CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

APPROVAL LETTER

ANDA 76-112

OCT 31 2001

Dr. Reddy's Laboratories, Inc.
Attention: Paul Campanelli
U.S. Agent for: Dr. Reddy's Laboratories Limited
One Park Way
Upper Saddle River, NJ 07458

Dear Sir:

This is in reference to your abbreviated new drug application dated February 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ibuprofen Tablets USP, 400 mg, 600 mg and 800 mg.

Reference is also made to your amendments dated September 7, October 1, and October 24, 2001.

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 Tablets USP, 400 mg, 600 mg, and 800 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Motrin® Tablets, 400 mg, 600 mg, and 800 mg, respectively, of McNeil Consumer Products Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, 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 and 314.98. 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 that 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/ for
10/31/2001

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

APPROVED DRAFT LABELING

DR. REDDY'S

NDC 55111-002-06

IBUPROFEN

Tablets, USP

400 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 400 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

LOT EXP

000030

DR. REDDY'S

NDC 55111-002-11

IBUPROFEN

Tablets, USP

400 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 400 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

LOT EXP

DR. REDDY'S

NDC 55111-003-06

IBUPROFEN
Tablets, USP

600 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 600 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

LOT

EXP

DR. REDDY'S

NDC 55111-003-11

IBUPROFEN
Tablets, USP

600 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 600 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

LOT

EXP

DR. REDDY'S

100 Tablets

NDC 55111-004-06

IBUPROFEN
Tablets, USP

800 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 800 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

OCT 3 1 2001

LOT

EXP

DR. REDDY'S

500 Tablets

NDC 55111-004-11

IBUPROFEN
Tablets, USP

800 mg

Rx only

Each tablet contains:
Ibuprofen, USP ..... 800 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

APPROVED

OCT 3 1 2001

LOT

EXP

Ibuprofen Tablets, USP

Rx Only

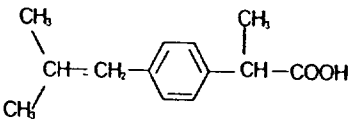
Issued: September 2001

APPROVED

OCT 31 2001

DESCRIPTION

en tablets contain the active ingredient ibuprofen, which is (±) - 2 - (*p* - isobutylphenyl) propionic acid. Ibuprofen is e powder with a melting point of 74-77°C and is very slightly soluble in water (< 1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.
The structural formula is represented below:



Ibuprofen, a nonsteroidal anti-inflammatory agent, is available in 400 mg, 600 mg, and 800 mg tablets for oral administration. Inactive ingredients: microcrystalline cellulose, copovidone (plasdone-S630), sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, opadry white (OY-LS-58900), polysorbate 80.

CLINICAL PHARMACOLOGY

Ibuprofen tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other non-steroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, ibuprofen has been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder 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 patients with rheumatoid arthritis treated for up to one year, 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 show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using ^{51}Cr-tagged red cells indicate that fecal blood loss associated with ibuprofen tablets in doses up to 2400 mg daily did not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, ibuprofen has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal (see ADVERSE REACTIONS) and CNS side effects.

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

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 intrauterine fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The possible mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

The ibuprofen in ibuprofen tablets is rapidly absorbed. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When ibuprofen is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

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

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[*p*-(2hydroxymethyl-propyl)phenyl] propionic acid and metabolite B (37%), (+)-2-[*p*-carboxypropyl)phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and %, respectively.

INDICATIONS AND USAGE

Ibuprofen tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Ibuprofen tablets is indicated for relief of mild to moderate pain.

Ibuprofen tablets is also indicated for the treatment of primary dysmenorrhea.

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

Controlled clinical trials to establish the safety and effectiveness of ibuprofen in children have not been conducted.

CONTRAINDICATIONS

Ibuprofen tablets should not be used in patients who have previously exhibited hypersensitivity to the drug, or in individuals with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-Inflammatory 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 nonsteroidal anti-inflammatory drugs. 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 nonsteroidal anti-inflammatory drugs 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 (eg, 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 nonsteroidal anti-inflammatory agents in causing such reactions. High doses of any such agents 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.

PRECAUTIONS

General Precautions

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving ibuprofen tablets, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

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.

Ibuprofen like other nonsteroidal anti-inflammatory agents, 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 (but within the normal range) in normal subjects. 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.

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.

In order to avoid exacerbation of disease or 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.

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.

Liver Effects: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver 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 SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction 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 (eg eosinophilia, rash, etc.), ibuprofen should be discontinued.

Hemoglobin Levels: In cross-study comparisons 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. With daily doses of 3200 mg, the total decrease in hemoglobin may exceed 1 gram; if there are no signs of bleeding, it is probably not clinically important.

In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 gram 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.

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

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, 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 a nonsteroidal anti-inflammatory drug 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 nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment 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.

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.

Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis and have a major role in the treatment of pain, 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 nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this followup (see Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-inflammatory therapy).

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 when administered to individuals on coumarin-type anticoagulants. However, 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 nonsteroidal anti-inflammatory agents, 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 nonsteroidal anti-inflammatory drugs, probably reduces the tubular secretion of methotrexate based on *in-vitro* studies in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if ibuprofen is administered concomitantly with methotrexate.

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

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: 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. 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 pregnancy.

Nursing Mothers: 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, ibuprofen is not recommended for use in nursing mothers.

ADVERSE REACTIONS

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

In controlled studies 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 at an incidence greater than 1% are listed in the table. Those reactions listed in Column one 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: Column two of the table lists reactions with therapy with ibuprofen where the probability of a causal relationship exists; for the reactions in Column three, a causal relationship with ibuprofen has not been established.

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within the ranges reported in the table.

Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship**	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown**
GASTROINTESTINAL Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence).	Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests, pancreatitis.	
CENTRAL NERVOUS SYSTEM Dizziness*, headache, nervousness	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma (See PRECAUTIONS)	Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri
DERMATOLOGIC Rash* (including maculopapular type), pruritus	Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia.	Toxic epidermal necrolysis, photoallergic skin reactions
SPECIAL SENSES Tinnitus	Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS)	Conjunctivitis, diplopia, optic neuritis, cataracts
HEMATOLOGIC	Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs Positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS)	Bleeding episodes (eg epistaxis, menorrhagia)
METABOLIC/ENDOCRINE Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis
CARDIOVASCULAR Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS)	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations.	Arrhythmias (sinus tachycardia, sinus bradycardia)
ALLERGIC	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS)	Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema.
RENAL	Acute renal failure (see PRECAUTIONS), decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria.	Renal papillary necrosis
MISCELLANEOUS	Dry eyes and mouth, gingival ulcer, rhinitis	

* Reactions occurring in 3% to 9% of patients treated with ibuprofen. (Those reactions occurring in less than 3% of the patients are unmarked.)

** Reactions are classified under "*Probable Causal Relationship (PCR)*" if there has been one positive rechallange or if three or more cases occur which might be causally related. Reactions are classified under "*Causal Relationship Unknown*" if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE

Approximately 1½ hours after the reported ingestion of from 7 to 10 ibuprofen tablets (400 mg), a 19-month old child weighing 12 kg was seen in the hospital emergency room, apneic and cyanotic, responding only to painful stimuli. This type of stimulus, however, was sufficient to induce respiration. Oxygen and parenteral fluids were given; a greenish-yellow fluid was aspirated from the stomach with no evidence to indicate the presence of ibuprofen. Two hours after ingestion the child's condition seemed stable; she still responded only to painful stimuli and continued to have periods of apnea lasting from 5 to 10 seconds. She was admitted to intensive care and sodium bicarbonate was administered as well as infusions of dextrose and normal saline. By four hours post-ingestion she could be aroused easily, sat by herself and respond to spoken commands. Blood level of ibuprofen was 102.9 µg/mL approximately 8½ hours after accidental ingestion. At 12 hours she appeared to be completely recovered.

