CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-010

***Name*:** Ibuprofen Tablets USP, 200 mg
(round and capsule shaped tablets, colored brown)

***Sponsor*:** LNK International, Inc.

***Approval Date*:** March 1, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

APPROVAL LETTER

ANDA 75-010

MAR 1 1999

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

Dear Sir:

This is in reference to your abbreviated new drug application dated November 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen Tablets USP, 200 mg (round and capsule shaped tablets, colored brown).

Reference is also made to your amendments dated April 10, and August 1, 1997; March 5, August 10, August 14, and December 21, 1998; and January 4, January 19, and February 10, 1999.

We have completed the review of this abbreviated application and have concluded that the drug product is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Ibuprofen Tablets 200 mg (round and capsule shaped tablets, colored brown) are bioequivalent to the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

D. L. Sporn 3/1/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-010
Division File
FIELD COPY
HFD-610/RLWest
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/

Endorsements:
HFD-623/U.Atwal/ U.Atwal 2/8/99
HFD-623/V.Sayeed/2-2-99 V. Sayeed 2/9/99.
HFD-617/M.Anderson, PM/2-2-99 Mark Anderson 2/9/99
HFD-613/J.Barlow/J.Grace for/2-5-99
HFD-613/J.Grace 2/9/99

X:\new\firmsam\lnk\ltrs&rev\75010.apd
F/T by: bc/2-8-99

APPROVAL
Revised per cc'd 2/24/99 (new addendum)

2/24/99

Robert Lewis
3/1/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

LABELING

B16415

EXPIRATION DATE

LOT NO.

0 50844-292-02 4

QUALITY PLUS

NDC 50844-292-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-shaped Tablets)

QUALITY PLUS

NDC 50844-292-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-shaped Tablets)

QUALITY PLUS

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-Shaped Tablets)

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin.

INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

DIRECTIONS: Adults: Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist.
Children: Do not give this product to children under 12 except under the advice and supervision of a doctor.
Store at room temperature. Avoid excessive heat 40°C (104°F).

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg.

INACTIVE INGREDIENTS: Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

dg99

98-81 Ibup. 12 Cplt. BX, DG 99, 08/06/98, MAC 8500, Process Yellow, Process, Blue, PMS 485, Black. LNK/Quality Plus. Rev,10/29/98.

B16501

LOT NO.

EXPIRATION DATE

0 50844-292-13 0

QUALITY PLUS

NDC 50844-292-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-shaped Tablets)

QUALITY PLUS

NDC 50844-292-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-shaped Tablets)

QUALITY PLUS

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Caplets*, 200 MG EACH

*Caplets (Capsule-Shaped Tablets)

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INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

DIRECTIONS: Adults: Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor.

Store at room temperature. Avoid excessive heat 40°C (104°F).

ACTIVE INGREDIENT: Each tablet contains Ibuprofen USP, 200 mg.

INACTIVE INGREDIENTS: Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide and triacetin.

WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take Ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although Ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other Ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

dg9821

QUALITY PLUS NDC 50844-292-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Caplets*, 200 MG EACH

***Caplets (Capsule-Shaped Tablets)**

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. **Store at room temperature. Avoid excessive heat 40°C (104°F).**

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

IBUPROFEN TABLETS 200mg. CAPSULE SHAPED FILM COATED BROWN 12 COUNT, ACTUAL LABELING

QUALITY PLUS NDC 50844-292-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Caplets*, 200 MG EACH

***Caplets (Capsule-Shaped Tablets)**

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. **Store at room temperature. Avoid excessive heat 40°C (104°F).**

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic iron oxide, titanium dioxide, and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

MAR 1 1996

ENLARGED TO 150%
BY FDA STAFF

QUALITY PLUS

NDC 50844-292-12

Pain Relief Formula

IBUPROFEN

Tablets USP, 200 mg

Pain Reliever • Fever Reducer

100 FILM COATED BROWN CAPLETS*

200 MG EACH

*Caplets (Capsule-Shaped Tablets)

PACKAGE NOT CHILD RESISTANT

EASY OPEN

WARNING ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take Ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although Ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other Ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. Store at room temperature. Avoid excessive heat 40°C (104°F).

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin. Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

0 50844-292-12 3

98-505 Ibup. 100 Br. C Lbl., 4.375" 1.375", ~~12/16~~/98, Mac 8500, PMS 485, Process Blue, Process Yellow, Black. LNK/Quality Plus.

IBUPROFEN TABLETS 200 mg. CAPSULE SHAPED FILM COATED BROWN 100 COUNT, ACTUAL LABELING

QUALITY PLUS

NDC 50844-292-12

Pain Relief Formula

IBUPROFEN

Tablets USP, 200 mg

Pain Reliever • Fever Reducer

100 FILM COATED BROWN CAPLETS*

200 MG EACH

***Caplets (Capsule-Shaped Tablets)**

PACKAGE NOT CHILD RESISTANT

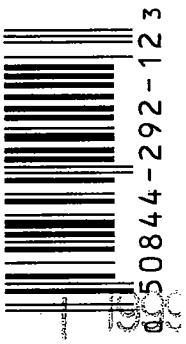
EASY OPEN

WARNING ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take ibuprofen and other pain relievers. Store at room temperature. Avoid excessive heat 40°C (104°F).

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin. Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788



ENLARGED TO 150%
BY FOIA STAFF

Margo

IBUPROFEN TABLETS 200mg. CAPSULE SHAPED FILM COATED BROWN 250 COUNT, ACTUAL LABELING

QUALITY PLUS

NDC 50844-292-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Caplets*, 200 MG EACH

***Caplets (Capsule-Shaped Tablets)**

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Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

Mango

98-81 Ibup. 12 Cplt. BX, DG 99, 08/06/98, MAC 8500, Process Yellow, Process, Blue, PMS 485, Black. LNK/Quality Plus. Rev,10/29/98.

Mango

98-490 Ibup. 250 Br. C Lbl 12/18/98 4:17 PM Page 1

QUALITY PLUS

NDC 50844-292-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Caplets*, 200 MG EACH

***Caplets (Capsule-Shaped Tablets)**

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take Ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although Ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other Ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. Store at room temperature. Avoid excessive heat 40°C (104°F).

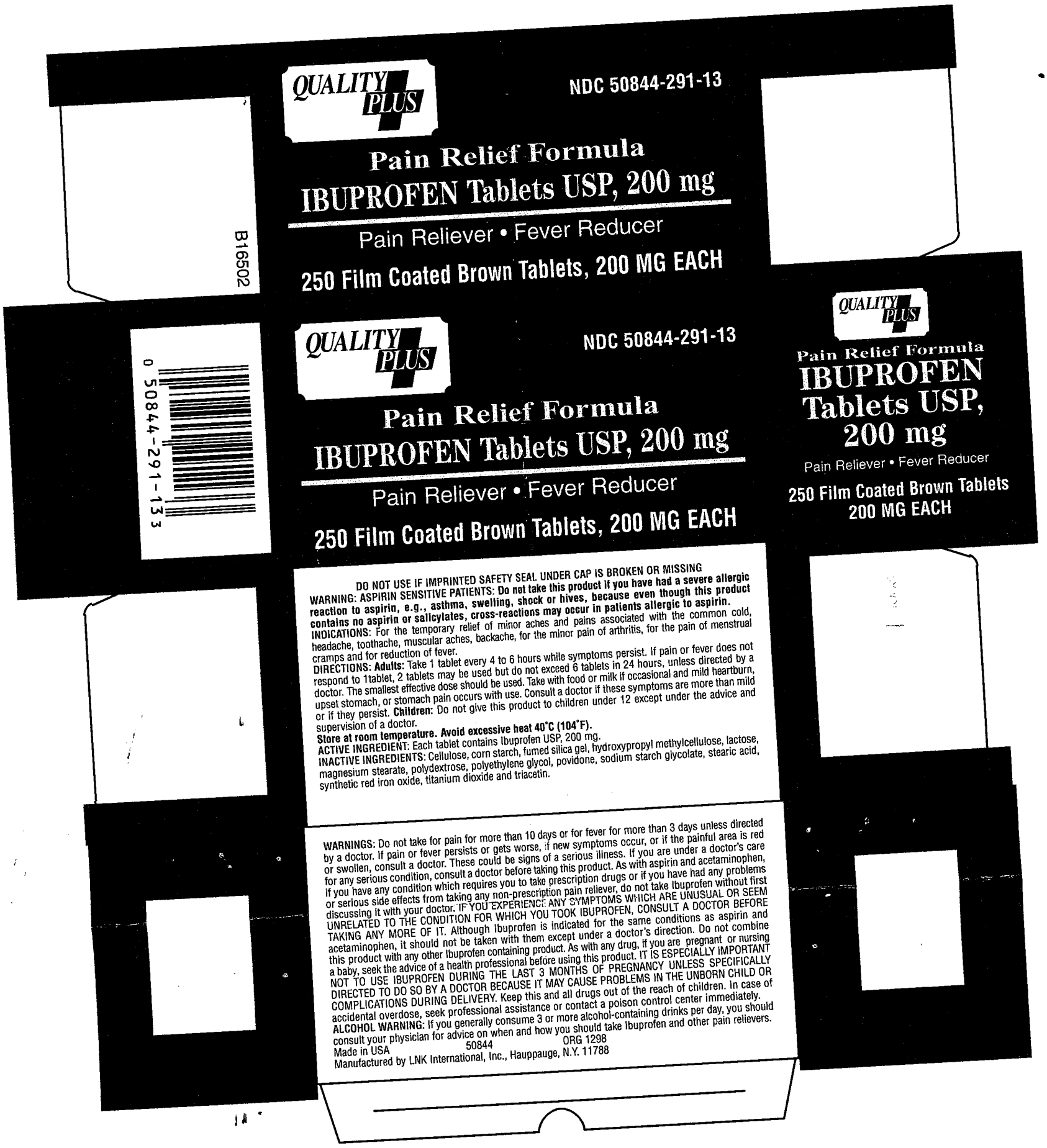
DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains Ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

98-490 Ibup. 250 Cplt. Lbl., 6" x 2", 12/16/98, Mac 8500, Process Yellow, Process Blue, PMS 485, Black. LNK/Quality Plus.


QUALITY PLUS
NDC 50844-291-13
Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg
Pain Reliever • Fever Reducer
250 Film Coated Brown Tablets, 200 MG EACH
B16502
0 50844-291-13 3
QUALITY PLUS
NDC 50844-291-13
Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg
Pain Reliever • Fever Reducer
250 Film Coated Brown Tablets, 200 MG EACH
QUALITY PLUS
Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg
Pain Reliever • Fever Reducer
250 Film Coated Brown Tablets 200 MG EACH
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INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.
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Store at room temperature. Avoid excessive heat 40°C (104°F).
ACTIVE INGREDIENT: Each tablet contains Ibuprofen USP, 200 mg.
INACTIVE INGREDIENTS: Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide and triacetin.
WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take Ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although Ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other Ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers.
Made in USA 50844 ORG 1298
Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

B16417

NDC 50844-291-02

QUALITY PLUS

Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Tablets, 200 MG EACH

NDC 50844-291-02

QUALITY PLUS

Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Tablets, 200 MG EACH

0 50844-291-027

QUALITY PLUS

Pain Relief Formula
IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Tablets
200 MG EACH

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin.

INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

DIRECTIONS: Adults: Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor.

Store at room temperature. Avoid excessive heat 40°C (104°F).

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg.

INACTIVE INGREDIENTS: Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

dg99

98-75 Ibup. 12 T BX, DG 99, 08/06/98, MAC 8500, Process Yellow, PMS 3155, PMS 485, Black. LNK/Quality Plus. Rev. 10/29/98.

QUALITY PLUS

NDC 50844-291-12

Pain Relief Formula

IBUPROFEN

Tablets USP, 200 mg

Pain Reliever • Fever Reducer

100 Film Coated Brown Tablets
200 MG EACH

PACKAGE NOT CHILD RESISTANT

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take Ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although Ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other Ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. Store at room temperature. Avoid excessive heat 40°C (104°F).

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains Ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin. Made in USA 50844 ORG1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

0 50844-291-12 6

98-506 Ibup. 100 Br. T Lbl., 4.375" 1.375", 12/16/98, Mac 8500, PMS 485, PMS 3155, Process Yellow, Black. LNK/Quality Plus.

IBUPROFEN TABLETS 200mg.
FILM COATED BROWN
100 COUNT, ACTUAL LABELING

QUALITY PLUS

NDC 50844-291-12

Pain Relief Formula

IBUPROFEN

Tablets USP, 200 mg

Pain Reliever • Fever Reducer

100 Film Coated Brown Tablets
200 MG EACH

PACKAGE NOT CHILD RESISTANT

MAR 1999

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DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

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Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

0 50844-291-12 6

ENLARGED TO 150%
BY FDA STAFF

Margo

IBUPROFEN TABLETS 200mg.
FILM COATED BROWN
250 COUNT, ACTUAL LABELING

QUALITY PLUS

NDC 50844-291-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Tablets, 200 MG EACH

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Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

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QUALITY PLUS

NDC 50844-291-13

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

250 Film Coated Brown Tablets, 200 MG EACH

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Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

Mary

IBUPROFEN TABLETS 200mg.
FILM COATED BROWN
1000 COUNT, ACTUAL LABELING

QUALITY PLUS

NDC 50844-291-16

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever · Fever Reducer

00 Film Coated Brown Tablets, 200 MG EACH

This Package for Households Without Young Children

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin.

INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

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ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers.

Store at room temperature. Avoid excessive heat 40°C (104°F).

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

MAR 1 19

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg.

