CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74978

Trade Name Ibuprofen Oral Suspension USP 100mg/5ml

Generic Name Ibuprofen Oral Suspension USP 100mg/5ml

Sponsor Alpharma

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74978

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74978

APPROVAL LETTER

ANDA 74-978

MAR 25 1998

Alpharma
U.S. Pharmaceuticals Division
Attention: Vincent Andolina
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated October 9, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen Oral Suspension USP, 100 mg/5 mL, labeled for prescription use.

Reference is also made to your amendments dated February 9, and March 19, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ibuprofen Oral Suspension USP, 100 mg/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Motrin® Suspension, 100 mg/5 mL of McNeil Consumer Products Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn 3-25-98
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74978

FINAL PRINTED LABELING

Ibuprofen Oral Suspension USP
Facsimile Amendment to ANDA#74-978
Alpharma USPD Inc.

DO NOT ACCEPT IF CAP SEAL IMPRINTED WITH ℞ IS BROKEN OR MISSING.

SHAKE WELL.

Store at controlled room temperature 15°-30°C (59°-86°F).

See package insert for complete product details.

See label or bottom of container for lot number and expiration date.

1270089781 VC102161

NDC 0472-1270-92

IBUPROFEN
ORAL SUSPENSION USP

ALPHARMA

100 mg/5 mL

CAUTION: Federal law prohibits dispensing without prescription.

2 fl oz (60 mL)

Manufactured by Alpharma USPD Inc., Baltimore, MD 21244

Ibuprofen Oral Suspension USP
Facsimile Amendment to ANDA#74-978
Alpharma USPD Inc.

NDC 0472-1270-92

IBUPROFEN
ORAL SUSPENSION USP

ALPHARMA

100 mg/5 mL

NDC 0472-1270-92

IBUPROFEN
ORAL SUSPENSION USP

ALPHARMA

100 mg/5 mL

TAMPER-EVIDENT CONTAINER ENCLOSED. CAP SEAL IMPRINTED WITH TE.

SHAKE WELL.

Store at controlled room temperature 15°-30°C (59°-86°F).

See package insert for complete product details.

See bottom of carton for lot number and expiration date.

1270089781 VC102162

Dosage Cup Included

CAUTION: Federal law prohibits dispensing without prescription.

2 fl oz (60 mL)

Manufactured by Alpharma USPD Inc., Baltimore, MD 21244

Dosage Cup Included

CAUTION: Federal law prohibits dispensing without prescription.

2 fl oz (60 mL)

Manufactured by Alpharma USPD Inc., Baltimore, MD 21244

N 04721 27092 7

1
530333
0897

048

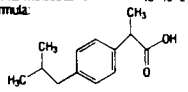
FORM NO. 1270-IN
VC1342
Rev. 8/97

IBUPROFEN ORAL SUSPENSION USP
100 mg/5 mL

IBUPROFEN ORAL SUSPENSION USP
100 mg/5 mL

DESCRIPTION

The active ingredient in Ibuprofen Oral Suspension USP is ibuprofen, which is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is a racemic mixture of [+]S- and [-]R-enantiomers. It is a white to off-white crystalline powder, with a melting point of 74° to 77°C. It is practically insoluble in water (< 0.1 mg/mL), but readily soluble in organic solvents such as ethanol and acetone. Ibuprofen has a pKa of 4.43 ± 0.03 and an n-octanol/water partition coefficient of 11.7 at pH 7.4. The chemical name for ibuprofen is (±)-2-*p*-isobutylhydratropic acid. The molecular weight of ibuprofen is 206.29. Its molecular formula is $C_{13}H_{18}O_2$ and it has the following structural formula:



Ibuprofen Oral Suspension USP is a sucrose-sweetened, orange-colored, berry-flavored liquid suspension containing 100 mg of ibuprofen in 5 mL (20 mg/mL). Inactive ingredients include citric acid, glycerin, hydroxypropyl methylcellulose, polysorbate 80, purified water, sodium benzoate, sucrose, xanthan gum, D&C Yellow #10 and FD&C Red #40, and artificial flavors (strawberry/vanillin).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. After absorption of the racemic ibuprofen, the [-]R-enantiomer undergoes interconversion to the [+]S-form. The biological activities of ibuprofen are associated with the [+]S-enantiomer.

In clinical studies in adult patients with rheumatoid arthritis and osteoarthritis, ibuprofen has been shown to be comparable to aspirin in controlling pain and inflammation, though causing fewer of the mild gastrointestinal side effects (see ADVERSE REACTIONS). Ibuprofen may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients, when treated with ibuprofen, should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether ibuprofen causes less peptic ulceration than aspirin, in one study involving 885 adult patients with rheumatoid arthritis treated for up to one year (438 patients on ibuprofen and 447 patients on aspirin), there were no reports of gastric ulceration with ibuprofen whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p < .001$).

