioequivalence study, under fasting (#207-04-11710), and non-fasting conditions (#207-04-11711), conducted by Interpharm, Inc., on its Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg, lot #E04402, comparing it to Abbott's Vicoprofen® Tablets, 7.5 mg/200 mg, lot #02PROF1017, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Interpharm's Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg, is bioequivalent to Abbott's Vicoprofen® Tablets, 7.5 mg/200 mg.

2. The dissolution testing conducted by the firm on its Hydrocodone Bitartrate/Ibuprofen Tablets, 7.5 mg/200 mg and 5 mg/200 mg, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 900 ml of phosphate buffer, pH 7.2 at 37°C using USP Apparatus II (Paddle) at 50 rpm. The test should meet the following specification:

   Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

3. The waiver of in vivo bioequivalence study requirements for the 5 mg/200 mg tablets of the test product is granted based on 21 CFR 320.22 (d) (2).

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.,
Branch III

Date 12/22/03

RT: Gurjaipal Singh

Gur Jai Pal Singh, Ph.D.,
Branch III

Date 12-23-03

Concur: for Barbara M Davit

Dale P. Conner, Pharm.D.,
Director, Division of Bioequivalence
Office of Generic Drugs

Date 12/23/03

IV. Appendix:

NA

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-642 APPLICANT: Interpharm, Inc.

DRUG PRODUCT: Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 m and 5 mg/200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing should be conducted in 900 mL of Phosphate buffer, pH 7.2, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Hydrocodone: Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Ibuprofen: Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the submitted SOPs for sample analysis were dated after analysis of the non-fasting study samples. This practice is unacceptable. For future studies, the SOPs should be effective before initiation of the analyses.

Please also note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Davit

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-642
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 12/22/03
HFD-658/ GJP Singh GJPS 12-23-03
for HFD-650/ D. Conner BMD 12/23/03

v:\\firmsam\Interpharm\LTRS&REV\76642a1103.doc

BIOEQUIVALENCE - ACCEPTABLE

submission date: 11/09/03

1. Study Amendment (STA)

Strength: 7.5/200 mg & 5/200 mg
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: # 76-642
SPONSOR : Interpharm Inc.
DRUG AND DOSAGE FORM : Hydrocodone Bitartrate and Ibuprofen Tablets
STRENGTHS: 7.5 mg/200 mg and 5 mg/200 mg
TYPES OF STUDIES : Two single-dose bioequivalence studies, under fasting and non-fasting conditions.
CLINICAL STUDY SITE(S): PharmacoKinetic Laboratories, Inc.
ANALYTICAL SITE(S) : PharmacoKinetic Laboratories, Inc.

STUDY SUMMARY: The two in vivo bioequivalence studies under fasting and non-fasting conditions for Interpharm's Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg, demonstrate its bioequivalence to the RLD Abbott's Vicoprofen® Tablets, 7.5 mg/200 mg.
DISSOLUTION : The dissolution testing for test and reference products (7.5 mg/200 mg and 5 mg/200 mg) is acceptable.
WAIVER: The waiver request for the 5 mg/200 mg, strength is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility ___ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH: III

INITIAL : ZZW DATE : 12/22/03

TEAM LEADER : Gur Jai Pal Singh, Ph.D. BRANCH: III

INITIAL : Gurjaipal Singh DATE : 12-23-03

for DIRECTOR, Division of Bioequivalence: Dale P. Conner, Pharm. D.

INITIAL : Barbara M Davit DATE : 12/23/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-642

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

JAN 16 2003

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(A) OK
21-MAR-2003

Reference: Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg
Abbreviated New Drug Application

Dear Sir/ Madam:

Pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, INTERPHARM, Inc. herewith submits an abbreviated new drug application (ANDA) for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg.

This ANDA references the listed drug, Vicoprofen® Tablets 7.5 mg / 20 mg (Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg) which are manufactured by Abbott Laboratories the holder of the approved application listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg have been developed and will be manufactured, tested, and packaged by INTERPHARM, Inc., 75 Adams Avenue, Hauppauge, NY 11788 manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturers of the drug substances used to produce the ANDA / Bioequivalence batch of this product are for (b) (4)

INTERPHARM, Inc. also provides for an alternate supplier for Ibuprofen, USP; (b) (4)

The required bioavailability / bioequivalence studies were conducted on Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and Vicoprofen® Tablets 7.5 mg / 200 mg at PharmaKinetics Laboratories, Inc. 302 W. Fayette Street, Baltimore, MD 21201. These studies demonstrate that INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg are bioequivalent to Vicoprofen® Tablets, 7.5 mg/ 200 mg.

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The *in vitro* dissolution profiles for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg tablets are comparable to Vicoprofen ® Tablets 7.5 mg/ 20 mg.

Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg are stable and a two-year expiration dating is requested. The two year expiration dating for these products is supported by three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) and controlled room temperature studies to date in each of the container / closure systems proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA Stability guidelines.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION & HOW SUPPLIED) for INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg tablets are same as those for Vicoprofen® Tablets, 7.5 mg/ 200 mg.

Both drug substances are USP items, but the drug product is not USP. Methods validations for the analytical methods for the drug product are submitted in two jackets. The firm commits to resolve all analytical issues post approval if necessary. The firm commits to provide sample for testing when requested.

This ANDA is submitted as archival, duplicate bioequivalence and field copies. See the table of contents for volumes and location of documentation.

This completes our submission. Please contact the undersigned at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

Nilkanth J. Patel
Vice President of Regulatory Compliance

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

NEW CORRESP

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/NC MAR 12 2003

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Gratuitous Chemistry and Labeling Amendment

Dear Sir/ Madam:

Pursuant to *Code of Federal Regulation* Title 21, Interpharm, Inc. here within submits gratuitous chemistry and labeling amendments in support of a 5 mg / 200 mg strength. Reference is made to the original application submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for ANDA 76-642 for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg.

Reference is also made to the Suitability Petition filed on July 12, 2002, and approved, on September 25, 2002, for the 5 mg / 200 mg strength and the Telephone Amendment submitted on March 10, 2003.

Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg have been developed and will be manufactured, tested, and packaged by INTERPHARM, Inc., 75 Adams Avenue, Hauppauge, NY 11788 manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturers of the drug substances are the same used to produce the ANDA / Bioequivalence batch of this product are (b) (4)

The required bioavailability / bioequivalence studies were conducted on Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and Vicoprofen® Tablets 7.5 mg / 200 mg at PharmaKinetics Laboratories, Inc. 302 W. Fayette Street, Baltimore, MD 21201. These studies demonstrate that INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg are bioequivalent to Vicoprofen® Tablets, 7.5 mg/ 200 mg. The in vitro dissolution profile test results provided in Section VI support the equivalence of the products.

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Gratuitous Chemistry and Labeling Amendment
ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg

Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg are stable and a two-year expiration dating is requested. The two year expiration dating for these products is supported by three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) and controlled room temperature studies to date in each of the container / closure systems proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA Stability guidelines.

The dosage form, route of administration, active ingredient, and labeling (except DESCRIPTION & HOW SUPPLIED) for INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg tablets are same as those for Vicoprofen® Tablets, 7.5 mg/ 200 mg. The labeling comparison is provided in Section IV Comparison and 4 copies of the draft labeling are provided in Section V Labeling.

Both drug substances are USP items, but the drug product is not USP. Methods validations for the analytical methods for the drug product are submitted in two jackets. The firm commits to resolve all analytical issues post approval if necessary. The firm commits to provide sample for testing when requested. The same methods are used to test both strengths. As part of this submission, the methods validation package is amendment to include the comparison of the formulation, the release testing of the lower strength and the revised samples page include the lot number of the 5 mg / 200 mg strength.

This ANDA is submitted as archival, and duplicate. See the table of contents for volumes and location of documentation.

This completes our submission. Please contact the undersigned at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

Nilkanth J. Patel
Vice President of Regulatory Compliance

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

MAR 19 2003

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Withdraw Letter

Dear Sir/ Madam:

Pursuant to *Code of Federal Regulation* Title 21, Interpharm, Inc. submitted gratuitous chemistry and labeling amendments in support of a 5 mg / 200 mg strength. Reference is made to the original application submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for ANDA 76-642 for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg.

At the request of the agency (Arianne Camphire) we are withdrawing without prejudice the amendment to add the lower strength with the intention of refilling the information once the agency receipt letter is issued.

Pursuant to *Code of Federal Regulations* Title 21 § 314.440 (a) (4), a copy of the technical sections of this application is being submitted to the District Office, Domestic Operations, The Food and Drug Administration, 158-15 Liberty Ave., Jamaica, NY 11433. The Firm hereby certifies that it is a true copy of the technical section as described in *Code of Federal Regulations* Title 21 § 314.50 (d) (1).

This letter is submitted as archival, and duplicate copies.

This completes our submission. Please contact Nil Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

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INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAR 19 2003

NEW CORRESP
NC

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg
Telephone Amendment

Dear Sir/ Madam:

Interpharm, Inc. here within submits a Telephone Amendment. Reference is made to the request for additional information form Regulatory Support and the original application submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for ANDA 76-642 for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg.

As requested we are providing herein a copy of the quantitative formulation for the (b) (4) cosmetic coatings and a table listing the suppliers of the raw materials.

This ANDA is submitted as archival, and duplicate. See the table of contents for volumes and location of documentation.

This completes our submission. Please contact the undersigned at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky for

Nilkanth J. Patel
Vice President of Regulatory Compliance

RECEIVED
MAR 20 2003
OGD / CDER

ANDA 76-642

Interpharm, Inc.
Attention: Nilkanth J. Patel
75 Adams Avenue
Hauppauge, NY 11788

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversations dated March 7, 2003 and March 18, 2003 and your correspondence dated March 19, 2003.