In two other reported cases where children (each weighing approximately 10 kg) accidentally, acutely ingested approximately 120 mg/kg, there were no signs of acute intoxication or late sequelae. Blood level in one child 90 minutes after ingestion was 700 µg/mL-about 10 times the peak levels seen in absorption excretion studies.

A 19-year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was noted. After hospitalization, parenteral hydration and three days bed rest, he recovered with no reported sequelae.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen.

DOSAGE AND ADMINISTRATION

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer ibuprofen tablets with meals or milk.

Suggested Dosage: 1200 mg-3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). 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.

The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of ibuprofen than do patients with osteoarthritis.

The smallest dose of ibuprofen that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (See CLINICAL PHARMACOLOGY for effects of food on rate of absorption).

The availability of three tablet strengths facilitates dosage adjustment.

In chronic conditions, a therapeutic response to therapy with ibuprofen 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.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than the 400 mg dose.

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

HOW SUPPLIED

Ibuprofen tablets are available in the following strengths, colors and sizes:

400 mg (white, round, biconvex film coated tablets embossed 'C101' on one side and '400' on other side)
Bottles of 100
Bottles of 500

600 mg (white, modified capsule shaped film coated tablets embossed 'C102' on one side and '600' on other side)
Bottles of 100
Bottles of 500

800 mg (white, capsule shaped, biconvex film coated tablets embossed 'C103' on one side and '800' on other side)
Bottles of 100
Bottles of 500

Store at controlled room temperature 20° to 25°C (68° to 77° F) [see USP]

Rx only

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: September 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

CHEMISTRY REVIEW(S)

AUG - 8 2001

38. Chemistry comments to be provided to the applicant.

ANDA 76-112 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen Tablets USP, 400 mg, 600 mg and 800 mg

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. Please identify the composition of the ink, Opadry White OY-LS-58900 by the percent per weight.

2. We request that you submit the limits for each test indicated in your in-process testing protocol, which includes the following stages: For monitoring only as a limit is not acceptable.

3. We request that your drug product maximum individual impurity and total impurities limit be the same at the drug substance or demonstrate that the impurities are degradants and increase with storage/time.

4. Your dissolution procedure refers to a General Test procedure, which employs pooled dissolution testing. Also, pages 2947 and 2989 indicate pooled samples for dissolution. Please clarify as to how the dissolution procedure was conducted (individual analysis or pooled analysis) for the ANDA submission, and stability testing. What is the proposed procedure for the future commercial lots? What is your definition of the term "pooled sample"?

5. It is indicated that batch #G001 was divided into batch numbers G001A 400 mg tablet) and G001B 600 mg tablets). Are you using the same batch number (G001) for the 800 mg tablets?

Sincerely yours,

for Mayank Rayen

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMIST'S REVIEW NO. 2

2. ANDA **76-112**

3. NAME AND ADDRESS OF APPLICANT
Dr. Reddy Laboratories Ltd.
66 South Maple Avenue
Ridgewood, NJ 07450

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of McNeil's, MOTRIN® (NDA 17-463). Patent certification and exclusivity statement are provided (pp. 003-010).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Ibuprofen Tablets

7. PROPRIETARY NAME
Motrin®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm			**FDA**	
Orig. submission		2/5/01		
Amendment		3/5/01	Acknowledgment letter	3/7/01
Amendment	(phone)	3/20/01	Labeling review	3/30/01
			Bio review	4/6/01
			Deficiency letter	8/8/01
Amendment		9/17/01		
Amendment	(Major)	10/1/01		
Amendment	(Phone)	10/24/01		

This review covers submission dated 10/1 and 10/24/01.

10. (PROPOSED) INDICATION(S) FOR USE
Anti-inflammatory -
Indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, for relief of mild to moderate pain and for the treatment of primary dysmenorrhea.

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets (Oral)

14. STRENGTH(S)
400 mg, 600 mg and 800 mg

15. CHEMICAL NAME AND STRUCTURE USP 23 (pp. 1360-1361)

Drug substance and drug product are official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS
a. Application **ADEQUATE** for approval.
b. Labeling: **ACCEPTABLE** dated 10/12/01.
b. Bio review: **ADEQUATE** dated 4/30/01
c. Drug Master File **ADEQUATE** dated 4/00.
d. Methods validation: **Not required**
e. Establishment evaluation: **ACCEPTABLE**, dated 3/16/01.

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVED

19. REVIEWER: Raymond Brown

DATE COMPLETED: October 24, 2001

Page(s) 18

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Alen Rev 2

10/24/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-112 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen tablets USP, 400 mg, 600 mg, and 800 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for

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

here 1.1

Ibuprofen Tablets, USP	**Dr. Reddy's Laboratories Limited**
400, 600 & 800 mg	**(Formerly Cheminor Drugs Limited)**
ANDA 76-112	**Ridgewood, NJ**
Reviewer: Lin-Whei Chuang	**Submission Date:**
V:\FIRMSNZ\REDDY\LTRS&REV\76112SDW.201	**February 2, 2001**

Review of One Fasting and One Non-Fasting Bioequivalence Studies; Dissolution Data; and Waiver Request

Background:

Chemical Nature:
Ibuprofen is a colorless crystalline stable solid. It is relatively insoluble in water and readily soluble in most organic solvent.

Reference Listed Drug (RLD):
Motrin 800 mg tablets of McNeil Consumers - Pharmacia & Upjohn approved through NDA #17463. It is also available as prescription drugs in 300 mg, 400 mg and 600 mg tablets, and 100 mg and 200 mg tablets in OTC drugs.

Pharmacology:
NSAID

Food Effects:
It was stated in the labeling of RLD that "Take with food or milk if occasional and mild heartburn, upset stomach or stomach pain occurs with use".

Indications and Recommended dose:
800 mg every 4-6 hours indicated as pain reliever and/or fever reducer.

Submission History:
1. This is not an EVA submission.

2. There are many generic ibuprofen tablets currently available in the market. Present submission of Dr. Reddy's Laboratories Limited contains 1 fasting BE study and 1 non-fasting, food study on the 800 mg tablet; dissolution data for all 3

strengths; and waiver requests for the 400 mg and 600 mg strengths.

Comparative Formulations - Not For Release through FOI:

The formulation data submitted by the firm (see attached copy from p. 180, Vol. 1.2) indicated that all 3 strengths of test product are proportionally similar per definition 1 of the general BA/BE guidance.

***In Vivo* Fasting Bioequivalence Study - 1 x 800 mg:**

Objective:
To compare the single-dose bioavailability of Reddy's ibuprofen 800 mg tablet and Motrin® 800 mg tablets of Pharmacia & Upjohn under fasting conditions.

Sites, Dates, and Principal Investigator:
Clinical: Phoenix International Life Sciences, Montreal, Canada
3/13-14/00 (period 1)
3/16-17/00 (period 2)
S. Serfaty, M.D.