Gastroscopic studies at varying doses of ibuprofen showed an increased tendency toward endoscopic lesions at higher doses. However, at clinically comparable doses (2400 mg of ibuprofen vs. 3600 mg of aspirin), endoscopic lesions were approximately half that seen with aspirin. Studies using ^{51}Cr-tagged red cells indicate that fecal blood loss associated with ibuprofen in doses up to 2400 mg daily did not exceed the range of normal, and was significantly less than that seen in aspirin-treated patients. The clinical significance of these findings is unknown.

Pharmacokinetics

As noted in the DESCRIPTION section, ibuprofen is a racemic mixture of [-]R-and [+]S-isomers. *In vivo* and *in vitro* studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The degree of interconversion in children is unknown, but is thought to be similar. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. Ibuprofen is well absorbed orally, with less than 1% being excreted in the urine unchanged. It has a biphasic elimination time curve with a plasma half-life of approximately 2 hours. Studies in febrile children have established the dose-proportionality of 5 and 10 mg/kg doses of ibuprofen. Studies in adults have established the dose-proportionality of ibuprofen as a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug.

Absorption - *In vivo* studies indicate that ibuprofen is well absorbed orally from the suspension formulation with peak plasma levels usually occurring within 1 to 2 hours. The observed differences in the table between adults and children, in terms of AUC and C_{max}, are due to both differences in dose per body weight and age- or fever-related change in volume of distribution (Vd/F).

Table 1
Pharmacokinetic Parameters of Ibuprofen Oral Suspension [Mean values (% coefficient of variation)]

Dose	200 mg (~2.8 mg/kg) in Adults	10 mg/kg in Febrile Children
Number of Patients	24	18
AUC_{inf} (mcg•h/mL)	64 (27%)	155 (24%)
C_{max} (mcg/mL)	19 (22%)	55 (23%)
T_{max} (h)	0.79 (69%)	0.97 (57%)
Cl/F (mL/h/kg)	45.6 (22%)	68.6 (22%)

Legend: AUC_{inf} = Area-under-the-curve to infinity
C_{max} = Peak plasma concentration
T_{max} = Time-to-peak plasma concentration
Cl/F = Clearance divided by fraction of drug absorbed

Antacid - A bioavailability study in adults has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Food Effects - Absorption is most rapid when ibuprofen is given under fasting conditions. Administration of ibuprofen with food affects the rate but not the extent of absorption. When taken with food, T_{max} is delayed by approximately 30 to 60 minutes, and peak levels are reduced by approximately 30 to 50%.

Distribution - Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable and at concentrations >20 mcg/mL binding is non-linear. Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown.

Metabolism - Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of

Controlled studies have demonstrated that ibuprofen is a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, ibuprofen has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

In clinical studies in adult patients with rheumatoid arthritis, ibuprofen has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity, with a lower incidence of milder gastrointestinal and CNS side effects than indomethacin.

Ibuprofen may be used in combination with gold salts and/or corticosteroids.

INDICATIONS AND USAGE

In Children Ibuprofen Oral Suspension is indicated:
- For the reduction of fever in patients aged 6 months and older.
- For the relief of signs and symptoms of juvenile arthritis.

In Adults Ibuprofen Oral Suspension is indicated:
- For relief of mild to moderate pain.
- For the treatment of primary dysmenorrhea.
- For relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Since there have been no controlled trials to demonstrate whether there is any beneficial effect or harmful interaction with the use of ibuprofen in conjunction with aspirin, the combination cannot be recommended (see PRECAUTIONS - Drug Interactions).

CONTRAINDICATIONS

Ibuprofen should not be used in patients with previously demonstrated hypersensitivity to ibuprofen, or in individuals with a history of allergic manifestations to aspirin or other NSAIDs. Severe anaphylactic-like reactions to ibuprofen have been reported in such patients, some with fatal outcome.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Anaphylactoid Reactions - Anaphylactoid reactions may occur even in patients without prior exposure to ibuprofen. Extreme caution should be exercised when giving ibuprofen to patients with bronchospastic reactivity (e.g., asthma), nasal polyps, or those with a history of angioedema. Emergency help should be sought in case such anaphylactoid reaction occurs.

PRECAUTIONS

Renal Effects: Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with 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 to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and 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 the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk, who chronically take ibuprofen, should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Fluid Retention: 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 or hypertension.

Hematologic Effects: Ibuprofen can inhibit platelet aggregation but, unlike aspirin, its effect on platelet function is reversible, quantitatively less, and of shorter duration. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Hepatic Effects: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver laboratory tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The ALT (SGPT) test

interconverted into the active [+]S species in adults. The degree of interconversion in children is unknown, but is thought to be similar. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. Ibuprofen is well absorbed orally, with less than 1% being excreted in the urine unchanged. It has a biphasic elimination time curve with a plasma half-life of approximately 2 hours. Studies in febrile children have established the dose-proportionality of 5 and 10 mg/kg doses of ibuprofen. Studies in adults have established the dose-proportionality of ibuprofen as a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug.

Absorption - *In vivo* studies indicate that ibuprofen is well absorbed orally from the suspension formulation with peak plasma levels usually occurring within 1 to 2 hours. The observed differences in the table between adults and children, in terms of AUC and C_{max}, are due to both differences in dose per body weight and age- or fever-related change in volume of distribution (Vd/F).