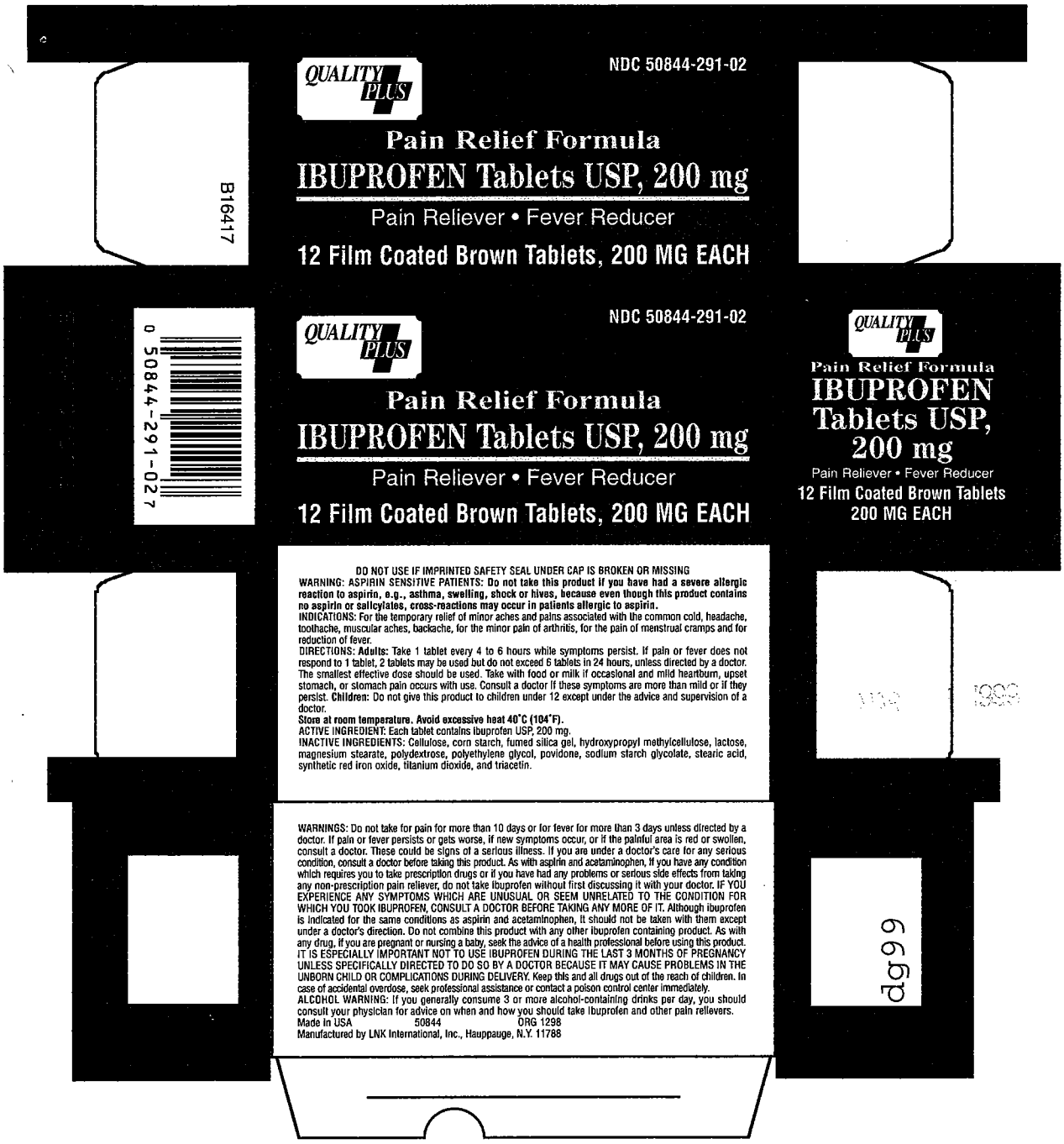
INACTIVE INGREDIENTS: Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

0 50844-291-16 4

Margo



98-75 Ibup. 12 T BX, DG 99, 08/06/98, MAC 8500, Process Yellow, PMS 3155, PMS 485, Black. LNK/Quality Plus. Rev. 10/29/98.

ACTUAL Size

QUALITY PLUS NDC 50844-291-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Tablets, 200 MG EACH

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. **Store at room temperature. Avoid excessive heat 40°C (104°F).**

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica gel, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

98-86 Ibup. 12 T Lbl., 4.375" x 1.375", 08/06/98, 10/26/98. Mac 8500, Process Yellow, PMS 3155, PMS 485, Black. LNK/Quality Plus. Rev. 10/29/98.

IBUPROFEN TABLETS 200mg.
FILM COATED BROWN
12 COUNT ACTUAL LABELING

QUALITY PLUS NDC 50844-291-02

Pain Relief Formula

IBUPROFEN Tablets USP, 200 mg

Pain Reliever • Fever Reducer

12 Film Coated Brown Tablets, 200 MG EACH

WARNING: ASPIRIN SENSITIVE PATIENTS: Do not take this product if you have had a severe allergic reaction to aspirin, e.g., asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin. INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. **DIRECTIONS: Adults:** Take 1 tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. **Children:** Do not give this product to children under 12 except under the advice and supervision of a doctor. **WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of a serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. **ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Ibuprofen and other pain relievers. **Store at room temperature. Avoid excessive heat 40°C (104°F).**

DO NOT USE IF IMPRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING

ACTIVE INGREDIENT: Each tablet contains ibuprofen USP, 200 mg. **INACTIVE INGREDIENTS:** Cellulose, corn starch, fumed silica, gelatin, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethylene glycol, povidone, sodium starch glycolate, stearic acid, synthetic red iron oxide, titanium dioxide, and triacetin.

Made in USA 50844 ORG 1298

Manufactured by LNK International, Inc., Hauppauge, N.Y. 11788

MAR 1 1999

ENLARGED TO 150%
BY FOIA STAFF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

LABELING REVIEWS

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

ANDA Number: 75-010 Date of Submission: November 27, 1996

Applicant's Name: LNK International, Inc.

Established Name: Ibuprofen Tablets USP, 200 mg (Brown round- and capsule-shaped tablets)

Labeling Deficiencies:

1. GENERAL COMMENTS

   Use "USP" rather than "U.S.P." throughout the labels and labeling.

2. CONTAINER - 12's, —, and 1000's

   a. Round-shaped tablets

      i. We encourage you to include the strength of the drug product to appear in conjunction with the established name, *i.e.* "Ibuprofen Tablets USP, 200 mg".

      ii. You may delete the statement "FILM COATED BROWN" and revise the net quantity statement to read "xx Film Coated Brown Tablets, 200 mg Each".

      iii. INDICATIONS

      ... for reduction of fever. [delete "the"]

      iv. OTHER INGREDIENTS

      A) We encourage you to replace "OTHER" with "INACTIVE".

      B) Please identify the botanical source of starch, *i.e.* "corn starch" rather than "starch".

      C) Please alphabetize the listing of other ingredients.

      D) Include the components of —

b. Capsule-shaped tablet

i. Please note that the term "caplet" is not an official USP dosage form classification, neither is it part of the established name as seen in the USP monograph. Therefore, revise the name of your drug product to read "Ibuprofen Tablets USP, 200 mg" to be in accordance with USP 23. The term "caplet" may be retained in the net quantity statement as long as it is defined as a "capsule-shaped tablet" as you have proposed.

ii. You may delete the statement "FILM COATED BROWN" and revise the net quantity statement to read as follows:

xx Film Coated Brown Caplets*, 200 mg Each

*Caplets (Capsule-shaped tablets)

iii. See comments (iii) and (iv) under Round-shaped tablets.

iv. Revise the statement "————————on the container labels for the package size of 12's to be same as the one appearing on the container labels for other package sizes.

3. CARTON - 12's and ——

a. Round-shaped tablet

See comments (i) through (iv) under CONTAINER for round-shaped tablet.

b. Capsule-shaped tablet

See comments (i) through (iii) under CONTAINER for capsule-shaped tablet.

4. CONSUMER LEAFLET LABELING

i. We ask you to propose a separate consumer leaflet labeling for your round-shaped and capsule-shaped tablets. Please revise the labeling according to the comments made for container labels except for the comment related to the net quantity statement.

ii. We ask you to revise the name of the product to read as follows in the leaflet for capsule-shaped tablets.

Ibuprofen Tablets* USP, 200 mg

*Caplets (Capsule-shaped tablets)

5. BULK LABELING

Although the Agency does not approve the bulk labeling, we have reviewed for accuracy and have following comments.

a. Round-shaped tablets

i. Revise the product name to read "Ibuprofen Tablets USP, 200 mg (Brown)

ii. Relocate the statement "PAIN RELIEVER/FEVER REDUCER" to immediately follow the name of the drug product.

iii. Refer to the comments (iv) under CONTAINER for round-shaped tablets.

b. Capsule-shaped tablets

i. We ask you to revise the name of the product to read as follows:

Ibuprofen Tablets* USP, 200 mg (Brown)

*Caplets (Capsule-shaped tablets)

ii. Refer to the comments (ii) & (iii) under round-shaped tablets.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 the last submitted labeling with all differences annotated and explained.

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

NOTES/QUESTIONS TO THE CHEMIST

I believe the closure system for the package sizes of 12's and [redacted] are CRC considering [redacted] inner seal? Do you concur? The container/closure system for Ibuprofen has specific requirement related to a safety issue.

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 23	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.			x
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?[See FTR]	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? (See FTR]	x		
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			
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.			

1. MODEL LABELING

Nuprin® - Bristol-Myers; approved February 16, 1988.

2. INACTIVE INGREDIENTS

Refer to comments (iv) under CONTAINER and the Components and Composition Statements on Page 115 in vol.B. 1.1.

3. PATENTS/EXCLUSIVITIES

No pending issue. The firm's statement is accurate.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store at room temperature. Avoid excessive heat 40ºC (104ºF).

ANDA - Store at room temperature. Avoid excessive heat 40ºC (104ºF).

5. CONTAINER/CLOSURE SYSTEM

Closure - CRC (12's & ⟶)
Non-CRC (1000's) (See page 542 in vol.B. 1.2) and note to chemist.

Date of Review: July 11, 1997 **Date of Submission: 11/27/96**

Cycle # 1 (Draft)

Primary Reviewer: Chan Park **Date:** 7/15/97

Secondary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:** 7/15/97

cc:
ANDA 75-010
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
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Review

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

ANDA Number: 75-010 Date of Submission: March 5, 1998

Applicant's Name: LNK International, Inc.

Established Name: Ibuprofen Tablets USP, 200 mg (Brown round- and capsule-shaped tablets)

Labeling Deficiencies:

1. CONTAINER - 12's, ——— & 1000's

   a. Please assure that the statement of identity (established name and pharmacological category) appear most prominently on the principal display panel. We refer you to 21 CFR 201.61(c) for guidance.

   b. Capsule-shaped tablets (Active ingredients) - Revise to read as follows:

      "Each tablet contains..." or "Each capsule-shaped tablet contains...".

2. CARTON - 12's & ———

   Refer to the comments under CONTAINER.

3. CONSUMER LEAFLET LABELING

   Refer to the comment (b) under CONTAINER.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

APPEARS THIS WAY
ON ORIGINAL

NOTES/QUESTIONS TO THE CHEMIST

I believe the closure system for the package sizes of 12's and [redacted] are CRC considering [redacted] inner seal? Do you concur? The container/closure system for Ibuprofen has specific requirement related to a safety issue.

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 23	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.			x
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? [See FTR]	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? (See FTR]	x		
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable).			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			

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.			

1. MODEL LABELING

   Nuprin® (72035 & 72036 - Bristol-Myers; approved February 16, 1988).

2. In the firm's 356h form, the sponsor indicated **"Nuprin"** as the RLD. However, according to the Orange Book (17th edition), **it is NOT indicated as a Reference Listed Drug.**

3. The firm has withdrew proposal for White tablets on February 5, 1997.

4. The firm has proposed **not to include the Consumer Information Leaflet** in the application. (see the firm's amendment dated March 5, 1998). Container labels and carton labeling of all proposed package sizes will contain full information. After conferring with the Team Leader, John Grace, we concluded that this is acceptable.

5. INACTIVE INGREDIENTS

   The firm has included all inactive ingredients contained in the coating material [redacted] as requested by the AGency. The listing of inactive ingredients appears to be accurate.

6. PATENTS/EXCLUSIVITIES

   No pending issue. The firm's statement is accurate.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   NDA - Store at room temperature. Avoid excessive heat 40°C (104°F).

   ANDA - Store at room temperature. Avoid excessive heat 40°C (104°F).

8. CONTAINER/CLOSURE SYSTEM

   Closure - CRC (12's & [redacted],
   Non-CRC (1000's) (See page 542 in vol.B. 1.2) and note to chemist.

Date of Review: March 27, 1998

Date of Submission: March 5, 1998

Cycle # 2 (Draft)

Primary Reviewer: Chan Park 4/3/98 Date:

Team Leader: John Grace John L. Grace Date: 4/3/98

cc:

ANDA 75-010
DUP/DIVISION FILE
HFD-613/CPark/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 75-010 Date of Submission: August 10, 1998 and August 14, 1998.

Applicant's Name: LNK International, Inc.

Established Name: Ibuprofen Tablets USP, 200 mg (Brown round- and capsule-shaped tablets)

Labeling Deficiencies:

1. GENERAL

   We notice that there is a discrepancy between your submissions of August 10, 1998 and August 14, 1998 pertaining to the withdrawal and the resubmission of the labeling for the bottles of 12 and —— count tablets and caplets. The following comments reflect a review of the August 14, 1998 submission which included the 12 and —— count labels and labeling.

2. CONTAINER - Bottles of 12, —— and 1000.

   Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and **clarity**. Please assure that these criteria are met prior to submission of final print. Also, you are required to submit 12 copies. We refer you to 21 CFR 314.94(a)(8)(ii) for guidance.

3. Carton - 12's and ——

   (See comment above.)

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

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

FOR THE RECORD:

1. MODEL LABELING

   Motrin IB (73-019 - McNeil Consumer Products Company; approved November 29, 1997).

2. **In the firm's previous 356h form, the sponsor indicated "Nuprin" as the RLD, however, this submission (August 10, 1998), the 356h form lists McNeil's "Motrin IB" as the RLD.**

3. The firm has withdrew proposal for White tablets on February 5, 1997.(From previous review)

4. The firm has proposed **not to include the Consumer Information Leaflet** in the application. (see the firm's amendment dated March 5, 1998). Container labels and carton labeling of all proposed package sizes will contain full information. After conferring with the Team Leader, John Grace, we concluded that this is acceptable.(Fome previous review)

5. The firm, as of August 10, 1998 submission, has withdrawn the bottles of 12 and — tablets & caplets from the application and will re-submit as a supplement at a later date. The later date was August 14, 1998.

6. INACTIVE INGREDIENTS

   The firm has included all inactive ingredients contained in the coating material ——————— as requested by the Agency. The listing of inactive ingredients appears to be accurate.(From previous review)

7. PATENTS/EXCLUSIVITIES

   No pending issue. The firm's statement is accurate. (From PR)

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON-(From PR)

   NDA - Store at room temperature. Avoid excessive heat 40°C (104°F).