NAME OF DRUG: Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg

DATE OF APPLICATION: January 16, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 21, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

    1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet A PATENT AMENDMENT with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a

settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Craig Kiester
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-642
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB GDavis 21-MAR-2003 date
HFD-615/ACamphire, CSO Brianna Camphire date 21-Mar-2003
Word File
V:/FIRMSAM/Interpharm/LTRS&REV/76642.ACK
FT/EEH 03/21/03
ANDA Acknowledgment Letter!

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

505(b)(2)(A)
Q-L 23 April 2003
Martin Miller

ORIG AMENDMENT
w/ AC

MAR 26 2003

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Gratuitous Chemistry and Labeling Amendment

Dear Sir/ Madam:

Pursuant to *Code of Federal Regulation* Title 21, Interpharm, Inc. here within submits gratuitous chemistry and labeling amendments in support of a 5 mg / 200 mg strength. Reference is made to the original application submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, for ANDA 76-642 for Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg.

Reference is also made to the Suitability Petition filed on July 12, 2002, and approved, on September 25, 2002, for the 5 mg / 200 mg strength and the Telephone Amendment submitted on March 10, 2003.

Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg have been developed and will be manufactured, tested, and packaged by INTERPHARM, Inc., 75 Adams Avenue, Hauppauge, NY 11788 manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturers of the drug substances are the same used to produce the ANDA / Bioequivalence batch of this product are for (b) (4)

The required bioavailability / bioequivalence studies were conducted on Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and Vicoprofen® Tablets 7.5 mg / 200 mg at PharmaKinetics Laboratories, Inc. 302 W. Fayette Street, Baltimore, MD 21201. These studies demonstrate that INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg are bioequivalent to Vicoprofen® Tablets, 7.5 mg/ 200 mg. The in vitro dissolution profile test results provided in Section VI support the equivalence of the products.

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Gratuitous Chemistry and Labeling Amendment
ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg

Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg are stable and a two-year expiration dating is requested. The two year expiration dating for these products is supported by three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) and controlled room temperature studies to date in each of the container / closure systems proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA Stability guidelines.

The dosage form, route of administration, active ingredient, and labeling (except DESCRIPTION & HOW SUPPLIED) for INTERPHARM's Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/ 200 mg tablets are same as those for Vicoprofen® Tablets, 7.5 mg/ 200 mg. The labeling comparison is provided in Section IV Comparison and 4 copies of the draft labeling are provided in Section V Labeling.

Both drug substances are USP items, but the drug product is not USP. Methods validations for the analytical methods for the drug product are submitted in two jackets. The firm commits to resolve all analytical issues post approval if necessary. The firm commits to provide sample for testing when requested. The same methods are used to test both strengths. As part of this submission, the methods validation package is amendment to include the comparison of the formulation, the release testing of the lower strength and the revised samples page include the lot number of the 5 mg / 200 mg strength.

This ANDA is submitted as archival, and duplicate. See the table of contents for volumes and location of documentation.

This completes our submission. Please contact the undersigned at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky for

Nilkanth J. Patel
Vice President of Regulatory Compliance

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

APR 21 2003

NEW CORRESP
NC

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 20 mg
Patent Amendment

Dear Sir/ Madam:

Pursuant *to Code of Federal Regulations* Title 21 § 314.96, Interpharm Inc., here within submits a Patent Amendment to their ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and 5 mg/ 200 mg. Reference is also made to the original submission dated, January 16, 2003, the Telephone Amendment, dated March 10, 2003, the gratuitous chemistry and labeling amendments, submitted March 12, 2003 adding the lower strength, and the Telephone Amendment providing a Bioequivalence jacket for the lower strength Labeling Deficiency Letter, dated April 10, 2003, and the Labeling Amendment, dated April 19, 2003.

Interpharm is providing herein copies of the Return Receipt for the notification of the NDA holder and the copy of the Factual and Legal Basis provided.

This ANDA amendment is submitted as archival and duplicate copies. This completes our submission. Please contact Nilkanth Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

RECEIVED
APR 22 2003
OGD / CDER

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

APR 21 2003

ORIG AMENDMENT
N/AF

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 20 mg
Labeling Amendment

Dear Sir/ Madam:

Pursuant *to Code of Federal Regulations* Title 21 § 314.96, Interpharm Inc., here within submits a Labeling Amendment to their ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and 5 mg/ 200 mg. Reference is made to the Labeling Deficiency Letter, dated April 10, 2003. Reference is also made to the original submission dated, January 16, 2003, the Telephone Amendment, dated March 10, 2003, the gratuitous chemistry and labeling amendments, submitted March 12 2003 adding the lower strength, and the Telephone Amendment providing a Bioequivalence jacket for the lower strength.