Table 1
Pharmacokinetic Parameters of Ibuprofen Oral Suspension [Mean values (% coefficient of variation)]

Dose	200 mg (~2.8 mg/kg) in Adults	10 mg/kg in Febrile Children
Number of Patients	24	18
AUC_{inf} (mcg•h/mL)	64 (27%)	155 (24%)
C_{max} (mcg/mL)	19 (22%)	55 (23%)
T_{max} (h)	0.79 (69%)	0.97 (57%)
Cl/F (mL/h/kg)	45.6 (22%)	68.6 (22%)

Legend: AUC_{inf} = Area-under-the-curve to infinity
C_{max} = Peak plasma concentration
T_{max} = Time-to-peak plasma concentration
Cl/F = Clearance divided by fraction of drug absorbed

Antacid - A bioavailability study in adults has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Food Effects - Absorption is most rapid when ibuprofen is given under fasting conditions. Administration of ibuprofen with food affects the rate but not the extent of absorption. When taken with food, T_{max} is delayed by approximately 30 to 60 minutes, and peak levels are reduced by approximately 30 to 50%.

Distribution - Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable and at concentrations >20 mcg/mL binding is non-linear. Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown.

Metabolism - Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of free and conjugated ibuprofen found in the urine were approximately 1% and 14%, respectively. The remainder of the drug was found in the stool as both metabolites and unabsorbed drug.

Elimination - Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2.0 hours. There is no difference in the observed terminal elimination rate or half-life between children and adults, however, there is an age- or fever-related change in total clearance. This suggests that the observed change in clearance is due to changes in the volume of distribution of ibuprofen (see Table 1 for Cl/F values).

Clinical Studies

Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen suspension and 10-15 mg/kg of acetaminophen elixir have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours, children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

Controlled single-dose clinical analgesia trials, comparing doses of 5 and 10 mg/kg ibuprofen suspension with acetaminophen suspension 12.5 mg/kg and placebo, have been conducted in children 5 to 12 years of age, with sore throat pain due to an infectious agent, or ear pain due to acute otitis media. Onset of pain relief provided by ibuprofen was similar to that of acetaminophen, occurring within the first hour, usually around the half-hour mark. All active treatments showed significant pain relief versus placebo, and the 10 mg/kg dose of ibuprofen had a duration of analgesic effect of 6 to 8 hours. Ibuprofen 10 mg/kg provided more overall pain relief than the 5 mg/kg dose.

such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Anaphylactoid Reactions - Anaphylactoid reactions may occur even in patients without prior exposure to ibuprofen. Extreme caution should be exercised when giving ibuprofen to patients with bronchospastic reactivity (e.g., asthma), nasal polyps, or those with a history of angioedema. Emergency help should be sought in case such anaphylactoid reaction occurs.

PRECAUTIONS

Renal Effects: Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with 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 to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and 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 the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk, who chronically take ibuprofen, should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Fluid Retention: 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 or hypertension.

Hematologic Effects: Ibuprofen can inhibit platelet aggregation but, unlike aspirin, its effect on platelet function is reversible, quantitatively less, and of shorter duration. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Hepatic Effects: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver laboratory tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT and AST (SGOT) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. 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.), treatment with ibuprofen should be discontinued.

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

Other Precautions - The pharmacological activity of ibuprofen may induce fever reduction and inflammation, thus diminishing their utility as diagnostic signs in detecting underlying conditions.

In order to avoid exacerbation of manifestations of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported.

Diabetics: Ibuprofen oral suspension contains 0.3 g sucrose and 1.6 calories per mL, or 1.5 g sucrose and 8 calories per teaspoon, which should be taken into consideration when treating diabetic patients with this product.

Information for Patients

Ibuprofen, like other drugs of its class, 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.

NSAIDs are often essential agents in the management of arthritis, pain and fever, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Patients on ibuprofen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS).

Patients should also be instructed to seek medical emergency help in case of an occurrence of an anaphylactoid reaction (see WARNINGS).

Laboratory Tests

Hemoglobin Levels: In cross-study comparisons, in adults, with doses ranging from 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. This has been observed with other nonsteroidal anti-inflammatory drugs; the mechanism is unknown. However, even with daily doses of 3200 mg, the total decrease in hemoglobin usually does not exceed 1 g/dL; if there are no signs of bleeding, it is probably not clinically important.

In two postmarketing clinical studies with ibuprofen, the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 g/dL or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

Drug Interactions

Coumarin-type anticoagulants: Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors administered to individuals on coumarin-type anticoagulants. Because bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering ibuprofen to patients on anticoagulants.

Aspirin: Animal studies show that aspirin given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been done.

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, therefore, if ibuprofen is administered concomitantly with methotrexate.

H-2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

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

Furosemide: Clinical studies, as well as random observations, have shown that ibuprofen can 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 ibuprofen, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparation before use of such concurrent therapy.)

Pregnancy

Teratogenic Effects — Pregnancy Category B: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. Administration of ibuprofen is not recommended during pregnancy.