   ANDA - Store at room temperature. Avoid excessive heat 40°C (104°F).

9. CONTAINER/CLOSURE SYSTEM

   Closure -

   Bottles of 1000 utilize screw caps.

   Bottles of 12 and — will utilize the snap cap
   (See page 542 in vol.B. 1.2)

Date of Review: 9/25/98 Date of Submission: August 10, 1998
& August 14, 1998.

Primary Reviewer: Jim Barlow Date: 10/21/98

Team Leader: John Grace Date:

John Grace 10/23/98

cc:

ANDA: 75-010
DUP/DIVISION FILE
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Review

APPEARS THIS WAY
ON ORIGINAL

(Approval Summary)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-010 Date of Submission: December 21, 1998

Applicant's Name: Lnk International, Inc.

Established Name: Ibuprofen Tablet and Caplets USP, 200 mg

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels - bottles of 12, 100, 250 & 1000 tablets.

Satisfactory in final print as of December 21, 1998.

Carton Labeling - for bottles of 12 and 250 count.

Satisfactory in final print as of December 21, 1998.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Motrin IB

NDA Number: 73-019

NDA Drug Name: Motrin IB

NDA Firm: McNeil Consumer Products Company

Date of Approval of NDA container/carton & supplement: November 29, 1997.
Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: approved labeling for Motrin IB 73-019/S-002 November 29, 1997.

Basis of Approval for the Carton Labeling:
Most recently approved carton labeling.

All of the FTR below is from previous reviews.

1. MODEL LABELING

   Motrin IB (73-019 - McNeil Consumer Products Company; approved November 29, 1997).

2. **In the firm's previous 356h form, the sponsor indicated "Nuprin" as the RLD, however, this submission (August 10, 1998), the 356h form lists McNeil's "Motrin IB" as the RLD.**

3. The firm has withdrew proposal for White tablets on February 5, 1997.(From previous review)

4. The firm has proposed **not to include the Consumer Information Leaflet** in the application. (see the firm's amendment dated March 5, 1998). Container labels and carton labeling of all proposed package sizes will contain full information. After conferring with the Team Leader, John Grace, we concluded that this is acceptable.(Fome previous review)

5. The firm, as of August 10, 1998 submission, has withdrawn the bottles of 12 and — tablets & caplets from the application and will re-submit as a supplement at a later date. The later date was August 14, 1998.

6. INACTIVE INGREDIENTS

   The firm has included all inactive ingredients contained in the coating material ——————→ as requested by the Agency. The listing of inactive ingredients appears to be accurate.(From previous review)

7. PATENTS/EXCLUSIVITIES

   No pending issue. The firm's statement is accurate. (From PR)

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON-(From PR)

   NDA - Store at room temperature. Avoid excessive heat 40ºC (104ºF).

   ANDA - Store at room temperature. Avoid excessive heat 40ºC (104ºF).

9. CONTAINER/CLOSURE SYSTEM

Closure -

Bottles of 1000 utilize screw caps.

Bottles of 12 and — will utilize the snap cap
(See page 542 in vol.B. 1.2)

Date of Review: 1/7/99 **Date of Submission: December 21, 1998**

Primary Reviewer: Jim Barlow **Date:** 1-8-99

Team Leader: John Grace **Date:**

John Grace 1-8-99

---

cc: 1/11/99

ANDA: 75-010
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\LNK\LTRS&REV\75010AP.S.DOC
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-010

3. NAME AND ADDRESS OF APPLICANT
LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, LI, NY 11788

4. LEGAL BASIS FOR SUBMISSION
Approved Product Nuprin® of Bristol Myers

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ibuprofen

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

9. AMENDMENTS AND OTHER DATES:
Original Application Date November 27, 1996
`Refuse To File' Letter Date February 3, 1997
Amendment Date February 5, 1997
`Acceptable For Filing' Date February 6, 1997

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antipyretic

11. Rx or OTC
OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical Name: ∝-methyl-4-(2-methylpropyl) benzene acetic acid
Structure: As in USP 23

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Review Sections

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, **Major**

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
June 30, 1997

DATE REVISED:
July 8, 1997

Redacted 12 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #1

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

1. Please provide the pharmaceutical function of each excipient used in the manufacture of the drug product.

2. The facilities referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval. We have requested an evalution from the Division of Manufacturing and Product Quality.

3. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality.

4. Please be advised that since the drug product is an official article, use of an in-house analytical procedure does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, the USP analytical method will be regarded as the regulatory method.

Sincerely yours,

7/11/97

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

cc: ANDA 75-010
Division File
DUP Jacket
Field Copy

Endorsements:

HFD-623/U. Atwal, Ph.D./7-8-97
HFD-623/V. Sayeed, Ph.D./7-8-97
HFD-617/J. Wilson, PM/7-8-97
X:\NEW\FIRMSAM\LNK\LTRS&REV\75010.RV1
F/T by: bc/7-8-97

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-010

3. NAME AND ADDRESS OF APPLICANT
LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, LI, NY 11788

4. LEGAL BASIS FOR SUBMISSION
Approved Product Nuprin® of Bristol Myers

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ibuprofen

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

9. AMENDMENTS AND OTHER DATES:
Original Application Date November 27, 1996
`Refuse To File' Letter Date February 3, 1997
Amendment Date February 5, 1997
`Acceptable For Filing' Date February 6, 1997
Amendment Date April 10, 1997 (Re: Method Validation)
Amendment Date August 1, 1997 (Re: Bioavailability)
New Correspondence Date February 12, 1998 (Re:Letter faxed by the firm to OGD on January 22, 1998, and firm's Tcon. with J. Wilson)
Amendment Date March 5, 1998 (This Review)

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antipyretic

11. Rx or OTC
OTC

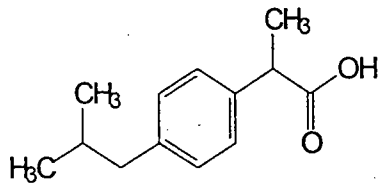
12. RELATED IND/NDA/DMF(s)
ANDA 75-139, Ibuprofen Tablets USP, 200mg (White)

13. DOSAGE FORM
Tablet (Brown)

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Ibuprofen. Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-. $C_{13}H_{18}O_2$. 206.29. 15687-21-1, 58560-75-1.
Anti-inflammatory. USP 23, p785.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Review Sections

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, *Facsimile*

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
July 28, 1998

DATE REVISED:
August 3, 1998

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CHEMISTRY REVIEW #2

Response:
A list of the DMF's referred to in the ANDA was provided.

Comment:
All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality.

Response:
Firm acknowledged the comment. **Response is satisfactory.**

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The deficiencies presented below represent FACSIMILE Deficiencies.

A. Deficiencies:

Since you do not wish to market the product in the 12's (40cc container/33mm closure) and the ——— container/——— closure) packaging, please withdraw labeling for these package sizes.

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

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

Sincerely yours,

4/5/98

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-010
Division File
DUP Jacket
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./8/3/98
HFD-623/V. Sayeed, Ph.D./8/4/98
HFD-617/MAnderson, PM/8/4/98
X:\NEW\FIRMSAM\LNK\LTRS&REV\75010.RV2
F/T by: bc/8-4-98

USAtwal 8/4/98 Hayat Sayeed 8/5/98

CHEMISTRY REVIEW - NOT APPROVABLE - FACSIMILE

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-010

3. NAME AND ADDRESS OF APPLICANT
LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, LI, NY 11788

4. LEGAL BASIS FOR SUBMISSION
Approved Product Nuprin® of Bristol Myers

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ibuprofen

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

9. AMENDMENTS AND OTHER DATES:
Original Application Date November 27, 1996
`Refuse To File' Letter Date February 3, 1997
Amendment Date February 5, 1997
`Acceptable For Filing' Date February 6, 1997
Amendment Date April 10, 1997 (Re: Method Validation)
Amendment Date August 1, 1997 (Re: Bioavailability)
New Correspondence Date February 12, 1998 (Re:Letter faxed by the firm to OGD on January 22, 1998, and firm's Tcon. with J. Wilson)
Amendment Date March 5, 1998
Amendment Date August 10, 1998 (This Review)
Amendment Date August 14, 1998 (Re: Labeling issues)

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antipyretic

11. Rx or OTC
OTC

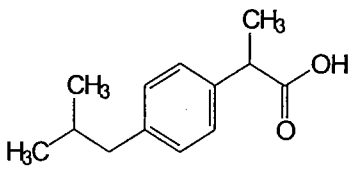
12. RELATED IND/NDA/DMF(s)
ANDA 75-139, Ibuprofen Tablets USP, 200mg (White)

13. DOSAGE FORM
Tablet (Brown)

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Ibuprofen. Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-. $C_{13}H_{18}O_2$. 206.29. 15687-21-1, 58560-75-1.
Anti-inflammatory. USP 23, p785.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Review Sections

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, ***Minor***

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
September 4, 1998

DATE REVISED:
October 6, 1998

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CHEMISTRY REVIEW #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The deficiencies presented below represent FASCIMILE Deficiencies.

Deficiencies:

As already informed in our previous telephone communications, you are required to submit stability data for both the round tablets and the capsule-shaped tablets in the smallest and the largest container closure system proposed for marketing.

Sincerely yours,

10/20/98

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-010
Division File
DUP Jacket
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./9-21-98 10/13/98
HFD-623/V. Sayeed, Ph.D./9-22-98 10/14/98
HFD-617/M. Anderson, PM/9-27-98 10/14/98
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F/T by: bc/

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

Letter to be written by project manager concerning stability data.

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-010

3. NAME AND ADDRESS OF APPLICANT
LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, LI, NY 11788

4. LEGAL BASIS FOR SUBMISSION
Approved Product MOTRIN IB of McNeil Consumer Products

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ibuprofen

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

9. AMENDMENTS AND OTHER DATES:
Original Application Date November 27, 1996
`Refuse To File' Letter Date February 3, 1997
Amendment Date February 5, 1997
`Acceptable For Filing' Date February 6, 1997
Amendment Date April 10, 1997 (Re: Method Validation)
Amendment Date August 1, 1997 (Re: Bioavailability)
New Correspondence Date February 12, 1998 (Re:Letter faxed by the firm to OGD on January 22, 1998, and firm's Tcon. with J. Wilson)
Amendment Date March 5, 1998
Amendment Date August 10, 1998
Labeling Amendment Date August 14, 1998
Correspondence Date October 30, 1998
Correspondence Date December 11, 1998
Labeling Amendment Date December 21, 1998
Amendment Date January 4, 1999 (This Review)
Amendment Date January 19, 1999 (This Review)
Telephone Amendment Date February 10, 1999 (This Review)

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antipyretic

11. Rx or OTC
OTC

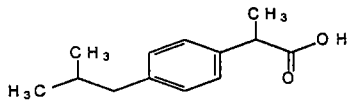
12. RELATED IND/NDA/DMF(s)
ANDA 75-139, Ibuprofen Tablets USP, 200mg (White)

13. DOSAGE FORM
Tablet (Brown)

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Ibuprofen. Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-. $C_{13}H_{18}O_2$. 206.29. 15687-21-1, 58560-75-1. Anti-inflammatory. USP 23, p785.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

See Individual Review Sections

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable

19. REVIEWER:

U.S. Atwal

DATE COMPLETED:

February 1, 1999

DATE REVISED:

February ~~10~~ 17, 1999

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CHEMISTRY REVIEW #4

ANDA 75-010
Division File
DUP Jacket
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./ 2/17/99
HFD-623/V. Sayeed, Ph.D./ 2/18/99.
HFD-617/M. Anderson, PM/
X:\NEW\FIRMSAM\LNK\LTRS&REV\75010.RV4
F/T by: bc/

CHEMISTRY REVIEW - APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

ADDENDUM

To: ANDA 75-010, Review No. 4

1. After the review of the ANDA was completed and the approval package left the branch, the COMIS system showed that the DMF holder had submitted Annual Update to the DMF. The DMF update of January 29, 1999, was reviewed on February 23, 1999 and was found to be satisfactory. The DMF is Adequate.

2. [redacted] was entered into the EES system. See EER acceptable dated January 22, 1999.

3/24/99

APPEARS THIS WAY
ON ORIGINAL

ANDA **75-010** APPROVAL SUMMARY

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg (brown round shape tablet and brown capsule shape tablet).

FIRM: LNK International, Inc.

DOSAGE FORM: brown round shape tablet and brown capsule shape tablet.

STRENGTH: 200 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER Acceptable Date August 24, 1998

BIO STUDY: APPROVE, Per Bio Review Dated 11/13/97

VALIDATION: N/A (DS and DP are compendial)

STABILITY: Stability data under CRT 25-30°C and Ambient RH, and Accelerated 40±2°C and 75%±5% (RH) condition for both round shape tablet and capsule shape tablet in the smallest and largest marketing size container/closure system are provided:

Round Tablets:
Lot P18658 (Provided in Amendment dated 01/04/99, vol. 4.1):
12's Snap Cap, 3 months RT and 3 months accelerated, Exhibit 1.
12's Screw Cap, 3 months RT and 3 months accelerated, Exhibit 3.
100's Easy Off, 3 months RT and 3 months accelerated, Exhibit 5.
250's Snap Cap, 3 months RT and 3 months accelerated, Exhibit 2.

Lot R&D 728 (Provided in Amendment dated 01/04/99, vol. 4.1):
1000's Screw Cap,24 months RT and 3 month Accelerated, Exhibit 4.

Lot #P13517B, Nine months RT in Bulk [redacted] (Provided in Amendment dated 3/5/98, vol. 2.1, Exhibit 20).

Capsule Shape Tablets:
Lot P19515 (Provided in Amendment dated 01/04/99, vol. 4.1):
12's Snap Cap, 3 months RT and 3 months accelerated, Exhibit 6.
100's Easy Off, 3 months RT and 3 months accelerated, Exhibit 8.
250's Snap Cap, 3 months RT and 3 months accelerated, Exhibit 7.
12's Screw Cap, 3 months RT and 3 months accelerated (Provided in Amendment dated 01/19/99, Exhibit 3).

Note: Data for capsule shape tablets in 1000's and in bulk packaging were not provided as firm does not intend to market these configurations.

Proposed Expiration Period: 24 months for all commercial packages; 6 months for the product packaged in bulk.