Analytical: Phoenix International Life Sciences, Montreal, Canada
3/23-4/12/00

The maximal storage period for the study samples was 29 days.

Design and IRB:
A randomized, 2-way crossover study conducted in 24+2 male subjects under fasting conditions.

Protocol nd the informed consent form were approved by the Institutional Review Board of Phoenix International Life Sciences on 2/29/00.

Washout Period:
3 days

Subject Selection:
Twenty-six (26) male Caucasian subjects with 21-45 years of age were selected based on the screening procedure and exclusion

criteria stated in the protocol (pp. 125-126, Vol. 1.2). They had the mean age of 32.9 years, mean height of 176.5 cm, and mean weight of 75.5 Kg.

Restriction:
Subjects were instructed of the prohibitions stated in the protocol (p. 126, Vol. 1.2).

Treatments:
Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the morning of 3/14/00 according to the randomly assigned sequence (AB for #4, 5, 8, 9, 11, 12, 15, 16, 18, 20, 22, 23, 25; and BA for the rest of subjects):

Treatment A - Test Drug: One ibuprofen 800 mg tablet, USP, Cheminor Drugs, batch #G001, potency 98.6%, batch size tablets.

Treatment B - Reference Drug: One Motrin® 800 mg tablet (ibuprofen 800 mg tablet, USP, Pharmacia & Upjohn Company, lot #33CTT, potency 101.6%, expires 10/03.

In the morning of 3/17/00, subjects received the alternate treatment.

Post-dose Procedure:
1. Subjects remained fasted and ambulatory for 4 hours post-dose.
2. Fluids were restricted from 1 hour before to 1 hour after dosing except water administered with the study drug.
3. Blood samples were drawn at 0, 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after dosing. Plasma samples were stored in duplicate tubes at -22°C pending assay of ibuprofen.
4. Subjects left the clinical facility after the 12-hour blood draw.

Study Drug Accountability:
It was stated in the protocol that any unused study drug would be retained per Agency's requirements.

Analytical Method:
Ibuprofen and internal standa... were extracted from plasma by and injected onto with

Pre-study and during-study validations are presented below in Tables 1&2:

TABLE 1: PRE-STUDY ASSAY VALIDATION FOR IBUPROFEN ASSAY

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.3, 20.012, 40.024, 0.1, 100.059	0.1, 0.2, 2.504, 7.511, 25.037, 38.057, 45.067, 50.075, 90.134, 125.187
Between-Batch Precision (%CV)	1.3 - 15.7	0.5 - 6.8
Between-Batch Accuracy (% Actual)	94.8 - 98.5	95.1 - 110.4
Within-Batch Precision of QC (%CV)	1.3 - 10.7	
Within-Batch Accuracy of QC (% Actual)	92.5 - 99.8	
Linearity	R >0.9990	
Linear Range (ng/mL)	0.1 - 125.187	
Sensitivity/LOQ (ng/mL)	0.1	
Recovery (%)	91.5 - 99.7 (4 QC samples of 0.3-100.059 ng/mL) 101.97-103.24 (internal std. of 0.808-3.203 ug/mL)	
Stability in Plasma/Serum (%) a) 5.5 Hr @ 22°C b) 3 Freeze-Thaw Cycles c) 105 days at -22°C	a) 99.2 - 100.9 b) 100.1 - 100.8 c) 90.0 - 103.0	
Specificity	Specific, no interference noted in blank plasma.	

TABLE 2: DURING STUDY ASSAY VALIDATION -- FASTING STUDY

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.299, 39.928, 99.82	0.101, 0.202, 2.5, 7.501,25.003, 37.908, 45.167, 50.007, 112.918, 125.017
Between-Batch Precision (%CV)	1.3 - 5.5	0.7 - 7.9
Between-Batch Accuracy (% Actual)	97.3 - 98.8	97.7 - 103.2
Linearity	r>0.9996	
Linear Range (ng/mL)	0.101 - 125.017	
Sensitivity/LOQ (ng/mL)	0.101	

Comments on the Analytical Method:
The method and data presented in this analytical section are acceptable.

Results:

Drop-out:
None

Protocol Deviation:
None

Adverse Events:
Two (2) cases of mild headaches were reported, both occurred during treatment A and were judged possibly related to the study drug.

Plasma Concentration and Pharmacokinetic Analysis
A total of 768 plasma samples from 24 subjects were assayed for ibuprofen in 14 batches of assay. A total of 12 samples were repeated because of poor chromatography, anomalous value, or high/low standard missing. The 4 samples repeated due to anomalous value were each repeated twice and the median values were reported:

Subject #	Period (TRT)	Hour	Initial	1st Repeat	2nd Repeat	Final
14	1 (B)	4	42.062	42.526	44.785	42.526
16	1 (A)	4	47.736	46.992	48.387	47.736
12	2 (B)	6	35.902	8.857	9.211	9.211
23	2 (B)	6	42.583	42.792	44.291	42.792

Among the above 4 samples, 3 coincided with the observed Tmax of the time-concentration profile. The one from subject #12 was not, or adjacent to, the Tmax.

The mean plasma concentrations of ibuprofen at each sampling time point after both treatments are presented in Figure 1. The same data and the mean pharmacokinetic parameters of ibuprofen are presented in Tables 3-4.

TABLE 3: ARITHMETIC MEAN PLASMA IBUPROFEN CONCENTRATIONS [ng/mL] VERSUS TIME AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)

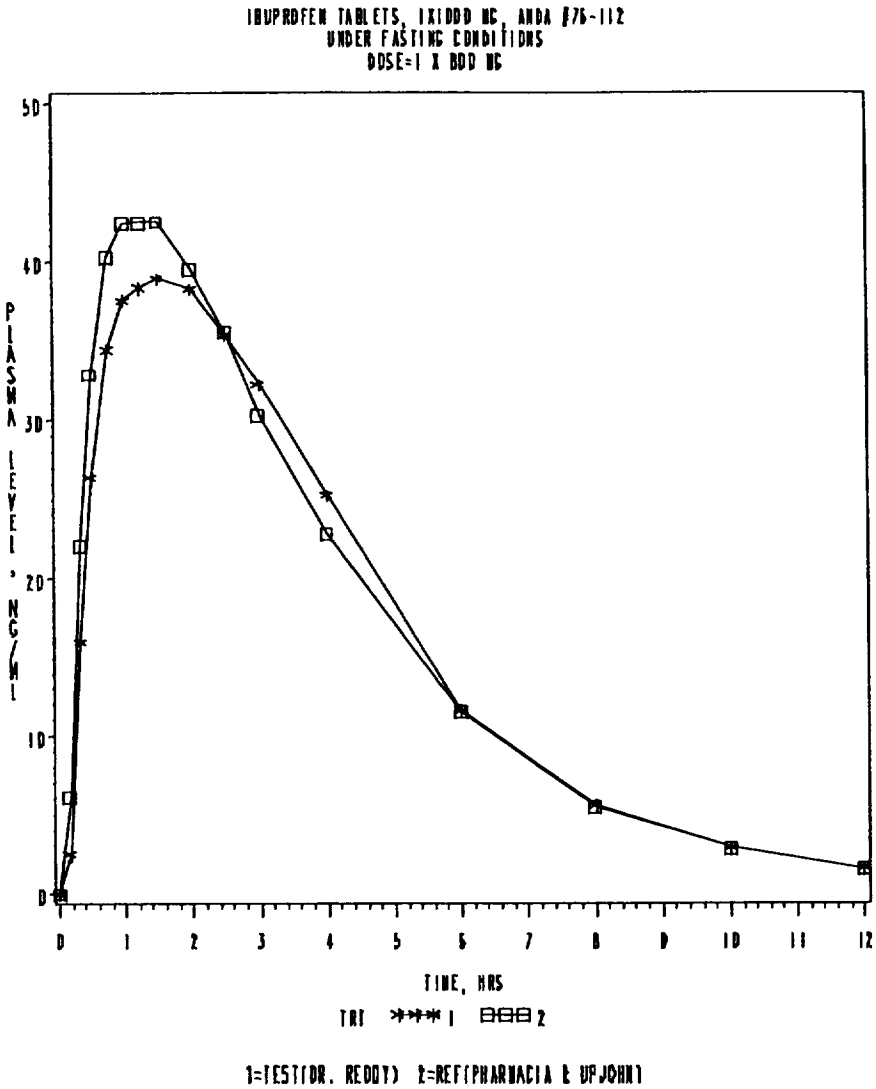
	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
0	0.000	0.000	0.000	0.000	.
0.167	2.500	2.963	6.125	7.182	0.408
0.33	16.080	11.668	22.026	14.020	0.730
0.5	26.411	14.359	32.876	17.637	0.803
0.75	34.475	16.116	40.266	19.311	0.856
1	37.595	16.267	42.471	19.346	0.885
1.25	38.397	16.064	42.486	18.035	0.904
1.5	38.972	14.673	42.518	15.584	0.917
2	38.331	13.304	39.571	12.547	0.969
2.5	35.445	12.725	35.566	10.819	0.997
3	32.264	11.405	30.326	9.050	1.064
4	25.292	8.690	22.811	8.117	1.109
6	11.648	6.136	11.580	7.807	1.006
8	5.589	2.795	5.482	3.026	1.019
10	2.882	1.536	2.870	1.597	1.004
12	1.587	0.916	1.578	0.904	1.005