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 ibuprofen is not recommended during labor and delivery.

Nursing Mothers: In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate ibuprofen in the milk of lactating mothers. Because of the limited nature of these studies, however, and the possible adverse effects of prostaglandin inhibiting drugs on neonates, ibuprofen is not recommended for use in nursing mothers.

Pediatric Use: Safety and efficacy of ibuprofen in pediatric patients below the age of 6 months has not been established (see CLINICAL PHARMACOLOGY—Clinical Studies). There is no evidence of age-dependent kinetics in patients 2 to 11 years old (see CLINICAL PHARMACOLOGY-Pharmacokinetics). Dosing of ibuprofen in children 6 months or older should be guided by their body weight (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies in adults, when ibuprofen was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials in adults at an incidence greater than 1% are listed in the chart. Those reactions listed under the heading "Incidence Greater than 1% (but less than 3%) Probable Causal Relationship," encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions, occurring less frequently than 1 in 100, were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: "Incidence less than 1%—Probable Causal Relationships," lists reactions with ibuprofen therapy for which the probability of a causal relationship exists; this category was completed over time with postmarketing serious adverse reactions. "Incidence less than 1%—Causal Relationship Unknown," lists reactions with ibuprofen therapy for which a causal relationship has not been established, but are presented as alerting information for physicians.

INCIDENCE OF 1% OR GREATER

Probable Causal Relationship:

*Incidence between 3 and 9%=ADR marked with **

Incidence between 1 and <3%=unmarked ADR

Cardiovascular system: Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS).

Digestive system: Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or

Digestive system: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, pancreatitis, melena, gastritis, duodenitis, esophagitis, hematemesis, hepatorenal syndrome, liver necrosis, liver failure, hepatitis, jaundice, abnormal liver tests.

Hematologic system: Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decrease in hemoglobin and hematocrit (see PRECAUTIONS), pancytopenia.

Nervous system: Depression, insomnia, confusion, emotional lability, somnolence, convulsions, aseptic meningitis with fever and coma (see PRECAUTIONS).

Respiratory: Bronchospasm, dyspnea, apnea.

Skin and appendages: Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reactions.

Special senses: Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS - Other Precautions).

Urogenital system: Acute renal failure in patients with pre-existing significantly impaired renal function (see PRECAUTIONS), renal papillary necrosis, tubular necrosis, glomerulitis, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria.

Miscellaneous: Dry eyes and mouth, gingival ulcer, rhinitis.

INCIDENCE LESS THAN 1%

Causal Relationship Unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested by marketing experience under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician.

Allergic: Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.

Cardiovascular system: Arrhythmias (sinus tachycardia, sinus bradycardia).

Hematologic system: Bleeding episodes (e.g., epistaxis, menorrhagia).

Metabolic/endocrine: Gynecomastia, hypoglycemic reaction, acidosis.

Nervous system: Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri.

Special senses: Conjunctivitis, diplopia, optic neuritis, cataracts.

OVERDOSAGE

The *toxicity of ibuprofen overdose* is dependent upon the amount of drug ingested and the time elapsed since ingestion, though individual response may vary, which makes it necessary to evaluate each case individually. Although uncommon, serious toxicity and death have been reported in the medical literature with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other central nervous system symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnea (primarily in very young children) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation also have been reported.

The *treatment of acute ibuprofen overdose* is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary. In cases of acute overdose, the stomach should be emptied through ipecac-induced emesis or lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption and reabsorption of ibuprofen.

In children, the estimated amount of ibuprofen ingested per body weight may be helpful to predict the potential for development of toxicity although each case must be evaluated. Ingestion of less than 100 mg/kg is unlikely to produce toxicity. Children ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of four hours. Children ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation in a health care facility. Children ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Ipecac-induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

In adult patients the history of the dose reportedly ingested does not appear to be predictive of toxicity. The need for referral and follow-up must be judged by the circumstances at the time of the overdose ingestion. Symptomatic adults should be admitted to a health care facility for observation.

DOSAGE AND ADMINISTRATION

CHILDREN

Fever reduction: For reduction of fever in children, 6 months to 12 years of age, the dosage should be adjusted on the basis of the initial temperature level (see CLINICAL PHARMACOLOGY). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F, or 10 mg/kg if the baseline temperature is 102.5°F or greater. The duration of fever reduction is generally 6 to 8 hours. The recommended maximum daily dose is 40 mg/kg.

Juvenile Arthritis: The recommended dose is 30 to 40 mg/kg/day divided into three to four doses (see Individualization of Dosage). Patients with milder disease may be adequately treated with 20 mg/kg/day.

ADULTS

Analgesia: 400 mg every 4 to 6 hours as necessary for the relief of mild to moderate pain in adults. In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than the 400 mg dose.

Primary Dysmenorrhea: For the treatment of primary dysmenorrhea, beginning with the earliest onset of such pain, ibuprofen oral suspension should be given in a dose of 400 mg every 4 hours, as necessary, for the relief of pain.