LABELING: APPROVE, Per Labeling Review Dated 01/08/99

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO BATCH: The bio batch, #P13517B, size ——— tablets, is also one of the test batches. The drug substance source is ———, lot #LPL-4486 (applicant's lot #M31667), and lot #LPL-3701 (applicant's lot #29320). DMF #——— is adequate as of 03/06/98. There has been no DMF update since last review.

SIZE OF STABILITY BATCHES: Stability batches are the same as test batches, size ——— tablets.

PROPOSED PRODUCTION BATCHES: The proposed production batch size is ——— tablets. The manufacturing process for production batches remains the same as that for test batches.

CHEMIST: [signature] **DATE:** 2/17/99

SUPERVISOR: **DATE:**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

BIOEQUIVALENCE REVIEWS

JUN 20 1997

Ibuprofen Tablets, USP
200 mg
ANDA #75010
Reviewer: Kuldeep R. Dhariwal
Filename: 75010SDW.N96

LNK International, Inc.
60 Arkay Drive
Hauppauge, NY 11788
Submission Date:
November 27, 1996

Review of Fasting and Food Studies and Dissolution Data

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting and fed conditions and dissolution data comparing its ibuprofen tablets, 200 mg with Bristol-Myers Squibb's Nuprin® 200 mg tablets.

Introduction:

Ibuprofen is a non-steroidal, propionic acid derivative with analgesic, antipyretic and anti-inflammatory activities. 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 versus time curve. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. Nuprin® is an OTC product containing ibuprofen 200 mg and is indicated for the temporary relief of minor aches and pains associated with the common cold. The usual adult dosage is 1 tablet every 4 to 6 hours, and may be increased to 2 tablets but not exceeding 6 tablets in 24 hours.

Bioavailability of Ibuprofen Tablets, 200 mg under Fasting Conditions:

A. Objective:

To compare the ibuprofen serum levels produced after administration of the test formulation with those produced after a marketed reference product, under fasting conditions.

B. Study Sites and Investigators:

Clinical and analytical site: [redacted]
Principal Investigator: [redacted] M.D.
Protocol # 11013 Bioavailability of Ibuprofen Tablets, 200 mg was approved by the Institutional Review Board for [redacted]

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 86, vol.1.1.
Study Dates: Period I November 15-16, 1995
Drug was administered on November 16.
Period II November 18-19, 1995
Drug was administered on November 18 as per page 31; drug administered on November 19 as per page 8 17 vol. 1.1.

Analysis Dates: December 5 to 19, 1995

C. Study Design:

The study was designed as a randomized, single oral dose, two-treatment, two-period, cross-over study. There was a 3 day wash-out period between drug administrations. The subjects were housed in dormitory facility from approximately 12 hours prior to drug administration until at least 12 hours postdose each period. The subjects were assigned to two sequences as follows:

Sequence	Subject number	Period I	Period II
1	2,4,5,8,10,11,14,15,18	A	B
2	1,3,6,7,9,12,13,16,17	B	A

Subject number 12 did not complete the study.

A= Ibuprofen tablets, 200 mg; LNK International, Inc.; Lot #P13517B; Lot size: Theoretical yield: [redacted] tablets, Actual yield: [redacted] tablets; Manufacture Date: March 1995; Assay: 98.3%

B= Nuprin® tablets, 200 mg; Bristol-Myers Squibb; Lot #403159; Expiration Date: December 1998; Assay: not given.

The subjects fasted for no fewer than 10 hours prior to dosing and 5 hours after administration of study drug. Water was restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. Identical meals were served during both phases. Blood pressure and pulse measurements were obtained predose, 4 and 12 hours postdose. Diagnostic blood and urine

specimens were obtained from the subjects prior to discharge from the study at the end of period II.

D. Subject selection:

Eighteen healthy subjects (14 females, 4 males) were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-60 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study
- female subjects were given a serum pregnancy test at screening and urine pregnancy test at check-in for each period

Subjects were excluded from the study based on the following criteria:

- history of asthma, nasal polyps, esophagitis, peptic and duodenal ulcer, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to ibuprofen or sensitivity to aspirin or any other nonsteroidal anti-inflammatory drugs

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding aspirin, acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with no anticoagulant at 0 (predose), 15, 30, 45 minutes and 1, 1.33,

1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours. The serum was transferred to prelabeled tubes and samples were stored at -20°C.

F. Analytical Methods:

G. Pharmacokinetics/Statistics:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to five concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Eighteen subjects entered the study. Subject #12 voluntarily withdrew after 6 hour sample collection in period I. Three subjects experienced adverse events like headache, lightheaded, and decreased blood pressure.

Deviations in the study:

No protocol deviations are reported.

Reassays:

Of the 612 samples assayed for this study, 1 sample was reassayed due to pharmacokinetic anomaly.

2. Analytical:

SPECIFICITY: The serum used to prepare calibration standards and control samples was screened chromatographically to confirm the absence of endogenous compounds that would interfere with the analysis of ibuprofen and internal standard. Selectivity was also confirmed by assaying a predose serum sample from each study phase for every subject with and without the addition of internal standard. The predose samples were free from interferences.

LINEARITY: For most analytical runs, the coefficients of determination of the calibration lines were greater than ——— for ibuprofen. The weighting factor of [1/concentration] was used for least-squares linear regression analysis of all study data.

SENSITIVITY: The range of quantification for this assay was between —— and —— μg/mL for ibuprofen. The lower limit of quantification of the assay was —— μg/mL for ibuprofen. Serum sample values calculated to be less than ——— μg/mL were reported as zero.

ACCURACY AND PRECISION: The accuracy of the assay for ibuprofen was between ——— % and —— % for all standards and control samples. The inter-run precision of the calibration standards was —— % to ——— % for ibuprofen. The inter-run precision of the control samples was —— % to —— %.

STABILITY: Serum samples spiked with known concentrations of ibuprofen were prepared on November 15, 1995. These stability samples were transferred from the clinic and stored with the study samples in the laboratory freezer at -20°C on November 27, 1995. The concentrations prepared were 30 and 2.0 μg/mL of ibuprofen. These stability samples were assayed during the course of the sample analysis. The results demonstrate the stability of ibuprofen in serum for 35 days which covers both the clinical and analytical portion of the study.

The firm has provided following pre-study method validation results:

Accuracy:
Intra-day —— % to —— %
Inter-day —— % to —— %

Precision:
Intra-day —— % to —— %
Inter-day —— % to —— %

Sensitivity: The limit of quantitation was ——. The inter-day coefficient of variation for ibuprofen at this concentration was 12.9%

Specificity: Caffeine, salicylic acid, acetaminophen, and theophylline did not interfere with the assay.

Recovery:
Ibuprofen ——
——
——
Internal Standard ——

Stability:
a) Room temperature: stable for 24 hours
1 μg/mL 101%
50 μg/mL 105%
b) Freeze-thaw: stable over 2 cycles. Concentrations (%) after exposing to 2 freeze-thaw cycles:
1 μg/mL 106%
50 μg/mL 95.1%
c) Autosampler: stable for 40 hours

Theoretical	First assay conc.	Repeat assay conc. (after 40 hours)
	μg/mL	
30	30.7	30.8
10	10.4	10.5
2	2.01	2.16

3. Pharmacokinetics/Statistics:

The mean serum concentrations of ibuprofen at each time point after test and reference products are shown in Table 2. There were significant ($\alpha = 0.05$) differences in mean concentrations between the formulations at 0.25, 0.5 and 3.5 hours after dosing. The time courses of ibuprofen concentration after the two products are shown in Figure 1. The pharmacokinetic parameters are summarized in Table 2. There was almost no difference in AUC_{0-t} and AUC_{0-inf} of the test and reference products. The C_{max} of the test product was 9% lower than that of the reference product but occurred at the same time in both the products.

The individual test/reference ratio for AUC_{0-t} ranged from 0.91-1.16 (mean 1.01), AUC_{0-inf} ranged from 0.86-1.16 (mean 1.01) and for C_{max} ranged from 0.60-1.45 with a mean of 0.93 (Table 3).

The AUC_{0-t}/AUC_{0-inf} ratios range from 0.93-0.97 for test and 0.91 to 0.96 for reference product (Table 4).

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable limits of 80-125% (Table 2). There was no significant period, treatment or sequence effect for these parameters.

Bioavailability of Ibuprofen Tablets, 200 mg: Food Study

A. Objective: (1) To compare the ibuprofen serum levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal
(2) To compare the ibuprofen serum levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical and Analytical Site: [redacted]

Principal Investigator: [redacted], M.D.
Project Director: [redacted], Ph.D.
Protocol #11014 "Bioavailability of Ibuprofen Tablets, 200 mg: Effect of Food Study" was approved by the National Institutional Review Board for [redacted]
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 88, vol. 1.4.
Study Dates: Period I November 21-22, 1995
Period II November 28-29, 1995
Period III December 5-6, 1995
Analysis Dates: December 14-22, 1995

C. Study Design:

The study was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 12 hours after drug administration. The subjects (who completed the study) were assigned as follows:

Subject	Period I	Period II	Period III
1,11,14	B	C	A
2,9,15	A	B	C
3,8,16	B	A	C
4,12,17	C	B	A
5,10	C	A	B
6,7,13	A	C	B

A= Ibuprofen Tablets, 200 mg following a standard meal; LNK International; Lot #P13517B; Manufacture Date: March 1995; Assay: 98.3%
B= Nuprin® Tablets, 200 mg following a standard meal; Bristol-Myers Squibb; Lot #403159; Expiry Date: December 1998
C= Ibuprofen Tablets, 200 mg following an overnight fast; LNK International; Lot #P13517B

Lot numbers of the drug products administered in this study are the same as those used for the fasting study.

D. Subject Selection:

Eighteen female subjects were enrolled in the study with essentially same inclusion and exclusion criteria as used for fasting study.

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 35 minutes prior to dosing and subjects ate the entire meal within 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with no anticoagulant at 0 (predose), 15, 30, and 45 minutes and 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours.

G. Analytical Methods, Pharmacokinetics/Statistics:

Same as for fasting study.

H. Results:

1. Clinical:

Eighteen subjects entered the study. Subject #18 voluntarily withdrew after completing period II. Eight subjects reported adverse events like headache and cold.

Deviations in the study:

1. Five subjects (1,2,7,9, and 16) consumed alcohol during period I interphase and three subjects (1,9, and 13) consumed alcohol during period II interphase. All alcohol consumption occurred at least 24 hours prior to dosing.

2. One blood sample was withdrawn 1 minute late and one sample was withdrawn 2 minutes late than scheduled phlebotomy time.

Reassays:

Of the 816 samples assayed for this study, 8 samples (2 due to pharmacokinetic anomaly and 6 due to suspected or documented processing error) were reassayed.

2. Analytical:

LINEARITY: The coefficients of determination of the calibration lines were greater than 0.998 for ibuprofen.

SENSITIVITY: The range of the assay was — to — μg/mL. The LOQ was — μg/mL.

ACCURACY AND PRECISION: The accuracy of the assay was between — and —% for all standards and control samples. The inter-run precision of the calibration standards were — to —%. The inter-run precision of the control samples was — to —%.

STABILITY: Serum samples spiked with 2 μg/mL and 30 μg/mL of ibuprofen were prepared on November 21, 1995 and stored with study samples at -20°C. These samples were assayed during the course of study sample analysis. The results demonstrate the stability of ibuprofen in serum for 31 days which covers both clinical and analytical portion of the study.

Pre-study Method Validation: same as for fasting study.

3. Pharmacokinetics/Statistics:

The concentrations of ibuprofen measured at each time point after each product is summarized in Table 5. The time courses of ibuprofen concentration after the three treatments are plotted in Figure 2.

Test formulation after a meal vs. Reference formulation after a meal: When the test and reference formulations were administered after a meal, arithmetic means for AUC_{0-t} and AUC_{0-inf} for the test formulation were both 2% lower than the respective means for reference formulation. There was no difference in C_{max} of the two formulations. The T_{max} in test was about 16 minutes later (Table 6).

Test formulation after a meal vs. Test formulation after a 10 hour fast: The arithmetic means for AUC_{0-t} and AUC_{0-inf} after the meal were 22% lower compared to 10 hour fasting. The mean C_{max} was 13% lower and 18 minutes later in test fed compared to the test fasting conditions (Table 6).

The following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric means
AUC_{0-t}	0.983	0.981
AUC_{0-inf}	0.979	0.978
C_{max}	1.000	0.996

Test-fed/Test-fast

AUC_{0-t}	0.773	0.773
AUC_{0-inf}	0.783	0.784
C_{max}	0.870	0.845

In Vitro Dissolution Testing:

The dissolution testing was done using old USP method: 900 mL phosphate buffer, pH 7.2 using apparatus 1 (basket) at 150 rpm. The dissolution was performed on 6 test and 6 reference tablets. Two sets of samples were prepared from each tablet and analyzed. The new USP dissolution method recommends apparatus 2 (paddles) at 50 rpm.

Waiver Request:

The biostudy was done using ibuprofen brown coated round shape tablets. The firm also intends to market brown coated caplet shape tablet and has submitted dissolution data on 6 tablets of caplet shape. The firm however has not made a formal waiver request for brown caplet shape tablet.

Comments:

1. **Not to be released under FOI:** The firm originally submitted ANDA for four color/shapes (round white, caplet white, round brown, caplet brown) Ibuprofen tablets, 200 mg with a bio-study on round brown tablets. The agency sent refusal to file letter to the firm stating that separate applications are required for solid oral dosage forms that contain a single strength, multiple colors and multiple shapes when there is more than one shape per color. The agency asked the firm to withdraw one color from ANDA and submit it as a new application for the different color and shapes. In response, the firm withdrew the application for white color. This application is for brown coated tablets in round and caplet shapes. The firm has done biostudy on round shape tablet and is presumably seeking waiver for caplet shape tablet. However, the waiver request has not been made in the application.

2. **Not to be released under FOI:** The Orange book 1996 lists Nuprin (Bristol-Myers) 200 mg tablet as reference listed drug. The Orange book 1997 lists McNeil's 200 mg tablet as RLD. As per Don Hare, such a change was made because McNeil's product is also available as 100 mg tablet. The biostudy can be done on 200 mg tablet with a waiver request for 100 mg strength. Bristol-Myers Squibb's Nuprin is available only in 200 mg strength.