Labeling Comments and Interpharm Responses are as follows:

1. *CONTAINER- Bottles of 24, 100, 500 and 1000 tablets*
   a. *Front Panel: Revise to read as follows-*

HYDROCODONE BITATRATE *XX mg*
AND
IBUPROFEN *XX mg*
TABLETS

Rx only
XX Tablets.

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APR 22 2003
OGD / CDER

The requested changes were made.

b. *We encourage the use of boxing, contrasting color of other means to differentiate between your two proposed table strengths.*

We acknowledge your comment and will provide contrasting colors for the final printed labeling.

Labeling Amendment
ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 20 mg

2. PACKAGE INSERT
   See attached mocked-up copy of package insert labeling for requested revisions.

   a. The requested changes were made.
   b. The structure was modified as requested; however, please note that the change to the structure "5/2: rather than 2 1/5 is the official structure as listed in the USP.
   c. The 5 mg / 200 mg tablet is bisected. The information is updated herein.

In support of this submission, the firm is providing 4 copies of the revised draft labeling in Section V Labeling and Side-by–side comparisons of the changes in Section IV Comparison. The Certificate of Analysis for the 5 mg/ 200 mg showing the bisect on the description is provided in Section XIV Controls for Finished Dosage Form and copy of the agency letter is provided in Section XXI Other.

This ANDA amendment is submitted as archival, and duplicate copies. This completes our submission. Please contact Nilkanth Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

JUL 05 2003

NC

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 20 mg
Patent Amendment

Dear Sir/ Madam:

Pursuant *to Code of Federal Regulations* Title 21 § 314.96, Interpharm Inc., here within submits a Patent Amendment to their ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and 5 mg/ 200 mg. Reference is also made to the original submission dated, January 16, 2003, the Telephone Amendment, dated March 10, 2003, the gratuitous chemistry and labeling amendments, submitted March 12, 2003 adding the lower strength, and the Telephone Amendment providing a Bioequivalence jacket for the lower strength Labeling Deficiency Letter, dated April 10, 2003, and the Labeling and Patent Amendments, dated April 19, 2003.

Interpharm is hereby providing updated patent information regarding correspondence with the NDA holder. The innovator, Abbott, has indicated that they do not intend to sue on the Paragraph IV certification as to the '216 patent. Interpharm filed a paragraph III against the '252 patent, which is currently under appeal in litigation with another generic manufacturer.

This ANDA amendment is submitted as archival and duplicate copies. This completes our submission. Please contact Nilkanth Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

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JUL 08 2003
OGD/CDER

INTERPHARM INC.

Innovative Generics

AUG 22 2003

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
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Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Labeling Amendment

Dear Sir/ Madam:

Pursuant to Code of Federal Regulation Title 21 § 314.96, Interpharm Inc., here within submits a Labeling Amendment to its ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/ 200 mg and5 mg/ 200 m. Reference also made to the Labeling Deficiency Letter dated May 08, 2003. Reference also made to the original submission dated, January 16, 2003, Amendment, dated April 21, 2003, the gratuitous chemistry and labeling amendments, submitted March 12, 2003 adding the lower strength, and the telephone amendment providing a bioequivalence jacket for the lower strength, the telephone amendment dated, March 10, 2003.

Labeling Comments and Interpharm Responses are as follows:

1 CONTAINER – Bottles of 24, 100, 500 and 1000 Tablets

a. Front Panel: Revise to read as follows – Place "TABLETS" under "IBUPROFEN" as shown below, and add a space between "XX" (representative of the quantity of tablets per bottles) and "Tablets".

HYDROCODONE BITARTRATE XX mg
AND
IBUPROFEN XX mg
TABLETS

RX only
XX Tablets

RECEIVED
AUG 26 2003
OGD/CL...

Response: The requested changes were made. Please refer to the final printed labels submitted with this.

75 Adams Avenue • Hauppauge, NY 11788
Phone: (631) 952-0214 • Fax: (631) 952-9587

INTERPHARM INC.

Innovative Generics

2 PACKGE INSERT

a. Title; Revised to read –

Hydrocodone Bitartrate and Ibuprofen Tablets CIII

b. Dosage and Administration

Second sentence; revise to read –

Dosage should not exceed five 7.5 mg/200 mg tablets…..

Response: The requested changes were made. Please refer to the final printed Package Insert submitted with this.

In support of this submission, the firm is providing 12 copies of the final printed labeling. This ANDA amendment is submitted as archival and duplicate copies. As suggested a courtesy copy is submitted to Mr. Jim Barlow providing one final printed labeling.

This completes our submission. Please contact Nilkanth J. Patel at (631) 952-0214 ext 106, FAX (631) 952-9587 or C. Jeanne Taborsky at (410) 309-3145, and FAX (410) 309-6145, if you have any questions concerning this submission.