TABLE 4: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS OF IBUPROFEN AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI (NG*HR/ML)	196.83	43.51	199.83	45.97	0.98
AUCT (NG*HR/ML)	191.71	41.09	194.75	43.99	0.98
CMAX (NG/ML)	48.32	10.00	51.36	11.97	0.94
KE	0.34	0.05	0.33	0.04	1.02
LAUCI	192.53a	0.21c	195.03a	0.22c	0.99b
LAUCT	187.77a	0.21c	190.24a	0.22c	0.99b
LCMAX	47.29a	0.22c	49.93a	0.25c	0.95b
THALF	2.11	0.35	2.14	0.27	0.99
	(1.52-3.23)		(1.72-2.82)		
TMAX	2.02	1.29	1.82	1.28	1.11

a = GEOMETRIC MEANS
b = RATIO OF GEOMETRIC MEANS
c = SD OF LOG-TRANSFORMED PARAMETER

FIG 1: PLASMA IBUPROFEN LEVELS



Statistical Analysis:

ANOVA was conducted by the firm on the non-transformed and log-transformed AUCT, AUCI and CMAX of ibuprofen using SAS GLM with model including sequence, subject within sequence, treatment and period as factors. No significant treatment effect was detected for any of the parameters. Results presented in Table 5 are from ANOVA conducted by the reviewer which are identical to those reported by the firm:

TABLE 5: LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS FOR IBUPROFEN PHARMACOKINETIC PARAMETERS AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)

PARAMETER	TEST LSM	REF. LSM	TEST/REF.	90% CONF. INT.	Root MSE[a]
AUCI [ng·hr/mL]	196.83	199.83	0.98	95.29 - 107.71	---
AUCT [ng·hr/mL]	191.71	194.75	0.98	95.23 - 101.65	---
CMAX [ng/mL]	48.32	51.36	0.94	84.19 - 103.98	---
LAUCI[b]	192.53	195.03	0.99	95.44 - 102.11	0.068648
LAUCT[b]	187.77	190.24	0.99	95.45 - 102.07	0.068025
LCMAX[b]	47.29	49.93	0.95	84.62 - 106.00	0.227249

a = From ANOVA Table b = Geometric LS Mean

Comments on Results of Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters and the 90% confidence intervals conducted by the firm has been confirmed by the reviewer using data submitted in the data diskette. The 90% confidence intervals of LNAUCT, LNAUCI and LNCMAX are all within the acceptable range of 80-125%.

2. Three re-assayed samples due to pharmacokinetic anomaly coincided with the observed Tmax of time-concentration profile (subject #14, hour 4, treatment B; #16, hour 4, treatment A; and #23, hour 6, treatment B). However, after deleting data from these 3 subjects, the outcome of the study remains unchanged.

3. Results of this fasting bioequivalence study are acceptable.

***In Vivo* Non-Fasting Bioequivalence Study - 1 x 800 mg:**

Objective:
To compare the single-dose bioavailability of Reddy's ibuprofen 800 mg tablet and Motrin® 800 mg tablets of Pharmacia & Upjohn under fed conditions; and to compare the bioavailability of Reddy's ibuprofen 800 mg tablet under fed and fasted conditions.

Sites, Dates, and Principal Investigator:
Clinical: Phoenix International Life Sciences, Montreal, Canada
5/18-19/00 (period 1)
5/25-26/00 (period 2)
6/1-2/00 (period 3)
S. Serfaty, M.D.

Analytical: Phoenix International Life Sciences, Montreal, Canada
6/8-7/7/00

The maximal storage period for the study samples was 49 days.

Design and IRB:
A randomized, 3-way crossover study conducted in 18 male subjects under non-fasting and fasting conditions.

Protocol and the informed consent form were approved by the Institutional Review Board of Phoenix International Life Sciences on 5/2/00.

Washout Period:
7 days

Subject Selection:
Eighteen (18) male Caucasian subjects with 18-45 years of age were selected based on the screening procedure and exclusion criteria stated in the protocol (pp. 1079-1080, Vol. 1.5). They had the mean age of 31.1 years, mean height of 173.9 cm, and mean weight of 69.7 Kg.

Restriction:
Subjects were instructed of the prohibitions stated in the protocol (p. 1080, Vol. 1.5).

Treatments:
Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the mornings of 5/19/00, 5/26/00, and 6/2/00 according to one of the following randomly assigned sequences:

ABC: #1, 2, 11	BCA: #9, 13, 14	CAB: #5, 15, 17
ACB: #6, 7, 10	BAC: #12, 16, 18	CBA: #3, 4, 8

Treatment A - Test Drug: One ibuprofen 800 mg tablet, USP, Cheminor Drugs, batch #G001, given under fasting conditions.

Treatment B - Test Drug: One ibuprofen 800 mg tablet, USP, Cheminor Drugs, given 30 minutes after the initiation of a standard breakfast*.

Treatment C - Reference Drug: One Motrin® 800 mg tablet (ibuprofen 800 mg tablet, USP, Pharmacia & Upjohn Company, lot #33CTT, given 30 minutes after the initiation of a standard breakfast*.

* = 240 mL of whole milk, 180 mL of orange juice, buttered English muffin, 1 fried egg, hash brown potatoes, 1 slice of American cheese and 1 slice of Canadian bacon.

Post-dose Procedure, safety monitoring and study drug accountability were the same as those conducted for the fasting study except that blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours post-dose.