The firm in the present study has used Nuprin 200 mg tablets (Bristol Myers) as RLD. The biostudy was done in 1995 and was submitted to the agency in November 1996. The change in RLD (from Bristol Myers to McNeil) was made in Orange book supplement 6 (Jan. 96-June 96).

3. None of the serum samples analyzed in the study had ibuprofen concentrations higher than 32.4 μg/mL. The firm has used the standard curve of 1-100 μg/mL and these QC sample concentrations: low 2.5 μg/mL, medium 15 μg/mL, and high 75 μg/mL.

4. The washout period was 3 days in fasting study and 7 days in nonfasting study.

Fasting study:

1. Eighteen subjects entered the study. Subject #12 voluntarily withdrew after 6 hour sample collection in period I. Three subjects experienced adverse events like headache, lightheaded, and decreased blood pressure.

2. There was almost no difference in AUC_{0-t} and AUC_{0-inf} of the test and reference products. The C_{max} of the test product was 9% lower than that of the reference product and occurred at the same time in both the products.

3. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%.

4. The reviewer repeated pharmacokinetic and statistical analysis of the data. In general, there was good agreement between the reviewer's and firm's calculations.

Food study:

1. Eighteen subjects entered the study. Subject #18 voluntarily withdrew after completing period II. Eight subjects reported adverse events like headache and cold.

2. When the test and reference formulations were administered after a meal, arithmetic means for AUC_{0-t} and AUC_{0-inf} for the test formulation were both 2% lower than the respective means for reference formulation. There was no difference in C_{max} of the two formulations. The T_{max} in test was about 16 minutes later.

3. The arithmetic means for AUC_{0-t} and AUC_{0-inf} after the meal were 22% lower compared to 10 hour fasting. The mean C_{max} was 13% lower and 18 minutes later in test fed compared to the test fasting conditions.

4. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test-fed and reference-fed are within acceptable limits.

5. There was good agreement between reviewer's and firm's calculations.

Dissolution Testing:

The dissolution testing was done by old USP method. The USP revised the dissolution method and specification for ibuprofen tablets in November 1996. The firm would be asked to submit dissolution results on 12 individual test and reference tablets using new USP method given in fifth supplement to USP 23.

Waiver request:

The caplet shape tablets dissolve more than 80% in 60 minutes. However, the data are presented with only 6 tablets using old USP method. The composition of caplet shape tablet is same as round shape tablet which underwent bioequivalency testing.

Deficiencies:

1. Please provide shape (round or caplets), assay and content uniformity data of the reference product used in the biostudy.

2. Please note that dissolution testing should be done on 12 individual tablets. Therefore, dissolution data should be submitted on 12 test and 12 reference products used in the biostudy. Also, dissolution data on 12 individual caplet shape tablets should be submitted. Please be advised that USP revised the dissolution method and specification for ibuprofen tablets in November 1996 (fifth supplement to USP 23). The disssolution testing should be done using new method.

3. Fasting study, Period II: Drug was administered on November 18 as per page 31 (washout period 2 days); on November 19, 1995 as per page 8 17 vol 1.1 (washout period 3 days). In clinical summary on page 31 vol. 1.1, it is stated that washout period was one week between drug administrations. Please clarify.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by LNK International on its Ibuprofen round brown coated tablets, 200 mg, lot #P13517B, comparing it to the reference product Nuprin® 200 mg tablets, lot #403159 manufactured by Bristol-Myers Squibb has been found incomplete by the Division of Bioequivalence for the reasons given in the deficiencies.

2. The *in vivo* bioequivalence study conducted under fed conditions by LNK International on its Ibuprofen round brown coated tablets, 200 mg, lot #P13517B, comparing it to the reference product Nuprin® 200 mg tablets, lot #403159 manufactured by Bristol-Myers Squibb has been found incomplete by the Division of Bioequivalence for the reasons given in deficiencies #1 and 2.

3. The dissolution data are unacceptable for the reasons given in the deficiency #2.

4. From the bioequivalence point of view, the application is incomplete.

The firm may be informed of the recommendations, deficiencies and the following comment:

The waiver request should be submitted for *in vivo* bioequivalence study requirements for caplet shape brown coated test tablets.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 6/19/97

Concur: _____ Date 6/20/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #75010 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), HFD-650 (Director), Drug File, Division File

Draft: 060397; Final 060497

Table 1

Quantitative Composition of Ibuprofen Tablets

Component	mg/tablet
Ibuprofen, USP	200
Lactose [redacted] NF	[redacted]
Sodium Starch Glycolate, NF	
[redacted] Starch, NF	
[redacted] Cellulose, NF	
Stearic Acid, NF	
Magnesium Stearate	
Fumed Silica Gel, NF	
Total	325.0
Brown Coating	
[redacted] Brown	[redacted]

APPEARS THIS WAY
ON ORIGINAL

Table 2

MEAN SERUM IBUPROFEN LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY
(μg/mL) (n=17)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	1.34	2.00	3.83	3.95	0.35
0.5	6.98	5.24	13.18	8.10	0.53
0.75	13.71	7.46	16.13	8.60	0.85
1	17.22	6.99	17.58	6.01	0.98
1.33	20.07	3.80	17.89	5.31	1.12
1.67	19.18	2.91	17.67	5.86	1.09
2	17.85	2.80	16.40	5.10	1.09
2.33	16.72	2.90	15.22	4.82	1.10
2.67	15.59	3.18	13.84	3.83	1.13
3	13.57	2.69	12.24	3.25	1.11
3.5	11.75	2.19	10.50	2.65	1.12
4	10.33	1.93	10.09	4.30	1.02
5	7.62	1.34	7.53	3.78	1.01
6	5.02	1.12	5.05	2.74	0.99
8	2.48	0.74	2.67	1.65	0.93
10	1.12	0.79	1.26	1.21	0.88
12	0.28	0.53	0.51	0.88	0.56

ARITHMETIC MEANS AND RATIOS
UNIT: AUC=μg/mLxh, CMAX=μg/mL, TMAX=hr

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	85.18	15.54	85.41	18.91	1.00
AUCT	81.11	15.28	80.88	17.41	1.00
CMAX	21.74	3.43	23.82	4.29	0.91
KE	0.35	0.06	0.34	0.06	1.03
LAUCI	83.84	0.18	83.49	0.22	1.00
LAUCT	79.75	0.19	79.15	0.21	1.01
LCMAX	21.48	0.16	23.43	0.19	0.92
THALF	2.03	0.34	2.11	0.40	0.96
TMAX	1.51	0.54	1.51	0.92	1.00

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	84.94	85.30	1.00	95.84	103.32
AUCT	80.87	80.76	1.00	96.85	103.41
CMAX	21.69	23.80	0.91	83.61	98.67
LAUCI	83.61	83.42	1.00	96.72	103.87
LAUCT	79.52	79.06	1.01	97.41	103.84
LCMAX	21.43	23.40	0.92	83.90	99.95

Table 3

TEST PRODUCT (1)/REFERENCE PRODUCT (2) RATIOS FOR INDIVIDUAL SUBJECTS IN FASTING STUDY

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2	0.98	0.98	0.80	1.77	1.04	0.96
2	2	1	1.05	1.05	0.98	1.33	1.04	0.96
3	3	2	0.96	0.96	1.45	0.43	0.97	1.03
4	4	1	1.16	1.15	0.70	3.34	0.92	1.08
5	5	1	1.11	1.10	0.84	1.50	0.94	1.07
6	6	2	1.05	1.06	0.75	2.23	1.09	0.91
7	7	2	0.91	0.86	0.89	1.15	1.79	0.56
8	8	1	1.04	1.04	1.00	0.80	1.02	0.98
9	9	2	1.03	1.07	0.60	5.34	0.90	1.11
10	10	1	1.16	1.16	1.01	1.00	0.95	1.05
11	11	1	1.04	1.04	1.02	1.77	1.04	0.96
12	13	2	1.03	1.03	0.93	2.23	1.03	0.97
13	14	1	0.93	0.93	0.87	0.60	1.01	0.99
14	15	1	0.98	0.95	1.11	0.19	0.94	1.06
15	16	2	0.91	0.91	1.04	0.57	1.01	0.99
16	17	2	0.93	0.93	0.98	0.67	0.98	1.02
17	18	1	0.91	0.91	0.91	0.80	1.19	0.84

STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	17	1.01	0.08	0.91	1.16
RAUCI12	17	1.01	0.09	0.86	1.16
RCMAX12	17	0.93	0.19	0.60	1.45
RTMAX12	17	1.51	1.27	0.19	5.34
RKE12	17	1.05	0.20	0.90	1.79
RTHALF12	17	0.97	0.13	0.56	1.11

Table 4

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

OBS	SUB	TRT	AUCRATIO
1	1	1	0.96
2	2	1	0.95
3	3	1	0.94
4	4	1	0.95
5	5	1	0.96
6	6	1	0.94
7	7	1	0.97
8	8	1	0.95
9	9	1	0.93
10	10	1	0.96
11	11	1	0.95
12	13	1	0.95
13	14	1	0.96
14	15	1	0.95
15	16	1	0.95
16	17	1	0.94
17	18	1	0.95
18	1	2	0.96
19	2	2	0.95
20	3	2	0.94
21	4	2	0.94
22	5	2	0.96
23	6	2	0.95
24	7	2	0.91
25	8	2	0.95
26	9	2	0.96
27	10	2	0.96
28	11	2	0.95
29	13	2	0.95
30	14	2	0.95
31	15	2	0.92
32	16	2	0.95
33	17	2	0.94
34	18	2	0.96

STATISTICS ON AUCT/AUCI RATIOS

	N	Mean	Std Dev	Minimum	Maximum
TRT=1 (Test)	17	0.95	0.01	0.93	0.97
TRT=2 (Ref)	17	0.95	0.01	0.91	0.96

Table 5

MEAN SERUM IBUPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (FOOD STUDY)
μg/mL; N=17

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	2.64	3.70	0.06	0.24	0.77	2.26	44.86
0.5	7.57	6.57	2.70	5.02	6.15	9.31	2.80
0.75	10.34	7.26	6.60	8.47	9.30	10.81	1.57
1	12.52	7.63	9.25	9.57	11.93	9.11	1.35
1.33	15.41	7.83	11.32	8.92	14.55	7.63	1.36
1.67	18.08	4.59	11.96	7.01	15.41	5.19	1.51
2	19.95	3.75	12.61	4.77	15.51	4.40	1.58
2.5	18.71	4.53	12.96	4.96	13.76	3.32	1.44
3	16.80	4.32	13.59	4.83	12.34	2.44	1.24
4	12.53	3.61	11.11	4.21	9.54	1.48	1.13
5	9.20	2.78	8.35	3.34	7.78	1.94	1.10
6	6.02	2.17	5.61	2.48	5.08	1.16	1.07
8	2.83	1.31	2.51	1.47	2.22	0.56	1.13
10	1.47	0.96	1.18	0.97	0.96	0.79	1.25
12	0.52	0.74	0.25	0.56	0.14	0.40	2.11

(CONTINUED)

UNIT: SERUM LEVEL=μg/mL TIME=HRS
MEAN SERUM IBUPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	3.44	0.08
0.5	1.23	0.44
0.75	1.11	0.71
1	1.05	0.78
1.33	1.06	0.78
1.67	1.17	0.78
2	1.29	0.81
2.5	1.36	0.94
3	1.36	1.10
4	1.31	1.16
5	1.18	1.07
6	1.19	1.11
8	1.27	1.13
10	1.53	1.22
12	3.69	1.75

Mean 1= Test-fasting
Mean 2= Test-fed
Mean 3= Ref-fed

RMEAN 12= Test-fast/Test-fed, ratio of means
RMEAN 13= Test-fast/Ref-fed, ratio of means
RMEAN 23= Test-fed/Ref-fed, ratio of means

Table 6

ARITHMETIC MEANS AND RATIOS
FOOD STUDY

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	93.17	19.36	72.93	14.86	74.50	15.12	1.28
AUCT	89.26	18.58	69.03	14.66	70.19	14.43	1.29
CMAX	22.35	3.79	19.46	5.94	19.46	5.68	1.15
KE	0.36	0.06	0.37	0.06	0.37	0.07	0.97
LAUCI	91.24	0.21	71.58	0.20	73.20	0.19	1.27
LAUCT	87.41	0.21	67.61	0.21	68.93	0.19	1.29
LCMAX	22.07	0.16	18.66	0.30	18.73	0.28	1.18
THALF	1.97	0.35	1.90	0.29	1.96	0.39	1.04
TMAX	1.81	0.68	2.11	0.99	1.85	1.02	0.86

(CONTINUED)

UNIT: AUC=μg/mLxh CMAX=μg/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.25	0.98
AUCT	1.27	0.98
CMAX	1.15	1.00
KE	0.99	1.02
LAUCI	1.25	0.98
LAUCT	1.27	0.98
LCMAX	1.18	1.00
THALF	1.01	0.97
TMAX	0.98	1.14

Mean 1= Test-fasting
Mean 2= Test-fed
Mean 3= Ref-fed

RMEAN 12= Test-fast/Test-fed, ratio of means
RMEAN 13= Test-fast/Ref-fed, ratio of means
RMEAN 23= Test-fed/Ref-fed, ratio of means

Table 7. In Vitro Dissolution Testing

Drug (Generic Name): Ibuprofen
Dose Strength: 200 mg
ANDA No.: 75-010
Firm: LNK International
Submission Date: November 27, 1996
File Name: 75010SDW.N96

I. Conditions for Dissolution Testing: Old USP method

USP XXIII Basket: x Paddle: RPM: 150
No. Units Tested: 6
Medium:Phosphate buffer, pH 7.2 Volume: 900 mL
Specifications: NLT (Q) 70% in 30 minutes (New: NLT (Q) 80% in 60 minutes)
Reference Drug: Nuprin (Bristol Myers Squibb)
Assay Methodology: uV absorbance at 221 nm

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # P13517B Strength(mg) 200, round shape			Reference Product Lot # 403159 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
15	102.92		1.08	103.48		6.75
30	103.05		0.85	102.60		6.75
45	103.58		0.79	107.0		7.12
60	103.78		0.97	103.46		6.90

Sampling Times (Minutes)	Test Product Lot # P14752 Strength(mg) 200, caplet shape			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.70		5.62			
30	97.71		6.31			
45	99.26		4.90			
60	98.88		6.44			