Sincerely yours,

Nilkanth J. Patel
VP Regulatory Compliance

75 Adams Avenue • Hauppauge, NY 11788
Phone: (631) 952-0214 • Fax: (631) 952-9587

INTERPHARM INC.
75 ADAMS AVENUE
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Tele. (631) 952-0214

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Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

SEP 2 7 2003

ORIG AMENDMENT
N/AM

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets 7.5/200 mg, 5/ 200 mg MINOR Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a MINOR AMENDMENT to ANDA 76-642 Ibuprofen Tablets 7.5/200 mg, and 5/200 mg. Reference is also made to the original submission, dated January 16, 2003, the Major Amendment adding the lower strength, dated March 12, 2003, the patent amendment, dated April 12, 2003, and the labeling amendment, dated April 21, 2003. Reference is also made to the agency deficiency letter, dated July 11, 2003, and our teleconference with Al Mueller in reference to the review of the lower strength.

The agency comments in the July 11, 2003 deficiency letter and Interpharm's responses are as follows:

A. Deficiencies:

1. (b) (4)

Following this page, 6 pages are withheld in full (b)(4).
InterPharm Letter dated September 27, 2003.

5. (b) (4)

C. Additional items and clarifications

1. (b) (4)

2.

3.

This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance at (631) 952-0214 ext 106 or C. Jeanne Taborsky Regulatory Affairs at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky

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Food and Drug Administration
Center for Drug Evaluation and Research
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ORIG AMENDMENT

OCT 06 2003

N/AM

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets 7.5 mg /200 mg, 5 mg / 200 mg Gratuitous Chemistry Minor Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a MINOR AMENDMENT to ANDA 76-642 Ibuprofen Tablets 7.5 mg /200 mg, and 5 mg /200 mg. Reference is also made to the original submission, dated January 16, 2003, the Major Amendment adding the lower strength, dated March 12, 2003, the patent amendment, dated April 12, 2003, and the labeling amendment, dated April 21, 2003. Reference is also made to the agency deficiency letter, dated July 11, 2003, and our teleconference with Al Mueller in reference to the review of the lower strength and our response to the Minor NA letter, dated September 27, 2003.

In preparation for approval, Interpharm conducted an internal audit of the documentation. The following sections are being amended at this time;

1. Section XIII Packaging Material Controls

(b) (4)

2. Section XIV Controls for Finished Dosage Form

   The descriptions of the tablets have been revised to use the identical wording on all documents for the 7.5 mg/ 200 mg strength. The tests for identification and water have been added for both strengths.

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MW 10/7

Gratuitous Chemistry Minor Amendment
ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg / 200 mg, 5 mg/ 200 mg

3. Section XV Analytical Methods

   The description for the 7.5 mg strength is revised to use the identical wording on all documents. The previously submitted stability indicating method listed an identification test, which was based upon the retention time. In accordance with industry practice, the ID test is conducted upon release and not on stability; therefore the test is removed from stability requirements.

4. Section XVI Stability

   (b) (4)

   To maintain consistency in the stability studies, the 24-count will be tested as well as the largest size of 1000-count.

   The description is revised on the 7.5 mg / 200 mg strength to be consistent on all documents.

   The requested testing for description and moisture are added to the stability data results as requested by the agency.

This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

INTERPHARM INC.
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Tele. (631) 952-0214

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Rockville, MD 20855-2773

NOV 1 1 2003

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets 7.5 mg /200 mg, 5 mg / 200 mg
Gratuitous Chemistry Minor Amendment

ORIG AMENDMENT
N/AA.

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Minor Amendment to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg, and 5 mg /200 mg. Reference is made to the original submission, dated January 16, 2003, the Major Amendment adding the lower strength, dated March 12, 2003, the patent amendment, dated April 12, 2003, and the labeling amendment, dated April 21, 2003. Reference is also made to the agency deficiency letter, dated July 11, 2003, and our minor chemistry amendments dated September 27, 2003 and October 6, 2003.

During a semi annual update of supplier information, Interpharm discovered that the supplier for (b) (4) had changed for both closure manufacturers. Interpharm is therefore providing the changes in the DMF letters of authorization as well as updating the supplier information in the packaging Section XIII.

Also while conducting the test for impurities in the Hydrocodone Bitartrate, Interpharm discovered a typographical error and mistake in the calculation. The explanation and changed Test Procedure are provided in Section III Raw Materials. Please be advised that in the September 27, 2003 amendment the results were properly reported.

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Gratuitous Chemistry Minor Amendment
ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg / 200 mg, 5 mg/ 200 mg

The following sections are revised at this time:

1. Section VIII Raw Materials

   Revised Standard Test Procedure

2. Section XIII Packaging Material Controls

   The closure information is revised and the data sheets for the resin are provided

3. Section XXI

   Revised DMF letters of Authorization

This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

INTERPHARM INC.
75 ADAMS AVENUE
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Rockville, MD 20855-2773

NOV 13 2003

RE: Bioequivalence Amendment
ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5/200 mg, 5/ 200 mg

ORIG AMENDMENT
N/AB

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Bioequivalence Amendment to ANDA 76-642 Ibuprofen Tablets 7.5/200 mg, and 5/200 mg. Reference is also made to the original submission, dated January 16, 2003, the Gratuitous Amendment, dated March 12, 2003, and the agency deficiency letter, dated October 15, 2003.