Analytical Method:
The analytical method is the same as that in the fasting study. The during study validation data are presented in Table 6:

TABLE 6: DURING STUDY ASSAY VALIDATION - Non-FASTING STUDY

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.3, 29.994, 59.988	0.1, 0.2, 3.753, 11.009, 35.028, 45.036, 57.546, 67.554, 75.06

Between-Batch Precision (%CV)	2.0 - 7.9	1.2 - 7.1
Between-Batch Accuracy (% Actual)	97.8 - 104.8	96.2 - 102.8
Linearity	r >0.9993	
Linear Range (ng/mL)	0.1 - 75.06	
Sensitivity/LOQ (ng/mL)	0.1	

Comments on the Analytical Method:
Data presented in this analytical section are acceptable.

Results:

Drop-out:
One (1) subject, #11 assigned sequence of ABC , chose to withdraw from the study after the completion of period 2 due to personal reason. It was stated in the protocol that samples from subjects who completed at least 2 periods will be assayed and included in statistical analysis. Therefore his samples were included in the analysis.

Protocol Deviation:
None

Adverse Events:
Only 1 case of mild headache was reported which occurred during treatment A (test-fasting) and was judged possibly related to the study drug.

Plasma Concentration and Pharmacokinetic Analysis
A total of 954 plasma samples from 18 subjects (subject # 11 only gave samples for treatment A and B) were assayed for ibuprofen in 19 batches of assay. A total of 7 samples were repeated because of exceeding curve limits, loss in processing, or anomalous value. Only 1 sample was repeated due to anomalous value which was a none-zero (0.108 ng/mL) pre-dose value and was repeated twice, both confirms the zero value.

The mean plasma concentrations of ibuprofen at each sampling time point after both treatments are presented in Figure 2. The same data and the mean pharmacokinetic parameters of ibuprofen are presented in Tables 7-8.

TABLE 7: ARITHMETIC MEAN PLASMA IBUPROFEN CONCENTRATIONS [ng/mL] VERSUS TIME AFTER 1 X 800 MG TABLET UNDER NON-FASTING AND FASTING CONDITIONS (N=18 EXCEPT FOR REF.-FED WHERE N=17)

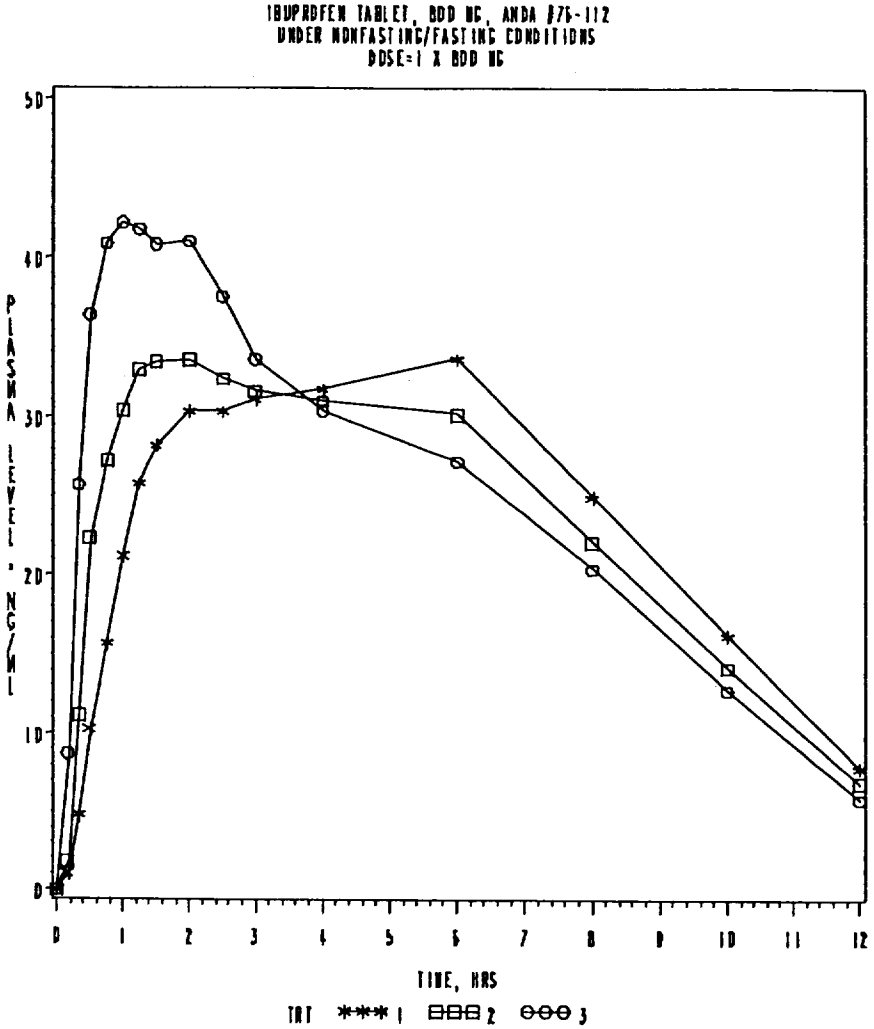
	TEST-FED	SD	REF.-FED	SD	TEST-FAST	SD	TEST-FED/REF.-FED
TIME HR							
0	0.000	0.000	0.000	0.000	0.000	0.000	.
0.25	1.069	2.751	1.824	4.516	8.688	7.357	0.586
0.5	4.754	9.886	11.202	15.584	25.700	15.768	0.424
0.75	10.303	14.740	22.292	22.635	36.381	18.422	0.462
1	15.660	17.020	27.287	21.725	40.856	19.970	0.574
1.25	21.187	18.029	30.435	19.038	42.153	19.970	0.696
1.5	25.800	19.751	32.927	18.059	41.731	18.450	0.784
1.75	28.238	18.820	33.464	16.358	40.825	16.290	0.844
2	30.412	18.315	33.542	15.083	40.987	14.575	0.907
2.5	30.362	11.767	32.388	12.917	37.541	12.113	0.937
3	31.140	8.497	31.631	9.626	33.615	9.936	0.984
3.5	31.734	7.703	30.992	10.532	30.397	7.943	1.024
4	33.650	8.777	30.201	13.214	27.208	7.333	1.114
5	24.935	7.949	22.067	11.042	20.372	11.445	1.130
6	16.235	5.037	14.168	6.567	12.772	6.260	1.146
8	7.857	2.506	6.880	3.318	5.824	2.738	1.142
10	3.820	1.553	3.403	1.628	2.829	1.338	1.123
12	2.088	1.085	1.721	0.870	1.394	0.772	1.213

TABLE 8: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS OF IBUPROFEN AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=18 EXCEPT FOR REF.-FED WHERE N=17)

	TEST-FED	SD	REF.-FED	SD	TEST-FAST	SD	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
PARAMETER								
AUCI	191.89	23.65	193.29	29.56	207.89	30.39	0.99	0.92
AUCT	184.61	24.33	188.24	28.51	203.94	29.50	0.98	0.91
CMAX	45.96	11.75	50.11	9.29	54.43	9.61	0.92	0.84
KE	0.35	0.07	0.35	0.05	0.37	0.04	0.98	0.94
LAUCI	190.56a	0.12c	191.06a	0.16c	205.79a	0.15c	1.00b	0.93b
LAUCT	183.17a	0.13c	186.13a	0.16c	201.93a	0.15c	0.98b	0.91b
LCMAX	44.71a	0.24c	49.23a	0.20c	53.61a	0.18c	0.91b	0.83b
THALF	2.11	0.64	2.00	0.31	1.89	0.19	1.06	1.12
TMAX	2.89	1.25	2.01	1.09	2.15	1.32	1.43	1.34

a = GEOMETRIC MEANS
b = RATIO OF GEOMETRIC MEANS
c = SD OF LOG-TRANSFORMED PARAMETERS

FIG 2. PLASMA IBUPROFEN LEVELS



Statistical Analysis:
The firm conducted ANOVA on non-transformed and log-transformed AUCT, AUCI and CMAX of ibuprofen using SAS GLM with model including sequence, subject within sequence, treatment and period as factors. Results presented in Table 9 are from ANOVA conducted by the reviewer which are identical to those reported by the firm.