Rheumatoid arthritis and osteoarthritis, including flare-ups of chronic disease: Suggested dosage: 1200-3200 mg daily (300 mg q.i.d. or 400 mg, 600 mg or 800 mg t.i.d. or q.i.d.). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

Individualization of Dosage: The dose of ibuprofen oral suspension should be tailored to each patient, and may be lowered or raised from the suggested doses depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

One fever study showed that, after the initial dose of ibuprofen, subsequent doses may be lowered and still provide adequate fever control.

In a situation when low fever would require the ibuprofen oral suspension 5 mg/kg dose in a child with pain, the dose that will effectively treat the predominant symptom should be chosen.

In chronic conditions, a therapeutic response to ibuprofen therapy is sometimes seen in a few days to a week, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

In patients with juvenile arthritis, doses above 50 mg/kg/day are not recommended because they have not been studied and doses exceeding the upper recommended dose of 40 mg/kg/day may increase the risk of causing serious adverse events. The therapeutic response may require from a few days to several weeks to be achieved. Once a clinical effect is obtained, the dosage should be lowered to the smallest dose of ibuprofen oral suspension needed to maintain adequate control of symptoms.

In general, patients with rheumatoid arthritis seem to require higher doses than do patients with osteoarthritis. The smallest dose of ibuprofen oral suspension that yields acceptable control should be employed.

HOW SUPPLIED

Ibuprofen Oral Suspension USP, 100 mg/5 mL

Orange-colored, berry-flavored suspension

- Bottles of 60 mL
- Bottles of 473 mL

Shake well before using. Store at controlled room temperature [15° to 30°C (59° to 86°F)].

Dispense in a tight container as defined in the USP.

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. Administration of ibuprofen is not recommended during pregnancy.

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 ibuprofen is not recommended during labor and delivery.

Nursing Mothers: In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate ibuprofen in the milk of lactating mothers. Because of the limited nature of these studies, however, and the possible adverse effects of prostaglandin inhibiting drugs on neonates, ibuprofen is not recommended for use in nursing mothers.

Pediatric Use: Safety and efficacy of ibuprofen in pediatric patients below the age of 6 months has not been established (see CLINICAL PHARMACOLOGY—Clinical Studies). There is no evidence of age-dependent kinetics in patients 2 to 11 years old (see CLINICAL PHARMACOLOGY-Pharmacokinetics). Dosing of ibuprofen in children 6 months or older should be guided by their body weight (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies in adults, when ibuprofen was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials in adults at an incidence greater than 1% are listed in the chart. Those reactions listed under the heading "Incidence Greater than 1% (but less than 3%) Probable Causal Relationship," encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions, occurring less frequently than 1 in 100, were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: "Incidence less than 1%—Probable Causal Relationships," lists reactions with ibuprofen therapy for which the probability of a causal relationship exists; this category was completed over time with postmarketing serious adverse reactions. "Incidence less than 1%—Causal Relationship Unknown," lists reactions with ibuprofen therapy for which a causal relationship has not been established, but are presented as alerting information for physicians.

INCIDENCE OF 1% OR GREATER

Probable Causal Relationship:

*Incidence between 3 and 9%=ADR marked with **

Incidence between 1 and <3%=unmarked ADR

Cardiovascular system: Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS).

Digestive system: Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence).

Nervous system: Dizziness*, headache, nervousness.

Skin and appendages: Rash* (including maculopapular type), pruritus.

Special senses: Tinnitus.

INCIDENCE LESS THAN 1%

Probable Causal Relationship: The following adverse reactions were reported in clinical trials at an incidence of less than 1%, or were reported from postmarketing or foreign experience. The probability exists between the drug and these adverse reactions.

Body as a whole: Anaphylaxis and anaphylactoid reactions (see WARNINGS).

Cardiovascular system: Cerebrovascular accident, hypotension, congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations.

three to four doses (see Individualization of Dosage). Patients with these disease may be adequately treated with 20 mg/kg/day.

ADULTS

Analgesia: 400 mg every 4 to 6 hours as necessary for the relief of mild to moderate pain in adults. In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than the 400 mg dose.

Primary Dysmenorrhea: For the treatment of primary dysmenorrhea, beginning with the earliest onset of such pain, ibuprofen oral suspension should be given in a dose of 400 mg every 4 hours, as necessary, for the relief of pain.

Rheumatoid arthritis and osteoarthritis, including flare-ups of chronic disease: Suggested dosage: 1200-3200 mg daily (300 mg q.i.d. or 400 mg, 600 mg or 800 mg t.i.d. or q.i.d.). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

Individualization of Dosage: The dose of ibuprofen oral suspension should be tailored to each patient, and may be lowered or raised from the suggested doses depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

One fever study showed that, after the initial dose of ibuprofen, subsequent doses may be lowered and still provide adequate fever control.

In a situation when low fever would require the ibuprofen oral suspension 5 mg/kg dose in a child with pain, the dose that will effectively treat the predominant symptom should be chosen.