The Deficiency Comments and the firm's responses are as follows:

A. Deficiencies:

1. *The submitted long-term stability data of hydrocodone bitartrate and ibuprofen in frozen study samples (pages #191, and 1382) were not sufficient to cover the entire length of the sample storage period (from first blood sample drawn to the last plasma sample analyzed). Please submit data to support the long-term stability of hydrocodone bitartrate and ibuprofen in frozen study samples for a period that at least covers the entire length of the biostudy.*

   A second study was initiated and completed to support the stability of the test samples. The results of the study are provided herein.

2. *The submitted information on assay methodology description and validation was not adequate. The following raw data for pre-study validation ibuprofen are requested: 1) inter-day quality control (QC) samples; 2) recovery of the drug and internal standard; 3) Stock stability data, for how long (hours/days), and identify temperature; 4) In-process stability, for how long (hours); and Dilution integrity.*

   For hydrocodone bitartrate, only data on stock stability and dilution integrity are requested.

   For each item, the mean value for each sample set, range (minimum and maximum), precision (%CV), accuracy (%) accuracy, and number of samples, should be provided.

   A copy of the requested data is provided herein.

3. *The standard operation procedure (SOP) for describing the analytical method and data (sample acceptance and rejection criteria) for the studies under fasting and fed conditions was not provided in the submission. The SOP number, date of SOP approved, and SOP title should be included.*

   A copy of the SOP is provided as requested.

4. *The submitted dissolution testing data on the 5 mg / 200 mg strength are incomplete. Dissolution data for the Hydrocodone Bitartrate component of the 5 mg / 200 mg strength are requested. The dissolution testing data should include the dissolution mean for each time point, range (minimum and maximum), and the percentage of coefficient of variation (%CV) (in a side-by-side tabular format, if possible). The dissolution testing should be done on tablets from the same lot number that was used in the vivo bioequivalency study.*

   Interpharm acknowledges that the dissolution data as requested is required and the data on the lower strength was inadvertently omitted from the gratuitous amendment, dated March 12, 2003. The data is provided herein.

This concludes our response to the agency deficiency letter. Should you have any further questions you may contact C. Jeanne Taborsky at 410-309-3145; FAX 410-309-6145 or Nilkanth Patel at 631-952-0214 ext 106; FAX 631-952-9587.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

Telecon Record

Date: November 18, 2003

ANDA: 76-642

Firm: Interpharm

Drug: Hydrocodone Bitartrate and Ibuprofen Tablets

FDA Participants: Martin Shimer

Industry Participants: Jeanne Taborsky

Phone #: (410) 309-3145

Agenda: Marty called Jeanne and informed her that a certification to the '531 patent will be needed for this ANDA. The '531 patent was issued by USPTO on July 29, 2003 and received by the Agency(stamped) on August 11, 2003. Therefore this patent was timely filed and must be addressed by all applicants with pending ANDAs.

INTERPHARM INC.
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Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

NOV 24 2003

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg /200 mg, 5 mg / 200 mg
Telephone Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Telephone Amendment to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg, and 5 mg /200 mg. Reference is made to the following submissions;

Date	Submission
January 16, 2003	Original
March 12, 2003	Major Amendment adding the lower strength
April 12, 2003	Patent Amendment
April 21, 2003	Labeling Amendment
September 27, 2003	Chemistry Minor Amendment
October 6,2003	Chemistry Gratuitous Amendment
November 13, 2003	Bioequivalence Amendment

Reference is also made to the Teleconference with Team One of OGD held on November 20, 2003.

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NOV 25 2003
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Following this page, 1 page is withheld in full (b)(6).
InterPharm letter dated November 24, 2003.

Telephone Amendment
ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg / 200 mg, 5 mg/ 200 mg

This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

NA sued to A PIII to PIV & PIV to '531 S. Middleton 2/3/04

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XP

Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Patent Amendment

Dear Sir/ Madam:

Pursuant *to Code of Federal Regulations* Title 21 § 314.96, Interpharm Inc., here within submits a Patent Amendment to their ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg / 200 mg and 5 mg / 200 mg. Reference is also made to the original submission dated, January 16, 2003, and the Patent Amendments including but not limited to April 19, 2003.

Interpharm is providing updated patent information regarding correspondence with the NDA holder. The innovator, Abbott, has indicated that they do not intend to sue on the Paragraph IV certification as to the '216 patent. Interpharm filed a paragraph III against the '252 patent. The patent is currently under appeal in litigation with another generic manufacturer.