TABLE 9: LEAST-SQUARES MEAN OF PK FOR IBUPROFEN AFTER 1 X 800 MG TABLET UNDER NON-FASTING AND FASTING CONDITIONS (N=18)

	TEST-FED	REF.-FED	TEST-FAST	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
PARAMETER					
AUCI	191.89	192.94	207.89	0.99	0.92
AUCT	184.61	188.03	203.94	0.98	0.91
CMAX	45.96	50.04	54.43	0.92	0.84
LAUCI	190.56	190.82	205.79	1.00	0.93
LAUCT	183.17	186.03	201.93	0.98	0.91
LCMAX	44.71	49.22	53.61	0.91	0.83

Comments on Results of Non-Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters, LS means, and ratios of means has been confirmed by the reviewer.

2. When comparing the test to reference drugs under fed conditions, the ratios of LS means of LNAUCT, LNAUCI, and LNCMAX are all within the acceptable range of 0.8-1.25.

3. When comparing the test drug under fed to fasting conditions, results in Tables 8&9 indicated a small decrease of mean AUC (8-9%), a 16-17% decease of mean Cmax, and a 0.75-hour delay of mean Tmax (2.89 under test-fed conditions versus 2.15 hours under test-fasting conditions).

4. Because subject #11 did not complete both treatments under fed conditions, the reviewer re-conducted ANOVA without his data and the outcome of the study remains unchanged.

5. Results of this non-fasting bioequivalence study are acceptable.

IN-VITRO DISSOLUTION TESTING RESULTS:

Ibuprofen tablet is a USP product with the following recommended method and tolerance:

Medium: pH 7.2 phosphate buffer; 900 mL.
Apparatus 2: 50 rpm.
Time: 60 minutes.
Tolerance: NLT in 60 minutes.

The firm conducted comparative dissolution testing for the test and reference products using the USP method as presented in Table 10:

Table 10 : In Vitro Dissolution Testing -

Drug: Ibuprofen Tablets
Dosage Strength: 400 mg, 600 mg, & 800 mg
ANDA No: 76-112
Submission Date: 2/2/01

Conditions for Dissolution/Release Testing

Apparatus: Apparatus II (Paddle) RPM: 50
Medium: pH 7.2 phosphate buffer Volume: 900 mL
No. Units Tested: 12
Tolerance (Q): in 60 minutes
Reference Drug: M/s. Pharmacia & Upjohn Company

Results of In Vitro Dissolution

Sampling Time (min)	Test Product: Ibuprofen Tablets Batch #: G001A Strength: 400 mg			Reference Product: Motrin Tablets Lot #: 90CPTA Strength: 400 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	96		2.0	99		1.1
20	97		1.5	101		1.0
30	97		1.5	102		0.9
45	98		1.7	101		1.2
60	98		1.8	102		1.1
75	99	96 - [illegible]	1.8	103	[illegible]	0.8

Sampling Time (min)	Test Product: Ibuprofen Tablets Batch #: G001B Strength: 600 mg			Reference Product: Motrin Tablets Lot #: 45CST Strength: 600 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	97		1.5	99		1.4
20	98		1.7	100		1.4
30	99		1.4	100		1.2
45	99		1.8	100		0.7
60	99		1.7	100		0.8
75	100		2.0	101		0.5

Sampling Time (min)	Test Product: Ibuprofen Tablets Batch #: G001 Strength: 800 mg			Reference Product: Motrin Tablets Lot #: 33CTT Strength: 800 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	96		2.0	99		1.9
20	98		0.9	100		1.4
30	98		1.3	100		1.4
45	99		1.0	101		1.3
60	99		0.9	101		0.9
75	100		1.2	101		0.7

Comments on Dissolution Tests:

1. Results of all 3 strengths of the test and reference products comply with the specification of " *in 60 minutes".*

2. All 3 strengths of the test and reference products are rapidly dissolved, i.e., more than 90% are dissolved within 10 minutes.

REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:

The firm is requesting waiver of the in-vivo bioequivalence study requirements for its 400 mg and 600 mg strengths of the test product based on the fasting and non-fasting *in vivo* bioequivalence studies conducted on the 800 mg strength, the proportionality of formulations, and comparative dissolution data.

Comments on Waiver Request:

1. The fasting and non-fasting bioequivalence studies conducted on the 800 mg strength are acceptable.

2. The dissolution data of all 3 strengths of the test product meet the specification of *in 60 minutes".*

3. The formulations of the 2 lower strengths are proportionally similar to the formulation of the 800 mg tablets.

4. Therefore the waiver for the firm's 400 mg and 600 mg tablets can be granted per 21 CFR 320.22(d)(2).

Recommendation:

1. Both fasting and non-fasting bioequivalence studies conducted by Dr. Reddy's Laboratories Limited on its ibuprofen 800 mg tablet, batch #G001, comparing it to Motrin® 800 mg tablet, lot #33CTT, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Dr. Reddy's Laboratories' ibuprofen 800 mg tablet is bioequivalent to the reference product, Motrin® 800 mg Tablet manufactured by Pharmacia & Upjohn under fasting and non-fasting conditions.

2. The dissolution tests conducted by Dr. Reddy's Laboratories Limited on its ibuprofen 400 mg, 600 mg, and 800 mg tablets, batch #G001A, #G001B, and #G001, respectively, comparing them to Motrin® 400 mg, 600 mg, and 800 mg tablets, lot #90CPTA, #45CST, and #33CTT, respectively, have been found acceptable by the Division of Bioequivalence.

   The formulations of the 400 mg and 600 mg strengths are both proportionally similar to the 800 mg test product which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 400 mg and 600 mg tablets is granted per 21 CFR 320.22(d)(2). The 400 mg and 600 mg tablets of the test product are therefore deemed bioequivalent, respectively, to the 400 mg and 600 mg tablets of Motrin® manufactured by Pharmacia & Upjohn.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of pH 7.2 phosphate buffer at 37^0 C using USP 24 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

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

Lin-Whei Chuang 4/6/01

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG

4/6/2001

Concur: _____ Date: 4/30/2001

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-112 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen tablets USP, 400 mg, 600 mg, and 800 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

ADMINISTRATIVE DOCUMENTS

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

ANDA Number:	76-112	Date of Submission:	February 2, 2001
Applicant's Name:	Dr. Reddy's Laboratories Limited		
Established Name:	Ibuprofen Tablets USP, 400 mg, 600 mg & 800 mg		

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 500 tablets

   Satisfactory in **draft** as of the February 2, 2001 submission.