In chronic conditions, a therapeutic response to ibuprofen therapy is sometimes seen in a few days to a week, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

In patients with juvenile arthritis, doses above 50 mg/kg/day are not recommended because they have not been studied and doses exceeding the upper recommended dose of 40 mg/kg/day may increase the risk of causing serious adverse events. The therapeutic response may require from a few days to several weeks to be achieved. Once a clinical effect is obtained, the dosage should be lowered to the smallest dose of ibuprofen oral suspension needed to maintain adequate control of symptoms.

In general, patients with rheumatoid arthritis seem to require higher doses than do patients with osteoarthritis. The smallest dose of ibuprofen oral suspension that yields acceptable control should be employed.

HOW SUPPLIED

Ibuprofen Oral Suspension USP, 100 mg/5 mL

Orange-colored, berry-flavored suspension

- Bottles of 60 mL
- Bottles of 473 mL

Shake well before using. Store at controlled room temperature [15° to 30°C (59° to 86°F)].

Dispense in a tight container as defined in the USP.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Alpharma USPD Inc.
Baltimore, MD 21244

Form No. 1270-IN

Rev. 8/97
VC1342

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74978

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-978 (Rx)

3. NAME AND ADDRESS OF APPLICANT
Alpharma
U.S. Pharmaceuticals Division
Attention:Vincent Andolina
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION
Listed drug: McNeil-PPC's Motrin® Ibuprofen Suspension USP, 100 mg/5 mL (N19842); Listed drug US patent #5,374,659 will expire on 12/20/2011 and the exclusivity will expire on 3/24/98.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Ibuprofen Oral Suspension USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FDA:
1/30/98 TA letter issued to firm.

Firm:
10/9/96 Orig.submission
2/9/98 Amendment
3/19/98 1 Amendment 3/19/98

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
AND 74-916

13. DOSAGE FORM
Liquid (Suspension)

14. POTENCY
100 mg/5 mL

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
J.Fan

DATE COMPLETED:
2/24/98

cc: ANDA 74-978
DIV FILE
Field Copy

Endorsements:

HFD-623/J.Fan/ 2/24/98 3/3/98
HFD-623/V.Sayeed, Ph.D./
x:\new\firmsam\alpharma\...rs&rev\74978n3.d
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74978

BIOEQUIVALENCE REVIEW(S)

Ibuprofen Oral Suspension, USP
100mg/5ml
ANDA #74-978
Reviewer: A.P.Patel
File: x:/wpfile/biofinal/74978a.297

Alpharma
Baltimore, MD
Submitted:
Feb. 10, 97
Nov. 11, 97

Review of an Amendment

The firm has submitted an amendment for review of dissolution data.

Deficiencies reported to the firm:

1. The application is incomplete. The acceptability of the application is dependent on an approved ANDA#74-916. At present, ANDA#74-916 is under review and has not been approved by the Agency.

2. The firm should provide dissolution data as per USP method and specifications (USP23-suppl 3,p2941).

Responses:
1. Status of ANDA#74-916 - acceptable.

2. The firm has submitted acceptable dissolution data as per USP method and specifications (USP23-suppl 3,p2941), attached.

Comments:
1. Dissolution data are acceptable.
2. Approveability of this application is based on an approved ANDA# 74-916, Ibuprofen Oral Suspension,USP 100mg/5ml, OTC.

Recommendation:

1. ANDA#74-978, for Ibuprofen Oral Suspension-Prescription, 100 mg/5ml submitted by Alpharma is dependent on an Approved ANDA#74-916 for Ibuprofen Oral Suspension-OTC, 100mg/5ml sponsored by Barre-National. The Agency has found ANDA#74-916 acceptable. Thus, ANDA#74-978 for Ibuprofen Oral Suspension-Prescription, 100 mg/5ml made by Alpharma is acceptable.

2. The dissolution testing conducted by Alpharma on its Ibuprofen Oral Suspension-Prescription, 100 mg/5ml, Lot#PA6196 and Children's Motrin, #PMM984, is acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of phosphate buffer pH 7.2, at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than f the labeled amount of Ibuprofen in the dosage form is dissolved in 60 minutes.

   The firm should be informed of the recommendations.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74978

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA:74-978 DRUG PRODUCT:Ibuprofen Oral Suspension USP

FIRM:Alpharma DOSAGE FORM: Liquid STRENGTH:100 mg/5 mL

CGMP STATEMENT/EIR UPDATE STATUS: EER OK as of 1/26/98

BIO STUDY: Acceptable per Bio review dated 1/9/98 (A.P. Patel)

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Compendial product. FDA MV not needed.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?):

Three months of accelerated (40°C/75%RH) and RT (25°-30°C) stability data are provided for lot #PA6196 (packaged in 2 and 16 oz containers).

Containers are the same as those listed in the container/closure section.

LABELING: Satisfactory per labeling review dated 2/25/98(C.Park).

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

Lot #PA6196

NDS source OK

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Same as the biobatch (lot #PA6196).

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

Production batch size:

Manufacturing process is essentially the same as those of the biobatch.