Interpharm hereby amends this application with the attached "Paragraph IV" certification and the following certification of notice to each owner of U.S. Patent No. 4,587,252 and the holder of the approved application. U.S. Patent No. 4,587,252 was previously subject to a "Paragraph III" certification, which is hereby withdrawn.

In addition, Interpharm is also amending the patent certification to include Paragraph IV Certification on Patent # 6,599,531 and the following certification of notice to each owner of U.S. Patent No. 6,599,531 and the holder of the approved application.

This ANDA amendment is submitted as archival and duplicate copies. This completes our submission. Please contact Nilkanth Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,
C. Jeanne Taborsky
C. Jeanne Taborsky
Regulatory Affairs

INTERPHARM INC.
75 ADAMS AVENUE
HAUPPAUGE, NY 11788
Tele. (631) 952-0214

Delivered Via Federal Express

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MPI Cmt 2/18/04
RR - 216 + 531

JAN 27 2004

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Reference: ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets
7.5 mg/ 200 mg and 5 mg/ 200 mg
Correspondence Patent Amendment Certification

Dear Sir/ Madam:

On January 9, 2004, pursuant *to Code of Federal Regulations* Title 21 § 314.96, Interpharm Inc., submitted a Patent Amendment to their ANDA 76-642 Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg / 200 mg and 5 mg / 200 mg.

Interpharm provided updated patent information to each holder of the patents and the Reference Listed Drug NDA. We hereby provide Certification of Notice.

This ANDA correspondence is submitted as archival and duplicate copies. This completes our submission. Please contact Nilkanth Patel at (631) 952-0214 ext 106 or C. Jeanne Taborsky at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

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JAN 28 2004
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4.1

INTERPHARM INC.
75 ADAMS AVENUE
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Center for Drug Evaluation and Research
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ORIG AMENDMENT
N/Am

FEB 05 2004

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg /200 mg, 5 mg / 200 mg
Chemistry Minor Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Minor Amendment to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg, and 5 mg /200 mg. Reference is made to the original submission, dated January 16, 2003, the Major Amendment adding the lower strength, dated March 12, 2003, the Patent Amendment, dated April 12, 2003, and the Labeling Amendment, dated April 21, 2003. Reference is also made to the agency Deficiency Letter, dated July 11, 2003, our Minor Chemistry Amendments, dated September 27, 2003 and October 6, 2003, and the Bioequivalence Approval Letter, dated December 24, 2003.

The bioequivalence letter requested that we change our specifications for dissolution from Q = (b) (4) minutes to Q = (b) (4) at 15 minutes. We are hereby submitting the revised specification sheets and revised test methods, which incorporate those changes. We believe that all outstanding issues have been resolved.

Please note that Interpharm Inc. changed the Patent Certification and pursuant to 314.52 is currently waiting the required 45-day period from the date of notification. The date of the last notification receipt was January 16, 2004. If the patent and NDA holders do not notify us of their intension to sue, we would anticipate approval, on or about March 1, 2004. We note and acknowledge that we are required to notify you in writing, that we have not received notification of the holders of their intent to sue.

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Chemistry Minor Amendment
ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg / 200 mg, 5 mg/ 200 mg

This Amendment is being submitted as 3 copies, archival, duplicate, and bioequivalence. This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

4.1

INTERPHARM INC.
75 ADAMS AVENUE
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Tele. (631) 952-0214

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MAR 02 2004

ORIG AMENDMENT
N/Am

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg /200 mg, 5 mg / 200 mg
Correspondence: Request for Approval

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. here within submits correspondence to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg, and 5 mg /200 mg. Reference is made to the original submission, dated January 16, 2003, the Major Amendment adding the lower strength, dated April 11, 2003, the Patent Amendments, dated April 21, 2003, January 9, 2004 and January 27, 2004, the Labeling Amendment, dated April 21, 2003, the Agency Deficiency Letter dated May 8, 2003 and the response dated August 20, 2003. Reference is also made to the agency Deficiency Letter, dated July 5, 2003, our Chemistry Amendments, dated September 27, 2003, October 6, 2003, February 5, 2004, and the Bioequivalence Approval Letter, dated December 23, 2003.

Pursuant to *Code of Regulation* Title 21 § 314.52, Interpharm Inc. changed the Patent Certification. Interpharm sent notifications of the change to Paragraph IV status to three parties. The date of the last return receipt was January 16, 2004. Abbott contacted Interpharm by phone and indicted that they did not intend to sue. As required, Interpharm hereby notifies the agency in writing, that the required 45-day period from the date of notification of the patent holders has expired. Additional copies of those notification receipts are provided herein for the convenience of the reviewer.

This correspondence is being submitted as 2 hard copies; archival, duplicate, and FAX reviewer desk copy. This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

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INTERPHARM INC.
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4.1

MJ 3/5/04
~~Hand Delivered~~
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MAR 05 2004

ORIG AMENDMENT
N/AM

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg /200 mg, 5 mg / 200 mg
Telephone Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Telephone Amendment to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg and 5 mg /200 mg. Reference is made to the Teleconference, dated March 5, 2004, and our letter requesting approval, dated March 2, 2004.