2. **PACKAGE INSERT**

   a. **Title:**
   Revise to read **"Ibuprofen Tablets, USP"** [capitalize "Tablets"] [see **General Comments** below]

   b. **General Comments**
   Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or of the title of a package insert.

   c. **Adverse Reactions**
   Relocate the **table** found in your **Dosage and Administration** section to the end of this section **(Adverse Reactions)** and directly above the **Overdosage** section.

   d. **Dosage and Administration**
   Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:

      i. First sentence; revise to read -

      ***Suggested Dosage*:** 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). Individual...

      ii. Second to the last paragraph; revise to read -

      The availability of three tablet strengths facilitates dosage adjustment.

Please revise your labels and labeling, as instructed above, and submit in final print.

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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Chuang Li

1.1

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

ANDA Number:	76-112	Date of Submission:	February 2, 2001
Applicant's Name:	Dr. Reddy's Laboratories Limited		
Established Name:	Ibuprofen Tablets USP, 400 mg, 600 mg & 800 mg		

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 500 tablets

   Satisfactory in **draft** as of the February 2, 2001 submission.

2. **PACKAGE INSERT**

   a. **Title:**
   Revise to read "**Ibuprofen Tablets, USP**" [capitalize "Tablets"] [see **General Comments** below]

   b. **General Comments**
   Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or of the title of a package insert.

   c. **Adverse Reactions**
   Relocate the **table** found in your **Dosage and Administration** section to the end of this section **(Adverse Reactions)** and directly above the **Overdosage** section.

   d. **Dosage and Administration**
   Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:

      i. First sentence; revise to read -

      ***Suggested Dosage*:** 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). Individual...

      ii. Second to the last paragraph; revise to read -

      The availability of three tablet strengths facilitates dosage adjustment.

Please revise your labels and labeling, as instructed above, and submit in final print.

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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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			
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			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		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	
Labeling(continued)	Yes	No	N.A.
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.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # 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.			
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.			

FOR THE RECORD:

1. Professional Package Insert:
   Model labeling used by the firm for Motrin was approved February 16, 1988; revised September 1987.
   This is the correct model to use.

2. In the opinion of the applicant and to the best of our knowledge, there is no patent in existence. (Page 12 in Vol. B. 1.1)

3. Storage/Dispensing Conditions:
   NDA: Store at controlled room temperature 20°-25°C(68°-77°F) (400 mg & 800 mg)
   Store at controlled room temperature 15°-30°C(59°-86°F) (600 mg tablets)
   ANDA: Store at controlled room temperature 20°-25°C(68°-77°F) [See USP]

4. Product Line:
   The innovator markets their product in 30, 50, 60, 90, 100, 120 & 500 & unit-dose packages of 100.The

applicant proposes to market their product in bottles of 100 & 500 tablets.

5. Inactive Ingredients:
   The listing of the 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 pg.1978 vol. B. 1.3.

6. All manufacturing will be performed by Dr Reddy Laboratories Limited (See pg 2418 in Volume B. 1.4.)

7. Container/Closure: (400, 600 and 800mg tablets) Bottles of 100 will utilize a CRC-closure and bottles of 500 will utilize a non-CRC closure. All bottle sizes will utilize HDPE containers (Page 3008- 3012 in volume
   B.1.5.)

8. The description of the drug product found in the HOW SUPPLIED section of the package insert is in a accordance with the description of the product found in the Finished Dosage Form. (see pgs. 3272, 3275 and 3278 in vol. A. 1.12.)

Date of Review: 3/21/01 Date of Submission: 2/02/01

Primary Reviewer: J Barlow Date: 3/27/01

Team Leader: J Grace Date: 3/30/2001

cc:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-112

CORRESPONDENCE

DR. REDDY'S
Dr. Reddy's Laboratories, Inc.

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE: (201) 760-2880
FAX: (201) 760-0401

DELIVERED VIA FAX and Federal Express
301- 443-3839

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

OCT 24 2001

ORIG AMENDMENT

Reference: ANDA # 76-112 Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
TELPHONE AMENDMENT

Dear Sir or Madam:

Dr. Reddy's Laboratories Inc., US Agent for Dr. Reddy's Laboratories Limited, is providing on their behalf this response to the Telephone deficiently communicated on October 24, 2001. Reference is made to the original submission and the amendment dated September 7, 2001and the original submission dated February 2, 2001.

Agency Comment:

> *Your Reprocessing Statement references Code of Federal Regulations Title 21 §314.70. Please be advised that this section is no longer in force. Please revise your statement to eliminate all references to this regulatory section.*

As requested, the reprocessing statement has been revised. The following page supercedes the previously submitted reprocessing statement. This concludes our submission. Should you have any further issues, we can be contacted at 410-309-3145, FAX 410-309-6145.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 25 2001
DGD

10/5/01

DR. REDDY'S
Dr. Reddy's Laboratories, Inc.

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE: (201) 760-2880
FAX: (201) 760-0401

HAND DELIVERED

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

ORIG AMENDMENT
N/Am

Reference: ANDA # 76-112 Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
MINOR AMENDMENT

Dear Sir or Madam:

Dr. Reddy's Laboratories Inc., US Agent for Dr. Reddy's Laboratories Limited, is providing this response to the Minor NA dated August 8, 2001 on their behalf. Reference is made to the original submission and the amendment dated September 7, 2001and the original submission dated February 2, 2001.

The foreign firm inadvertently submitted the amendment without the knowledge of the US agent. At the request of the agency, the US agent obtained a copy from the foreign firm, and it is hereby being resubmitted at this time. As requested, the US agent has informed the foreign firm of the legal requirements to submit through the US agent. The firm apologies for this misunderstanding on their part and for any incontinence that this has caused. The following submission supercedes the minor amendment response previously provided.

A. Chemistry Deficiencies:

10/4/01

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

10/1/01

5)

B. Labeling Deficiencies

1) *CONTAINER – Bottles of 100 and 500 tablets*
Satisfactory in draft as of the February 2, 2001 submission

Twelve copies of the Final Printed Labels (FPL) for the containers (HDPE bottle) are provided in *Section V.*

2) PACKAGE INSERT

a. *Title*
Revise to read "Ibuprofen Tablets, USP" (capitalize "Tablets") (see General Comment below)

b. *General Comments*
Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case), Upper case may be used when the USAN name stands alone as on labels or of the title or a package insert.

c. *Adverse Reactions*
Relocate the table found in your Dosage and Administration section to the end of this section (Adverse Reactions) and directly above the Overdosage section.

d. *Dosage and administration*
Rheumatoid arthritis and osteoarthritis, including flare-ups or chronic disease

i. *First sentence: revise to read*

Suggested Dosage: 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg or qid), individual.

ii. *Second to the last paragraph; revise to read*
The availability of three tablet strengths facilitates dosage adjustment.

Please revise you labels and labeling as instructed above, and submit the final prints.

The Package Insert Labeling (PIL) has been revised to include all the changes as recommended by the agency. 12 copies each for the final printed inserts are provided in *Section V.* Similarities and Differences between Previously Submitted labeling against Proposed labeling is provided in *Section IV.*

The Firm acknowledges that it may be necessary to further revise the labeling subsequent to approved changes for the Reference Listed Drug.

The Firm commits to incorporate the dissolution test into the stability and quality control programs as specified in USP 24.

Please communicate any remaining questions or issues to C. Jeanne Taborsky, and they will be addressed and a response submitted. This concludes our submission. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

noted KJ 9/27/01

DR. REDDY'S
Dr. Reddy's Laboratories, Inc.