CHEMIST: J.Far 3/4/98 DATE:

SUPERVISOR: V.Sayeed, Ph.D.
x:\new\firmsam\alpharma\ltrs&rev\74978n2.sum DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74978

CORRESPONDENCE

ALPHARMA
U.S. Pharmaceuticals Division

12/23/96

October 9, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7200 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **Abbreviated New Drug Application**
Ibuprofen Oral Suspension USP, 100 mg/5 mL

Dear Mr. Sporn:

Alpharma, U.S. Pharmaceuticals Division (formerly Barre-National, Inc.) is herewith submitting an Abbreviated New Drug Application pursuant to 21 CFR §314.94(a) and Section 505(j) of the Federal Food, Drug and Cosmetic Act for the drug product Ibuprofen Oral Suspension USP, 100 mg/5 mL.

Ibuprofen Oral Suspension USP, 100 mg/5 mL is a prescription product which is based on the reference listed drug Motrin® (Ibuprofen) Suspension. Ibuprofen Oral Suspension USP, 100 mg/5 is indicated: *IN CHILDREN* for the reduction of fever in patients aged 6 months and older, for the relief of signs and symptoms of juvenile arthritis. And, *IN ADULTS* for relief of mild to moderate pain, for the treatment of primary dysmenorrhea, for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Alpharma is using the clinical study and all other data from ANDA 74-916 (Ibuprofen Oral Suspension-OTC) to support this application for prescription Ibuprofen Oral Suspension USP, 100 mg/5 ml. The decision to use this clinical study for our application is based on; (1) A study comparing the physicochemical properties of Children's Motrin® and Motrin® (Ibuprofen) Suspension performed at Alpharma, (2) U.S. patent #5,374,659 which both products reference, and (3) the summary basis of approval (SBOA) for Children's Motrin®. The SBOA indicates that Children's Motrin® and Motrin® (Ibuprofen) Suspension are the same product with two different NDA numbers assigned for administrative purposes. Also, both McNeil-PPC products are packaged and tested for release and stability in accordance to the provisions of the originally approved NDA 19-842. This data is included in section VI.3 of the application.

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

ALPHARMA™
U.S. Pharmaceuticals Division

The two Alpharma products, like those of the reference listed drug do not differ in any way except for labeling. A copy of the proposed draft labeling and side-by-side comparison are provided in section V of the application.

Production batches of Alpharma's Ibuprofen Oral Suspension-OTC, NDC#1255 and Ibuprofen Oral Suspension-Prescription, NDC#1270 to be produced at Alpharma-Baltimore will be manufactured using the Master Product and Control Record (MPCR) #1255. As a result, MPCR #1255 has been submitted in this application. It will be the packaging records for Ibuprofen Oral Suspension which will differentiate packaging of the drug product as an OTC or Prescription product with the correct NDC number being assigned. Also, the Packaged, Bulk, and Stability Specifications included in this application reflect the OTC Specification #1255.

The abbreviated application is being submitted as follows:

1) **Archival Copy** (Blue Folder) - consisting of two volumes which contains items required for an ANDA per 21 CFR § 314.94(a) plus all the information required under section 505(j)(2)(A)(B) of the FD&C Act (see Table of Contents of this application). Under separate cover, as required by 21 CFR 314.94(d)(5), Alpharma USPD Inc. hereby certifies that a field copy that contains (a) the technical section required by 21 CFR § 314.94(a)(9), (b) a copy of the 356h form, and (c) a certification that the copy of the technical section is the same as that contained in the archival and review copies, has been sent simultaneously to the Baltimore District Office.

2) **Review Copy** - which contains items for an ANDA per 21 CFR 314.94(d)(2) in two separate sections:

   Red Folder - Items described under 314.94(a)(2) through (a)(6), (a)(8),(a)(9), analytical methods, and analytical methods validation.

   Orange Folder - Items described under 314.94(a)(3), (a)(7), and (a)(8).

Sincerely,
Alpharma

Deborah Miran
Senior Director, Regulatory Affairs

DM:ah
Enclosures

Research & Development Center
The Johns Hopkins Bayview Campus. 333 Cassell Drive. Suite 3500. Baltimore. MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

ALPHARMA
U.S. Pharmaceuticals Division

January 30, 1998

NEW CORRESP
NC

Mr. Douglas Sporn, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7200 Standish Place, Room 150
Rockville, Maryland 20855-2773

Note statement about no litigation in place
Unknown
2/9/98

RE: **ANDA 74-978**
Ibuprofen Oral Suspension USP, 100 mg/5 mL

CORRESPONDENCE TO A PENDING APPLICATION

Dear Mr. Sporn:

In response to our January 30, 1998 telephone conversation with Mr. Peter Rickman of the FDA, we are providing certification that Alpharma, U.S. Pharmaceuticals Division has not received notification of legal action from McNeil-PPC, Inc., the holder of approved NDA 19-842 for Motrin® Suspension, and the owner of U.S. Patent No. 5,374,659, in response to the notice of noninfringement sent by Alpharma for our Ibuprofen Oral Suspension USP.