As requested by the agency Interpharm revised standards and test methods listing the (b) (4) impurity with a limit of (b) (4) %. Additionally, Interpharm is providing dissolution results conducted on samples stored at accelerated conditions for three months followed by storage under room temperature conditions for approximately nine months. The dissolution results meet Q = (b) (4) at 15 minutes. We are hereby submitting the revised specification sheets and revised test methods which incorporate those changes.

This Telephone Amendment is being submitted as 1 fax copy and 2 hard copies. We believe that all outstanding issues have been resolved, and hereby request approval of our application. This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

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MAR 08 2004
OGD/CDER

SciRegs, Inc.
6333 Summercrest Dr.
Columbia, MD 21045

. NEW CORRESP

NC

urgent

facsimile

To:	**Rosario c/o Simon Eng**
Fax Number:	1 301 594-0180
From:	**C. Jeanne Taborsky**
Fax Number:	4103096145
Business Phone:	410.309.3145
Home Phone:	
Pages:	7
Date/Time:	3/8/2004 3:44:05 PM
Subject:	ANDA revised specs

Simon,

I will still send an offical copy with the mthod and filing form etc by email and Fed x. You will have hard copy tomorrow .

Thanks

Jeanne

INTERPHARM INC.
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MAR 09 2004

ORIG AMENDMENT
N/AM

RE: ANDA 76-642 Hydrocodone Bitartrate/ Ibuprofen Tablets
7.5 mg /200 mg and 5 mg / 200 mg
Telephone Amendment

Dear Sir/ Madam:

Pursuant to *Code of Regulation* Title 21 § 314.90 Interpharm Inc. herewith submits a Telephone Amendment to ANDA 76-642 Hydrocodone Bitartrate / Ibuprofen Tablets 7.5 mg /200 mg and 5 mg /200 mg. Reference is made to the Teleconference, dated March 8, 2004, and our Telephone Amendment, dated March 5, 2004.

As requested by the agency Interpharm has revised the wording on the specifications from *Unknown Degradants* to *Degradants.* At the request of the reviewer, the revised specifications sheets were faxed to the agency. The revised specifications and test methods are provided herein as official copies.

This Telephone Amendment is being submitted as a reviewer email copy and 2 hard copies. We believe that all outstanding issues have been resolved, and hereby request approval of our application. This completes our submission. Please contact Nilkanth J. Patel, Vice President of Regulatory Compliance, at (631) 952-0214 ext 106 or C. Jeanne Taborsky, Regulatory Affairs, at (410) 309-3145 FAX (410)-309-6145, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

RECEIVED
MAR 09 2004
OGD/CDER

ANDA 76-642

MAR 30 2004

SciRegs
Attention: C. Jeanne Taborsky
U.S. Agent for: INTERPHARM, Inc.
6333 Summercrest Drive
Columbia, MD 21045

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 16, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg and 7.5 mg/200 mg.

Reference is made to our letter dated March 18, 2004, granting final approval to your Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg, and granting tentative approval to your Hydrocodone Bitartrate and Ibuprofen Tablets, 7.5 mg/200 mg.

This letter addresses Interpharm, Inc.'s (Interpharm's) eligibility for 180-day generic drug exclusivity for Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg, under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments in Section 505(j)(5)(B)(iv) of the Act. The Agency has concluded that Interpharm was the first ANDA applicant to submit a substantially complete ANDA for Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg, containing paragraph IV certifications to each of the listed patents referenced in the March 18, 2004, approval letter. Therefore, upon the approval of this ANDA on March 18, 2004, Interpharm became eligible for 180-days of market exclusivity for the 5 mg/200 mg strength of the drug product. Since no action for infringement of the listed patents was brought against Interpharm within the statutory 45-day period, the exclusivity will begin to run on the date Interpharm begins first commercial marketing of its Hydrocodone Bitartrate and Ibuprofen Tablets, 5 mg/200 mg, under this ANDA.

With respect to the "first commercial marketing" trigger for the commencement of this exclusivity, please refer to 21 CFR 314.107(c)(4). The agency expects that Interpharm will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your ANDA stating the date that commercial marketing of this drug product commenced.

If you have any questions concerning the effective date of approval of an ANDA and the agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

If you have further questions concerning Interpharm's eligibility for 180-day generic drug exclusivity for the 5 mg/200 mg strength of this drug product, please contact Simon Eng, R.Ph., Project Manager, at (301) 827-5765.

Sincerely yours,

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

3/30/04

cc: ANDA 76-642
Division File
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HFD-600/D.Hare
HFD-600/C.Parise

Endorsements:
HFD-600/R.West 3/30/04

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LETTER OUT (180-Day EXCLUSIVITY)