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE: (201) 760-2880
FAX: (201) 760-0401

NEW CORRESP
NC

SENT VIA FEDERAL EXPRESS

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

SEP 14 2001

Reference: ANDA # 76-112 Ibuprofen Tablets USP 400 mg, 600 mg, and 800 mg Correspondence

Dear Sir/ Madam:

Dr. Reddy's Laboratories, Inc. US Agent for Dr. Reddy's Laboratories Limited, Bachepalli 502 325, INDIA, is submitting this correspondence to the previously submitted ANDA dated February 2, 2001.

Please be advised that the name of the US agent has changed. A Letter of Authorization for US Agent is also provided herein with the updated information.

Pursuant to *Code of Federal Regulations* Title 21 §314.440 (a) (4), a third copy of this communication is being provided. This is the required field copy and we certify that it is a true copy of the technical section as described in *Code of Federal Regulations* Title 21 §314.50 (d) (1).

This concludes our correspondence. Please contact C. Jeanne Taborsky at (410) 309-3145 or Paul V. Campanelli, Vice President Formulations Business, Reddy-Cheminor, Inc. at (201) 760-2880 ext 203, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs Consultant

Attachment: US Agent LOA

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 17 2001
OGD

NW 9-26-01

REDDY-CHEMINOR, INC.

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

March 19, 2001

Via Facsimile – 12 pages/Via Courier

NC

NEW CORRESP

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

Telephone Amendment

Reference: Ibuprofen Tablets 400 mg, 600 mg & 800 mg
ANDA: 76-112

Dear Ms. Middleton:

This is in reference to our telephone amendment on March 14th with respect to Copovidone used in the above referenced submission by Dr. Reddy's Laboratories, Ltd.

For your review we have attached the following documentation:

- Quantity of Copovidone (Plasdone S-630) used in Ibuprofen Tablets.
- Technical Profile for Plasdone S-630
- ISP Technical Data Sheet for Plasdone S-630
- PDR excerpt of listing Copovidone as an inactive ingredient.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456, if you have any questions concerning this submission.

Very truly yours,
REDDY-CHEMINOR, INC.

Paul V. Campanelli
Vice President, Formulations Business

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 2 0 2001
OGD

Attachments

ANDA 76-112

Reddy-Cheminor, Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Paul V. Campanelli
66 South Maple Avenue
Ridgewood, NJ 07450

MAR 7 2001

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 conversation dated March 2, 2001 and your correspondence dated March 2, 2001.

NAME OF DRUG: Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg

DATE OF APPLICATION: February 2, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 5, 2001

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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

4 | copy

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue,
Ridgewood, NJ 07450
Phone: 201-444-4424
Fax: 201-444-1456

March 2, 2001

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
Attention:
Emily Thomas

NEW CORRESP

Dear Emily:

Per your telephone conversation with Paul Campanelli, attached please find our response to the Telephone Deficiency regarding our Ibuprofen 400, 600 and 800 mg ANDA # 76-112 submission.

Should you have any questions or require additional information, please feel free to contact us.

Thanks and best regards,

REDDY-CHEMINOR, INC.

R. Campanelli

Robert A. Campanelli
Manager Formulations Business

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

February 2, 2001

505(j)(2)(A) OK
07-MAR-2001

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 : **Ibuprofen Tablets, USP 400 mg , 600 mg and 800 mg**
Abbreviated New Drug Application

Dear Sir/ Madam:

Dr. Reddy's Laboratories Limited (Formerly Cheminor Drugs Limited) herewith submits an abbreviated new drug application (ANDA) for Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, MOTRIN® (Ibuprofen) Tablets 400 mg, 600 mg and 800 mg which is manufactured by Pharmacia and Upjohn Co., the holder of the approved application and which is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

Ibuprofen Tablets, USP 400 mg , 600 mg and 800 mg have been developed and will be manufactured, tested and packaged by Dr. Reddy's Laboratories Limited (Formerly Cheminor Drugs Limited), Bachepally, Post Bag No.15, Kukatpally P.O., Hyderabad 500 072, INDIA manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturer of the drug substance used to produce the ANDA / Biobatch of this product is Dr. Reddy's Laboratories Limited-Bulk drugs division(formerly Cheminor Drugs Limited-Bulk Drug Division), Plot No. 9/A, Phase 3, I.D.A. Jeedimetla, Hyderabad – 500 055, INDIA DMF

The required bioavailability / bioequivalence studies were conducted on Dr Reddy's(formerly Cheminor's) Ibuprofen Tablets, USP 800 mg and MOTRIN® (Ibuprofen) Tablets 800 mg by Phoenix International Life Sciences Inc., 2350 Cohen Street, Saint-Laurent (Montreal), Quebec, Canada H4R2N6. These studies indicate that Ibuprofen Tablets USP, 800 mg are bioequivalent to MOTRIN® (Ibuprofen) Tablets, 800 mg.

The *in vitro* dissolution profiles for Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are comparable to those of MOTRIN® (Ibuprofen) Tablets, 400 mg and 600 mg and 800 mg respectively. The formulations of Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are dose proportional to Ibuprofen Tablets USP 800 mg. Based on the above, a waiver for the bioavailability/ bioequivalence study for the 400 mg and 600 mg is requested.

February 2, 2001

Food and Drug Administration
Ibuprofen Tablets, USP 400 mg , 600 mg and 800 mg
Abbreviated New Drug Application

Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) in the smallest and largest fill size of the container / closure system 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 Ibuprofen Tablets, USP 400 mg , 600 mg and 800 mg are same as those for MOTRIN® (Ibuprofen) Tablets, 400 mg, 600 mg and 800 mg.

This ANDA is submitted in thirteen volumes :

Volume I	:	Section I through Section V
Volume II through Volume VIII	:	Section VI
Volume IX	:	Section VII through Section VIII
Volume X	:	Section IX through Section XII
Volume XI	:	Section XII through Section XIII
Volume XII	:	Section XIV through Section XXII

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self addressed stamped envelope provided for your convenience.

REDDY-CHEMINOR, INC.

February 2, 2001

Food and Drug Administration
Ibuprofen Tablets, USP 400 mg , 600 mg and 800 mg
Abbreviated New Drug Application

Pursuant to 21 CFR 314.440 (a) (4), a third copy of this application is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

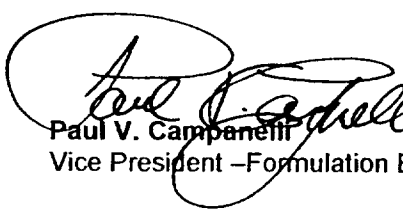
We also notify the agency that due to the recent merger of Cheminor Drugs Limited into Dr. Reddy's Laboratories Limited, our company name has been changed from Cheminor Drugs Limited —Pharma Division to Dr. Reddy's Laboratories Limited.

As far as this ANDA is concerned, as most of the documents have been executed prior to the change of name, we have maintained the company name as Cheminor Drugs Limited – Pharma Division throughout this ANDA. However, the labeling includes Dr Reddy's Laboratories Limited as the name of the manufacturer.

We request the agency, to henceforth to consider our company name as Dr. Reddy's Laboratories Limited for correspondence purpose. All the addresses remains the same.

Should you have any questions on this submission ,please feel free to contact the undersigned at (201)444-4424 or by fax at (201)444-1456 .

Sincerely,



Paul V. Campanelli
Vice President –Formulation Business