Notification of legal action was neither received during the 45 day period provided for in section 505(j)(4)(B)(iii) of the act, nor as of January 30, 1998, the date of this certification. The notice to McNeil-PPC was sent by certified mail, return receipt requested on May 16, 1997. As required by 21 CFR §314.95(e), the return receipt for this notice dated May 21, 1997 was sent to FDA in the June 9, 1997 amendment to this application.

Sincerely,

Vincent Andolina

Vincent Andolina
Manager, Regulatory Affairs

VA:va

FAX Copy to: Mr. Peter Rickman, OGD

RECEIVED
FEB 0 3 1998
GENERIC DRUGS

Madam
2-4

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

February 9, 1998

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

Re: **ANDA #74-978**
Ibuprofen Oral Suspension USP, 100 mg/5 mL

MINOR AMENDMENT

Dear Mr. Sporn:

As instructed in the Agency's tentative approval letter (enclosed) dated January 30, 1998, Alpharma, U.S. Pharmaceuticals Division, herewith submits a minor amendment for subject ANDA. The letter states,

> "Please provide the Agency, at least 45 days prior to March 24, 1998, an amendment to this application. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated as a MINOR AMENDMENT in your cover letter."

In this amendment we are providing updated chemistry, manufacturing, and controls data. The following documents have been updated: (1) Raw material specifications for Purified Water USP, and Hydroxypropyl Methylcellulose JSP, (2) Master Product and Control Record for Ibuprofen Oral Suspension USP, 100 mg/5 mL, and (3) Packaging Components for the 2 oz closure, 16 oz container, and dosage cup. We have enclosed each of the updated documents, and a comparison of the document to the version previously submitted in this application.

RECEIVED
FEB 10 1998
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Alpharma acknowledges that prior to issuance of the final approval letter by the Agency, our product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" prior to expiration of this exclusive marketing period on March 24, 1998.

In accordance with 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this minor amendment and has been sent to the Baltimore, MD FDA District Office.

We trust that our response fully addresses the Agency's concerns.

Sincerely,
Alpharma

Vincent Andolina

Vincent Andolina
Manager, Regulatory Affairs

VA:ah
Enclosures

Alpharma USPD Inc.

Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

March 19, 1998

Office of Generic Drugs
CDER, Food and Drug Administration
Attn.: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] AMENDMENT
/M

Re: **Ibuprofen Oral Suspension, 100 mg/5 mL (℞ Labeling)**
ANDA 74-978

TELEPHONE AMENDMENT TO A TENTATIVELY APPROVED APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR § 314.96(a), Alpharma USPD hereby submits a telephone amendment for our tentatively approved ANDA for Ibuprofen Oral Suspension, 100 mg/5 mL (℞ labeling).

Reference is made to the telephone deficiency communicated on March 12, 1998 by Mr. Jim Wilson, Project Manager and Dr. Vilayat A. Sayeed, concerning our February 9, 1998 Minor Amendment updating the chemistry, manufacturing and controls section of this application.

The Agency's comments have been restated and our responses follow.

1. **Submit calibration data for the dosage cup.**

We submitted the calibration study for the dosage cup on pages 073 to 082 of our Feb. 9, 1998 Minor Amendment. That study calculated the corrections needed to an existing vendor's cup, to be applicable for our product.

Please refer to Attachment 1 of this Telephone Amendment (pages 03 to 07) for an updated Release Specification for the dosage cup, Alpharma Part FT 053. The accuracy of the calibration markings of these dosage cups will be verified for each incoming shipment.

Please refer to Attachment 2 of this Telephone Amendment (page 08) for our recent verification of the calibration markings on the dosage cups.

RECEIVED
MAR 20 199[illegible]
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

2. **It is unclear whether the HDPE resin for the 16 fl. oz. bottle has changed. If the resin has changed, submit accelerated stability data.**

Our February 9 minor amendment (page 46 and following) described the addition of as a qualified resin designation, to our ANDA, for the 16 oz. white HDPE bottle.

Information supplied to us by the resin manufacturer indicates no qualitative modifications have been made to the HDPE resin, hence, the HDPE resin has not changed. The change from ' to ' in the resin designation prefix refers to the use of current technology for manufacturing the ' designated resin, while the -designated resin is manufactured using previous technology. The resin is being phased out by the resin manufacturer.

This technology update subsequently necessitated a small increase in the No chemical change was made in the This increase in the level is designated by the change in suffix from "

We are informed that contains a more detailed description of the revised designations above.

We apologize for any confusion that our February 9th Minor Amendment may have caused. We trust that our response adequately addresses the issues raised by the Agency's March 12, 1998 telephone deficiency.

In case of any questions or additional concerns, please call me at 410-558-7250 extension 209 or send a facsimile to my attention at 410-558-7258.

In accordance with 21 CFR § 314.96(b), Alpharma USPD certifies that the field copy is a true copy of the telephone amendment to the application and has been sent to the FDA Baltimore district office.

Sincerely,
ALPHARMA USPD INC.
Vincent Andolina

Vincent Andolina
Manager Regulatory Affairs
VA:va
Enclosures
K:\759\REGFILES\PRODUCTS\1270\SUBMISS\PHONEAMD.WPD