FIG P-1. SERUM IBUPROFEN LEVELS

IBUPROFEN TABLETS, 200 MG, ANDA #75-010
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG

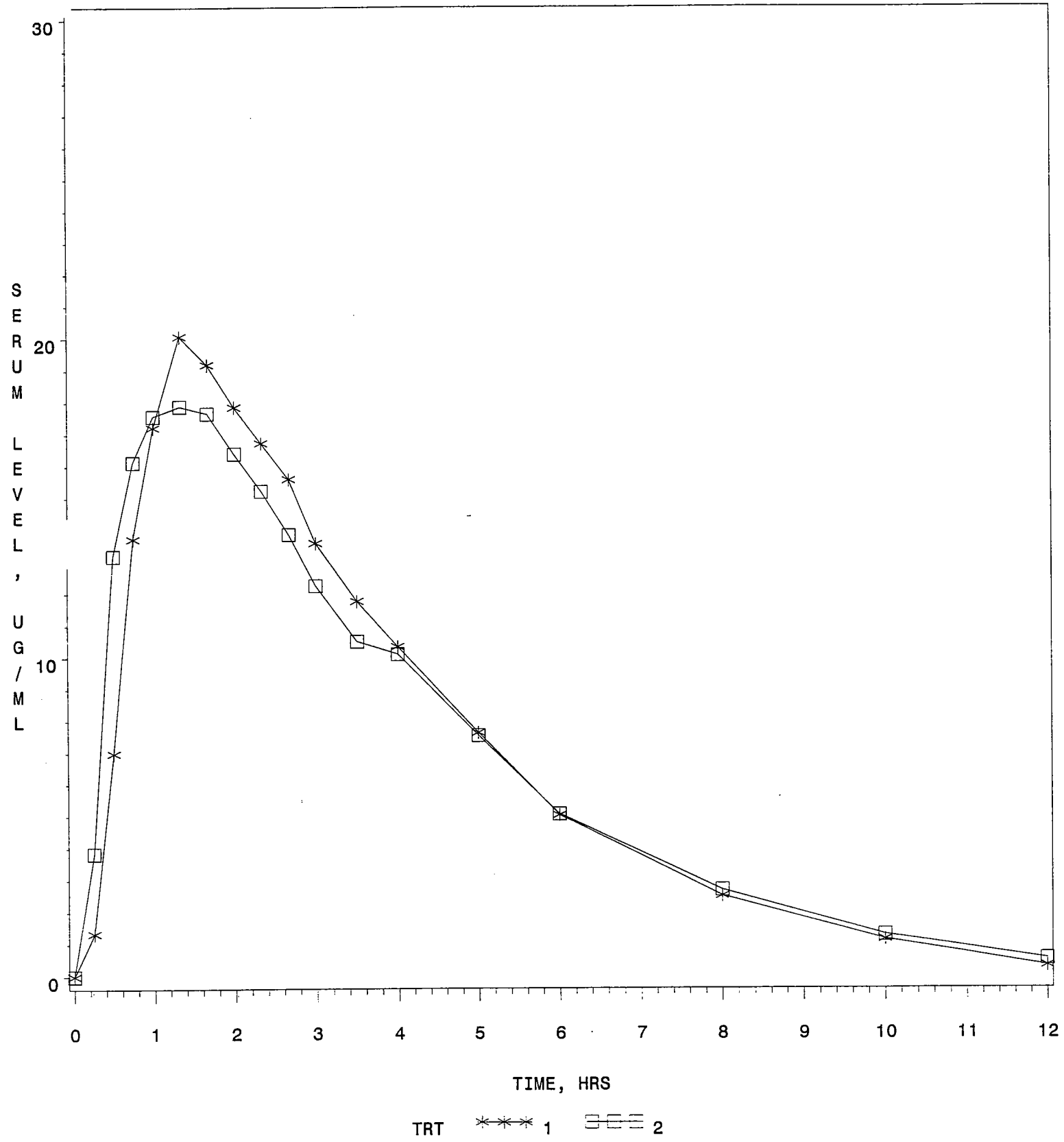
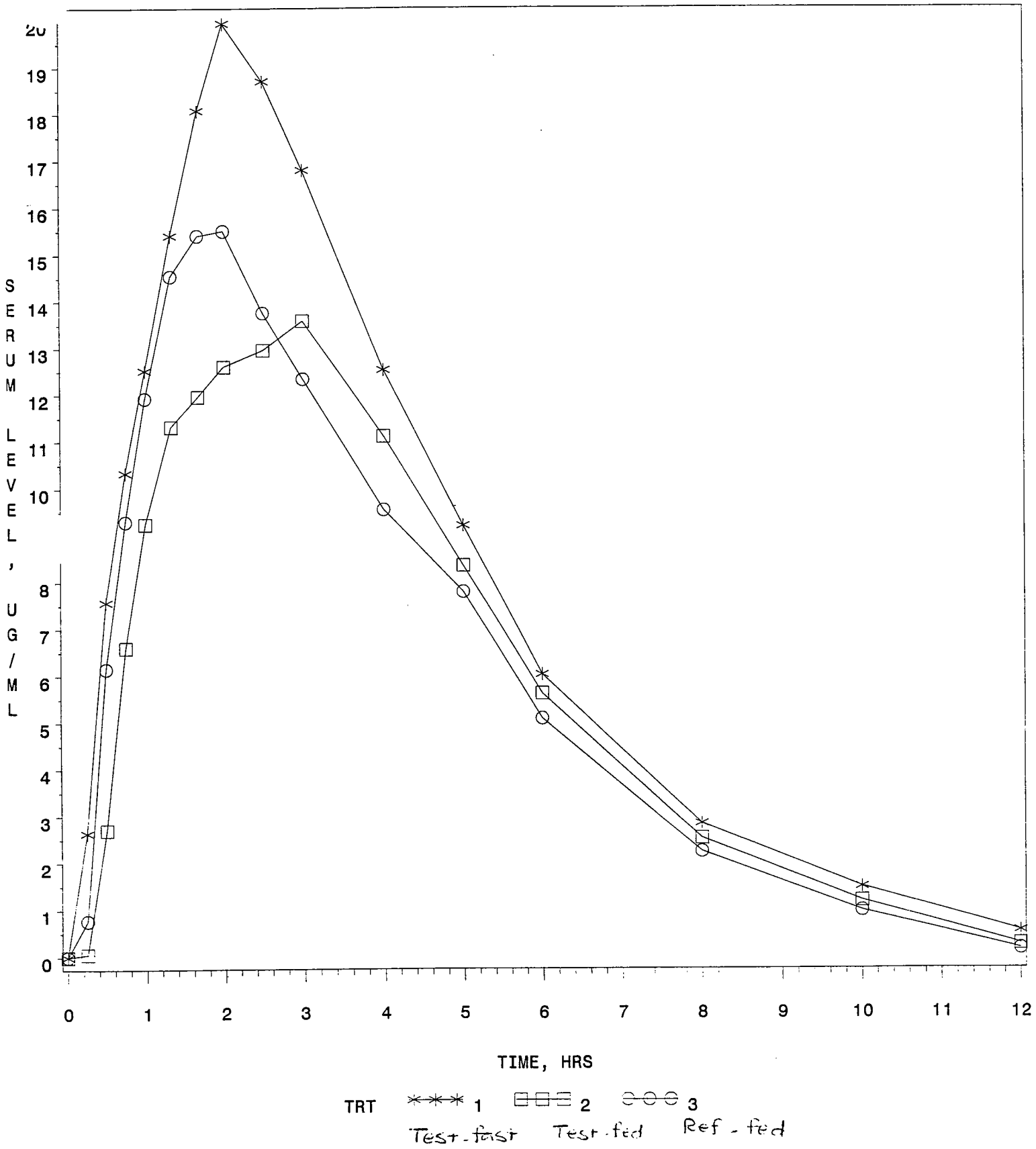


FIG P-2 SERUM IBUPROFEN LEVELS

IBUPROFEN TABLETS, 200 MG, ANDA #75-010
UNDER NONFASTING CONDITIONS
DOSE=1 X 200 MG



2.1

[redacted] 81.97 Subm

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (5th supplement):

> The dissolution testing should be conducted in 900 mL of pH 7.2 phosphate buffer, using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

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,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-010
ANDA DUPLICATE
DIVISION FILE
HFD-650/Division Sign Off
HFD-650/K. Dhariwal
BIO DRUG FILE
FIELD COPY

(X:NEW\FIRMSAM\LNK\LTRS&REV\75010bio.fs2)

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

2. **FOOD STUDY** (STP)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS)

   All Strengths

   Outcome: **AC IC UN NC**

(5.) **STUDY AMENDMENT** (STA)

Strengths: 200 mg

Outcome: (AC) IC UN NC

6. **WAIVER** (WAI)

   Strengths: _____

   Outcome: AC IC UN NC

7. **DISSOLUTION WAIVER** (DIW)

   Strengths: _____

   Outcome: AC IC UN NC

8. **OTHER** (OTH) _____

   Strengths: _____

   Outcome: AC IC UN NC

9. **OTHER OPTIONS** (less common):
   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)

   Strengths: _____
   d. Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)
   Outcome: AC IC UN NC

OUTCOME DECISIONS:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

Ibuprofen Tablets, USP
200 mg, Brown color
round and caplet shape
ANDA #75010
Reviewer: Kuldeep R. Dhariwal
File name: 75010SDW.897

LNK International, Inc.
60 Arkay Drive

Hauppauge, NY 11788
Submission Date:
August 1, 1997

Response to Review of Bioequivalence Studies and Dissolution Data

Background:

LNK International previously submitted a single-dose *in vivo* bioequivalence study under fasting and nonfasting conditions and dissolution data comparing its ibuprofen tablets, 200 mg brown color with Bristol-Myers Squibb's Nuprin® 200 mg tablets (File name: 75010SDW.N96). The studies were found incomplete and the deficiency comments were sent to the firm. The firm submitted the response as amendment on August 1, 1997 which was assigned to this reviewer on October 16, 1997.

Response:

Comment 1: **Please provide shape (round or caplets), assay and content uniformity data of the reference product used in the biostudies.**

Response: Nuprin® 200 mg yellow, round tablet
Assay: 102.6%
Content Uniformity: 103.0 to 106.6%

The response is satisfactory.

Comment 2: **Please note that the dissolution testing should be done on 12 individual tablets each of test and reference, not six as in the application. Therefore, dissolution data should be submitted on 12 tablets of test and 12 tablets of reference products that were used in the biostudies. Dissolution data on 12 individual caplet shape tablets also should be submitted. Please note that USP revised the dissolution methods and specifications for ibuprofen tablets in the November 1996 (5th supplement to USP 23). All dissolution testing should be done using the new method.**

Response: Dissolution testing was done on 12 individual reference tablets (Nuprin lot#403159), 12 individual test tablets lot #P14752 (brown, capsule shape), and 12 individual test tablets lot #P13517B (brown, round shape, bio-batch). The testing was done using revised USP method (5th supplement to USP). The test results are given in Table 1. All test and reference tablets dissolve more than 80% in 60 minutes.

The firm has conducted acceptable dissolution testing and the products meet USP specifications.

Comment 3: **Fasting Study, Period II: The drug was administered on November 18 as per page 31 (washout period 2 days); on November 19, 1995 as per page 8 17 vol 1.1 (washout period 3 days). In the clinical summary on page 31 vol. 1.1, it is stated that the washout period was one week between drug administrations. Please Clarify.**

Response: The firm states that drug administration for phases I and II were on November 16 and 19, respectively, with a washout period of three days. The statements in the clinical summary that the washout between drug administrations was one week, and that phase II drug administration was on November 18, were typographical errors.

The response is satisfactory.

Comment 4: **A request should be submitted for a waiver from *in vivo* bioequivalence study requirements for the caplet shape brown coated test tablets. The dissolution testing requested in #2 will serve as supporting data for this request.**

Response: The firm has requested for the waiver for caplet shape brown coated tablets.

Comments:

1. The firm has satisfactorily responded to all the deficiencies and the study is acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by LNK International on its Ibuprofen round brown coated tablets, 200 mg, lot #P13517B, comparing it to the reference product Nuprin® 200 mg round coated tablets, lot #403159 manufactured by Bristol-Myers Squibb has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions, LNK International's Ibuprofen round brown tablets are bioequivalent to the reference product Nuprin® 200 mg round tablets manufactured by Bristol-Myers Squibb.

2. The *in vivo* bioequivalence study conducted under nonfasting conditions by LNK International on its Ibuprofen round brown coated tablets, 200 mg, lot #P13517B, comparing it to the reference product Nuprin® 200 mg round coated tablets, lot #403159 manufactured by Bristol-Myers Squibb has been found acceptable by the Division of Bioequivalence. The study demonstrates that under nonfasting conditions, the bioavailability of LNK International's Ibuprofen 200 mg round coated tablets is similar to that of the reference product Nuprin® 200 mg round coated tablets manufactured by Bristol-Myers Squibb.

3. The dissolution testing conducted on Ibuprofen 200 mg tablets (round and caplet shape) 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 pH 7.2 phosphate buffer using apparatus 2 (paddles) at 50 rpm (USP 23, 5th supplement). The test product should meet the following specifications:

> Not less than 80% (Q) of the labeled amount of ibuprofen is dissolved in 60 minutes.

4. The brown caplet shape tablets are formulated similarily to brown round shape tablets which underwent bioequivalency testing. Both tablet shapes have the same quantitative formula, the only difference is in the shape of punches and dies. The dissolution testing results of brown caplet shape tablets are acceptable. The waiver of the *in vivo* bioequivalency study requirements for LNK International's 200 mg brown caplet shape tablet is granted.

5. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

Dhariwal 11/6/97

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 11/7/1997

Concur: _____ Date 11/13/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #75010 (amendment), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 101797; Final: 110697

APPEARS THIS WAY
ON ORIGINAL

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Ibuprofen Tablets
Dose Strength: 200 mg
ANDA No.: 75010
Firm: LNK International
Submission Date: August 1, 1997
File Name: 75010SDW.897

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL Volume: Phosphate buffer, pH 7.2
Specifications: NLT 80% (Q) in 60 minutes
Reference Drug: Nuprin (Bristol-Myers Squibb)
Assay Methodology: UV at 221 nm

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #P13517B Strength(mg) 200,round shape			Reference Product Lot #403159 Strength(mg) 200, round		
	Mean %	Range	%CV	Mean %	Range	%CV
15	99.25		2.39	97.0		2.84
30	102.63		2.76	103.47		1.96
45	99.76		1.77	103.71		2.43
60	100.77		1.63	101.01		2.09

Sampling Times (Minutes)	Test Product Lot #P14752 Strength(mg)200,caplet shape			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	97.24		2.5			
30	100.62		2.87			
45	101.07		2.45			
60	100.72		2.70			

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75010 SPONSOR: LNK International
DRUG: Ibuprofen brown color, round and caplet shape
DOSAGE FORM: Tablets
STRENGTHS/(s): 200 mg
TYPE OF STUDY: Single dose, Fasting and Nonfasting
STUDY SITE: [redacted]

STUDY SUMMARY: Fasting: Seventeen of eighteen enrolled subjects completed the study. There was almost no difference in AUC_{0-t} and AUC_{0-inf} of the test and reference products. The C_{max} of the test was 9% lower than that of the reference and occurred at the same time in both products. The 90% CI for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} were 97.4-103.8%, 96.7-103.8%, and 83.9-99.95% respectively.
Nonfasting Study: Seventeen of eighteen enrolled subjects completed the study. Ratio of means of AUC_{0-t}, AUC_{0-inf}, and C_{max} were within 0.80-1.20 limit. There was no difference in C_{max} of the two products. The T_{max} in test was about 16 minutes later.

DISSOLUTION: The dissolution testing was done by revised USP method (5th supplement). The brown caplet shape tablets are formulated similarly to brown round shape tablets which underwent biostudy. Both shapes of the tablets dissolve more than 80% in 60 minutes. The waiver of *in vivo* bio-study for brown caplet shape tablet is granted.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: Dhariwal DATE 11/6/97

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: [signature] DATE 11/7/1997

ACTING DIRECTOR
DIVISION OF BIOEQUIVALENCE: Rabindra Patnaik, Ph.D.

INITIAL: _____ DATE _____

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-010 SPONSOR: LNK International
DRUG: Ibuprofen
DOSAGE FORM: Brown round shape tablet and capsule shape tablet
STRENGTHS/(s): 200 mg
TYPE OF STUDY: Single Dose, Fasting and Non-Fasting
STUDY SITE: ———————————

STUDY SUMMARY: The fasting and non-fasting studies conducted on ibuprofen, brown round shape 200 mg tablets are acceptable.

DISSOLUTION: The dissolution testing conducted in 900 mL of phosphate buffer, pH 7.2, using apparatus II (paddles) at 50 rpm is acceptable. The brown caplet shape tablets are formulated similarly to brown round shape tablets. Both tablet shapes have the same quantitative formula, the only difference is in the shape of punches and dies. The dissolution testing on caplet shape tablets is acceptable. The waiver of the in vivo bioequivalency requirements for brown caplet shape tablet is granted.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: KRDhariwal DATE 2/3/99

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: [signature] DATE 2/4/1999

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: [signature] DATE 2/4/99

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Drs. Sayeed and Atwal and I spoke with Mr. Mollica and Pankaj Chudgar, about LNK's Ibuprofen tablet applicatons. The applications provide for round and caplet shaped tablets for brown (ANDA 75-010) and white (ANDA 75-139) colored tablets.

We said that, to date, the firm has not submitted sufficient stability data to qualify both shaped tablets. We have previously requested the firm provide stability data for the largest and smallest container closure system proposed for marketing for each tablet shape. Mr. Mollica said the firm has responded by stating it was their understanding based on discussions with OGD that data provided for one shaped tablet would support the other shaped tablet. (The firm has provided the executed batch records for both shaped tablets). We said that although they may have discussed this issue, the policy of the office is to require data for each shaped tablet.

We discussed the need for the firm to submit the requested information or withdraw the sizes which they wish to market and submit as supplemental applications with requested stability data. The firm proceded to say they may have stability for some of the other sizes which they haven't submitted based on above and advice given by a former consultant. We stated again that they need data for largest and smallest cont/closure for each shape. They will check. This concluded the discussion.

X:\new\firmsam\lnk\telecons\75010.001

10/23/98

9/30/98

APPLICATION NUMBER
75-010 (brown)
75-139 (white)

TELECON

INITIATED BY APPLICANT

PRODUCT NAME
Ibuprofen tablets/caplets

FIRM NAME
LNK

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Joseph Mollica

TELEPHONE NUMBER
516-435-3500

SIGNATURE
Mark Anderson

RECORD OF TELEPHONE CONVERSATION

Drs. Sayeed and Atwal and I spoke with Mr. Mollica, Pankaj Chudgar, and David Rosen about LNK's Ibuprofen tablet applicatons. The applications provide for round and caplet shaped tablets for brown (ANDA 75-010) and white (ANDA 75-139) colored tablets. This is a follow-up to the 9/30/98 T. Con. See that T. Con for background.

We discussed the need for the firm to submit the requested information or withdraw the sizes which they wish to market and submit as supplemental applications with requested stability data. The firm now claims to have adequate stabilty data.

We told them we would issue facsimile comments for each application and to not submit data until they received the comments.

This concluded the discussion.

X:\new\firmsam\lnk\telecons\75010.002

DATE
10/2/98

APPLICATION NUMBER
75-010
75-139

TELECON

INITIATED BY APPLICANT

PRODUCT NAME
Ibuprofen tablets/caplets

FIRM NAME
LNK

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Joseph Mollica

TELEPHONE NUMBER
516-435-3500

SIGNATURE
Mark Anderson

RECORD OF TELEPHONE CONVERSATION

Dr. Sayeed, Dr. Atwal and I called Mr. Chudgar regarding LNK's January 4, 1999 amendment to ANDA 75-010.

When asked, Mr. Chudgar confirmed that LNK manufactured new batches of product to comply with our previous request for stability data for the largest and smallest packaging (for each configuration - round and capsule shaped) of the product.

We explained that since we are using the data as the primary information to support approval of the package sizes that it is necessary that the manufacturing batch records and packaging records be submitted.

We also asked about bulk packaging for both products (75-010 - brown and 75-139 - white). IF firm intends to ship bulk product for repackaging elsewhere the bulk containers are considered marketing packages and stability data are required for approval.

Mr.Chudgar said the firm DID intend to ship bulk packaging. He said he had previously provided bulk stability data for round shaped tablets for each application (Confirmed); he said he would check availability of capsule shaped bulk stability and provide if available. He acknowledged that they would only be approved for round tablets in bulk if they don't have bulk capsule shaped data available. Submission will come to both applications as a telephone amendment.

1/28/99

X:\new\firmsam\lnk\telecons\75010.004

DATE
1/19/99

APPLICATION NUMBER
~~75-010~~ (brown)
75-139 (white)

TELECON

INITIATED BY FDA

PRODUCT NAME
Ibuprofen Tablets

FIRM NAME
LNK International

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Pankaj Chudgar

TELEPHONE NUMBER
516-543-3787

SIGNATURE
Mark Anderson

RECORD OF TELEPHONE CONVERSATION

Dr. Sayeed and I called Mr. Chudgar and Mr. Mollica and requested that the firm revise the storage condition statement for RT storage to state either 25 C at 60%RH or, alternatively, state 25-30 C at ambient humidity conditions (currently firm states 25 but does not state humidity conditions.)

Mr. Chudgar said he would submit a telephone amendment to each application to address our concern.

DATE
2/8/99

APPLICATION NUMBER
75-010 and 75-139

TELECON

INITIATED BY FDA

PRODUCT NAME
Ibuprofen
Tabs/Caplets

FIRM NAME
LNK

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
PJChudgar
Joe Mollica

TELEPHONE NUMBER

SIGNATURE
Mark Anderson

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-010 Applicant LNK International, Inc

Drug Ibuprofen Tablets USP (OTC)

Strength 200 mg Round + Capsule shaped (brown)

APPROVAL X TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐

REVIEWER:

1. Project Manager VM Anderson
   Review Support Br

DRAFT RECEIPT
Date 2/9/99
Initials MAS

FINAL ACTION
Date _____
Initials _____

Application Summary:
Original Rec'd date 11/29/96
Date Acceptable for Filing 2/6/97
Patent Certification (type) II
Date of Office Bio Review _____
Methods Val. Samples Pending Yes ☐ No ☐
30 Day Clock Start _____ End _____
Commitment rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status _____
Date Patent in effect _____
Citizens Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Comments:
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____

2. Div. Dir./Deputy Dir.
   Chemistry Div. (I) or II
   Comments:

Satisfactory

Date 2/24/99
Initials _____

Date 2/24/99
Initials _____

3. Office Level Chem Review **(1st Generic Only)**
   Chemistry Div. I or II
   Comments: Multiple generic ANDAs have been approved for this 200mg (OTC) drug product. Rwest 3/1/99

Date _____
Initials _____

Date _____
Initials _____

4. Pat Beers Block
   Supv., Review Support Branch
   Comments:
   - EER acceptable for all facilities as of 2/22/99 (none are OAI)
   - Final printed labels and labeling were revised for btls. of 12, 100, 250 and 1000 tablets and found acceptable for approval 1/11/99
   - Office level bioequivalence review was completed for the fasting & non-fasting studies and found acceptable for approval 2/4/99
   - CMC acceptable 2/24/99

Date 2/25/99
Initials PmBB

Date 2/25/99
Initials PmBB

- Patent information: Firm submitted para II certification for Nupin PD (ANDA = 72035). Exclusivity certification also provided for Nupin Tab. indicating that Nupin is not entitled to market exclusivity.
- No controlled correspondence - a citizen's petition against this ANDA.

REVIEWER:	DRAFT RECEIPT	FINAL ACTION

5. Peter Rickman
Supv., Reg. Support Branch
Contains certification Yes ☒ No ☐
(required by the GDEA if sub after 6/4/92)
Paragraph 4 Certification Yes ☐ No ☒
Comments:

Date 2/26/99 Initials [illegible]
Determ. of involvement? Yes ☐ No ☒
Pediatric Exclusivity Tracking System
Date Checked N/A
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Date 2/26/99 Initials [illegible]

NO PATENT OR EXCLUSIVITY ISSUES
MULTIPLE GENERICS APPROVED
OFFICE LEVEL BIO 2/4/99
EER ACCEPTABLE 2/22/99

3/1/99 (Rev.)

6. ~~Jerry Phillips~~
Dir. Div. Labeling & Prog. Support
Comments: Acceptable EES dated 2/22/99. No OTC aleks noted. Bioequivalence study (single-dose, fasting + fed against Nuprin Tablets) found acceptable 11/97. Waiver granted to 200mg capsule shaped tablets. Office level endorsed 2/4/99 (D. Conner). FPL Acceptable 3/1/99. CMC Acceptable 2/18/99. Methods validation waived. Note: Bio study performed against Nuprin Tablets of BMS RLD subsequently changed to Motrin IB Tablets (1:1 Ratio) based upon market share. Bio study remains valid - Refer to 7/21/98 Mail from R. Patrick (attached). At the time the bio study was conducted, Nuprin was the RLD. Recommend: Approval

Date 3/1/99 Initials [illegible]

Date 3/1/99 Initials [illegible]

7. Gordon Johnston
Deputy Director, OGD
Patent Cert - P_4 Yes ☐ No ☒
Pend. Legal Action Yes ☐ No ☒
Comments: No Controlled correspondence or Citizens Petitions currently pending. No patents or exclusivities currently pending. No pediatric exclusivity issues. FDA/IA has recertified (7/8/97) to RLD Motrin IB.

Date 3/1/99 Initials [illegible]
Petition Status NONE

Date 3/1/99 Initials [illegible] for

8. Doug Sporn
Dir., OGD
Comments:

Date 3/1/99 Initials [illegible]

Date 3/1/99 Initials [illegible]

Roger Williams, M.D.
Dep.Dir., CDER

Date _____ Initials _____

Date _____ Initials _____

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Mark Anderson
Review Support Branch

Date 3/2/99 Initials MA

Date 3/2/99 Initials MA

(Rev.) N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:
8:05am Time notified of approval by phone 8:08 a.m. Time approval letter faxed

FDA Notification:
3/2/99 Date e-mail message sent to "OGD approvals" account
3/2/99 Date Approval letter copied to "//cder/drugapp" directory

x:\wpfile\beersbl\aprovrou.wp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010

CORRESPONDENCE

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

November 27, 1996

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

Enclosed herewith are the Original and Archival copies of an abbreviated new drug application, ANDA, for Ibuprofen tablets, USP 200mg in four color/shapes (round white, caplet white, round brown, caplet brown). In addition to the bio batch, four additional commercial size lots, one for each color/shape, of ——— tablets were manufactured and fully packaged. Data from all of these lots are included in this application.

Volumes 1 and 2 contain chemistry, manufacturing and controls information. Volumes 3 through 8 of this application contain the clinical, analytical and statistical reports and data derived from the comparative bioequivalency trials entitled "Bioavailability of Ibuprofen Tablets, 200mg. - Effect of Food Study" and "Bioavailability of Ibuprofen Tablets, 200mg. - Fasting Study".

Thank you for your kind cooperation and prompt attention in assigning a number to this application.

Respectively yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 E. 57th Street
New York, NY 10022
Phone: 212-755-2339
Fax: 212-754-0704

ANDA 75-010

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

FEB 3 [illegible]

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 27, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ibuprofen Tablets USP, 200 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> Separate applications are required for solid oral dosage forms that contain a single strength, multiple colors and multiple shapes when there is more than one shape per color. Please refer to OGD Policy and Procedure Guide #20-90. You may submit a single application for a single strength, single color, and multiple shapes. Please withdraw one color from ANDA 75-010 and submit it as a new application for the different color and shapes. One application should be based on the product that contains the *in vivo* bioequivalence study. In addition, it will be necessary to request a waiver of *in vivo* bioequivalence requirements for the other application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

We note that you have submitted a debarment certification, list of convictions, 356h form and third copy certification. However these documents should have original signatures. Please provide these documents with original signatures.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR

314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Project Manager
(301) 594-0315

Sincerely yours,

2/3/97

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-010
cc: DUP/Jacket
Division File
HFD-93
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting date 2/3/97
HFD-615/HGreenberg,CSO date 2/3/97
HFD-6 /Chem Branch date
WP File x:\wpfile\greenberg\75\75010.rtf
F/T File tdb 02-03-97
ANDA Refuse to File!

APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

2/11/97 Open

1 Orig Ltr 2/6/97

February 5, 1997

Mr. Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NDA GMG AMENDMENT

N/AC

Reference: ANDA 75-010
Ibuprofen Tablets USP, 200mg

Dear Mr. Phillips:

Reference is made to your letter responsive to the submission of ANDA 75-010 for Ibuprofen Tablets USP, 200mg stating your refusal to file this application because of multiple colors and multiple shapes. We are taking your advice and withdrawing all references to the white color. This application will now include brown coated tablets, which were the subject of the bioequivalency study, in round and caplet shapes.

In addition, we are sending a set of original signed documents which you noted did not have original signatures (debarment certification, list of convictions, 356h form and third copy certification). Please note that originals of these documents were included in our initial submission.

We trust this now completes this file and that the official filing will be made.

Respectfully yours,

RECEIVED
FEB 06 1997
GENERIC DRUGS

Carol Frankel
Consultant in Regulatory Affairs
333 E. 57th Street
New York, NY 10022
Phone: 212-755-2339
Fax: 212-754-0704

CF/dju
Enc.

ANDA 75-010

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

FEB 14 1997

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 also made to our "Refuse to File" letter dated February 3, 1997, and your amendment dated February 5, 1997.

NAME OF DRUG: Ibuprofen Tablets USP, 200 mg (brown)

DATE OF APPLICATION: November 27, 1996

DATE OF RECEIPT: November 29, 1996

DATE ACCEPTABLE FOR FILING: February 6, 1997

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:

Jim Wilson
Project Manager
(301) 594-0310

Sincerely yours,

Jerry Phillips 2/14/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

April 10, 1997

AMENDMENT

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 75-010

Ibuprofen Tablets, 200mg

Dear Mr. Sporn:

Reference is made to a letter requesting samples dated March 24, 1997 which was received from the Northeast Regional Laboratory. All of the requested documents and materials were sent as directed on April 7, 1997. As part of that package we included updated revised test methods which include the test for the impurity 4-Isobutylacetophenone. Therefore, attached hereto is a copy of this same document to be included in the above referenced application. These are now the current test methods which will be used to test and release the product upon approval.

Thank you for your kind cooperation in including this in the file of reference.

RECEIVED

1997

GENERIC DRUGS

Respectfully yours,

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
Phone: 212-755-2339
Fax: 212-754-0704

CF/dju
Enc.

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

July 8, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

75-610 BROWN

Reference ANDA ~~75-139~~ Ibuprofen Tablets USP, 200mg (~~White~~)

Dear Mr. Sporn:

Reference is made to my telephone conversation on July 7, 1997 with Mr. Peter Rickman during which he requested the following pieces of information for ANDA 75-139:

Newly completed and signed FDA Form 356H

Certification Regarding Patent and Market Exclusivity

Comparison Between Generic Drug and Reference Listed Drug

Side-by-Side Label Comparisons

It is our understanding the FDA recently changed the reference drug product for ibuprofen to be used in Generic Applications from Nuprin to Motrin IB. We also understand that our Bioequivalency study performed using Nuprin will be acceptable as the reference drug.

Thank you for your kind cooperation in including this information in the filing of reference.

RECEIVED
JUL
GENERIC DRUGS

Respectively yours,

Carol Frankel
Consultant in Regulatory Affairs
333 E. 57th Street
New York, NY 10022
Phone: 212-755-2339
Fax: 212-754-0704

W. Wilson, T.

ANDA 75-010

JUL 11 1997

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on November 27, 1996, for Ibuprofen Tablets USP, 200 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Please provide shape (round or caplets), assay and content uniformity data of the reference product used in the biostudies.

2. Please note that the dissolution testing should be done on 12 individual tablets each of test and reference, not six as in the application. Therefore, dissolution data should be submitted on 12 tablets of test and 12 tablets of reference products that were used in the biostudies. Dissolution data on 12 individual caplet shape tablets also should be submitted. Please note that USP revised the dissolution methods and specifications for ibuprofen tablets in the November 1996 (fifth supplement to USP 23). All disssolution testing should be done using the new method.

3. Fasting study, Period II: The drug was administered on November 18 as per page 31 (washout period 2 days); on November 19, 1995 as per page 8 17 vol 1.1 (washout period 3 days). In the clinical summary on page 31 vol. 1.1, it is stated that the washout period was one week between drug administrations. Please clarify.

4. A request should be submitted for a waiver from *in vivo* bioequivalence study requirements for the caplet shape brown coated test tablets. The dissolution testing requested in #2 will serve as supporting data for this request.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: Date 7/11/97
ANDA 75-010, Orig File, Dup File
Div File
Director, DBE
Field Copy
HFD-650 Sanchez, CST
J. Wilson

BIO-LETTER INCOMPLETE

Endorsements:

K. Dhariwal 6/24/97
S. Nerurkar 6/24/1997
L. Sanchez 6/24/97

DRAFT	LSG	6/23/97	X:\WPFILE\BIO\75010BIO.DST
FINAL PRINT	ALS	6/24/97	X:\WPFILE\BIO\FINAL\75010BIO.DST

MAJOR AMENDMENT

ANDA/~~AADA~~: 75-010

JUL 22 1997

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT LNK INTERNATIONAL, INC PHONE 516 ~~[illegible]~~ 543-3787
ATTN: PANKAJ S. CHUDGAR FAX ~~212 754 0704~~ 516-543-2040

FROM: JIM WILSON PROJECT MANAGER (301-827-5848)

Dear Sir/~~Madam~~:

This facsimile is in reference to your abbreviated new drug/antibiotic application 75-010 dated NOV 27, 1996 , submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for IBUPROFEN TABLETS USP, 200 mg .

Reference is also made to your amendment(s) dated FEB 5, 1997 .

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (7 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.mjr

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

7/22/1997 FDA FAX

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

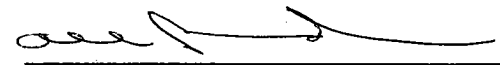
1. Please provide the pharmaceutical function of each excipient used in the manufacture of the drug product.

2. The facilities referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval. We have requested an evalution from the Division of Manufacturing and Product Quality.

3. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality.

4. Please be advised that since the drug product is an official article, use of an in-house analytical procedure does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, the USP analytical method will be regarded as the regulatory method.

Sincerely yours,



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

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

ANDA Number: 75-010 Date of Submission: November 27, 1996

Applicant's Name: LNK International, Inc.

Established Name: Ibuprofen Tablets USP, 200 mg (Brown round- and capsule-shaped tablets)

Labeling Deficiencies:

1. GENERAL COMMENTS

   Use "USP" rather than "U.S.P." throughout the labels and labeling.

2. CONTAINER - 12's, ——, and 1000's

   a. Round-shaped tablets

      i. We encourage you to include the strength of the drug product to appear in conjunction with the established name, *i.e.* "Ibuprofen Tablets USP, 200 mg".

      ii. You may delete the statement "FILM COATED BROWN" and revise the net quantity statement to read "xx Film Coated Brown Tablets, 200 mg Each".

      iii. INDICATIONS

      ... for reduction of fever. [delete "the"]

      iv. OTHER INGREDIENTS

      A) We encourage you to replace "OTHER" with "INACTIVE".

      B) Please identify the botanical source of starch, *i.e.* "corn starch" rather than "starch".

      C) Please alphabetize the listing of other ingredients.

      D) Include the components of ———.

b. Capsule-shaped tablet

i. Please note that the term "caplet" is not an official USP dosage form classification, neither is it part of the established name as seen in the USP monograph. Therefore, revise the name of your drug product to read "Ibuprofen Tablets USP, 200 mg" to be in accordance with USP 23. The term "caplet" may be retained in the net quantity statement as long as it is defined as a "capsule-shaped tablet" as you have proposed.

ii. You may delete the statement "FILM COATED BROWN" and revise the net quantity statement to read as follows:

xx Film Coated Brown Caplets*, 200 mg Each

*Caplets (Capsule-shaped tablets)

iii. See comments (iii) and (iv) under Round-shaped tablets.

iv. Revise the statement "DO NOT ... OPEN" on the container labels for the package size of 12's to be same as the one appearing on the container labels for other package sizes.

3. CARTON - 12's and [redacted]

a. Round-shaped tablet

See comments (i) through (iv) under CONTAINER for round-shaped tablet.

b. Capsule-shaped tablet

See comments (i) through (iii) under CONTAINER for capsule-shaped tablet.

4. CONSUMER LEAFLET LABELING

i. We ask you to propose a separate consumer leaflet labeling for your round-shaped and capsule-shaped tablets. Please revise the labeling according to the comments made for container labels except for the comment related to the net quantity statement.

ii. We ask you to revise the name of the product to read as follows in the leaflet for capsule-shaped tablets.

Ibuprofen Tablets* USP, 200 mg

*Caplets (Capsule-shaped tablets)

5. BULK LABELING

Although the Agency does not approve the bulk labeling, we have reviewed for accuracy and have following comments.

a. Round-shaped tablets

i. Revise the product name to read "Ibuprofen Tablets USP, 200 mg (Brown)

ii. Relocate the statement "PAIN RELIEVER/FEVER REDUCER" to immediately follow the name of the drug product.

iii. Refer to the comments (iv) under CONTAINER for round-shaped tablets.

b. Capsule-shaped tablets

i. We ask you to revise the name of the product to read as follows:

Ibuprofen Tablets* USP, 200 mg (Brown)

*Caplets (Capsule-shaped tablets)

ii. Refer to the comments (ii) & (iii) under round-shaped tablets.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 the last submitted labeling with all differences annotated and explained.

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

APPEARS THIS WAY
ON ORIGINAL

BIOAVAILABILITY

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

August 1, 1997

AMENDMENT

N/A

Nicholas Fleischer, Ph. D.
Food and Drug Administration
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

Reference: ANDA #75-010 Ibuprofen USP 200mg

Brown Color

Dear Dr. Fleischer:

Reference is made to your letter dated July 11, 1997 responsive to our ANDA submitted on 11/27/96 for Ibuprofen tablets USP 200mg.

The following are our response to the points you raise:

1) "Please provide shape (round or caplets), assay and content uniformity data of the reference product used in the biostudies."

Response:

Attached as Exhibit I is a Certificate of Analysis for Nuprin lot #403159 which provide data for the round shape, assay result of 102.6% and Content Uniformity of 103.0 to 106.6% with a relative standard deviation of 1.0%.

2) "Please note that the dissolution testing should be done on 12 individual tablets each of test and reference, not six as in the application. Therefore, dissolution data should be submitted on 12 tablets of test and 12 tablets of reference products that were used in the biostudies. Dissolution data on 12 individual caplet shape tablets also should be submitted. Please note that USP revised the dissolution methods and specifications for ibuprofen tablets in the November 1996 (fifth supplement to USP 23). All dissolution testing should be done using the new method."

RECEIVED

AUG 04 1997

GENERIC DRUGS

Response:

Attached as Exhibit II is a report of dissolution testing on 12 individual tablets for the reference product, Nuprin, lot #403159 and LNK International, Inc. lots P14752 (brown, capsule shape), lot P13517B (Biostudy lot, brown, round) using the USP revised dissolution methods and specification for ibuprofen tablets in the November, 1996 (fifth supplement to USP 23).

3) "Fasting study, Period II: The drug was administered on November 18 as per page 31 (washout period 2 days); on November 19, 1995 as per page 8 17 vol 1.1 (washout period 3 days). In the clinical summary on page 31 vol. 1.1, it is stated that the washout period was one week between drug administrations. Please clarify."

Response:

Attached hereto is a letter from the laboratory performing the study, ———— explaining the study and washout periods.

4) "A request should be submitted for a waiver from in vivo bioequivalence study requirements for the caplet shape brown coated test tablets. The dissolution testing requested in #2 will serve as supporting data for this request."

Response:

We request an in vivo bioequivalence study waiver for the caplet shape brown coated tablets based on the fact that the formulas are comparative. Attached hereto, as Exhibit IV, are a comparative formula, please note other than the shape of the punches and dies, both shapes have the same quantitative formula.

We trust this information will now complete this file. If you have any further questions, please feel free to contact us.

Respectfully yours,

Carol Frankel
Consultant in Regulatory Affairs
333 E. 57th Street
New York, NY 10022
Phone: 212-755-2339
Fax: 212-754-0704

CF/dju
Enc.

L N K INTERNATIONAL, INC.
OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

2/26/98

February 12, 1998

Mr. James Wilson
Project Manager
FOOD AND DRUG ADMINISTRATION
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

Re: ANDA 75-010 and 75-135
75-139

Dear Mr. Wilson:

It was a pleasure talking to you and your associate on January 29, 1998 regarding the letter we faxed to you on January 22, 1998.

This letter is to confirm our understanding of OGD's responses to the questions that we posed. Following we list those questions and our understanding of OGD's position as communicated during our telephone conversation.

Question:

1. Because the — formulations are identical, can stability information in a particular container/closure system for one tablet configuration be used to also gain approval for marketing a second tablet configuration in that same container/closure system (e.g., can stability data supporting approval in a container/closure system for Ibuprofen 200mg white round tablets also be used to support approval in that same container/closure system for Ibuprofen 200mg white capsule shaped tablets, or brown round or capsule shaped tablets)?

Response:

Stability performed for either tablet shape in a container closure system within the same ANDA will support marketing approval for both tablet shapes (of the same color) in that container closure system. Stability performed in the smallest size container for one tablet shape and in the largest size container for the other tablet shape can be combined for bracketing purposes to support marketing of intermediate size containers of either tablet shape in the same container closure system.

RECEIVED
FEB 17 1998
GENERIC DRUGS

Nadine 2-10-98

Question:

2. We are requesting clarification on Generic Drug current policy on the storage conditions for room temperature stability. Is humidity control as well as temperature control required? Please confirm the acceptable temperature and humidity ranges for both accelerated and room temperature stability.

Response:

OGD will accept stability data generated for the products which have been placed on stability between temperatures of 25 to 30°C and ambient relative humidity conditions. A stability study conducted within the temperature range of 25°C +/- 2°C and 60% Rh +/- 5% will also be acceptable.

Question:

3. Finally, we are requesting clarification on the requirements to add a package size to our product line using the identical container/closure system (i.e., ——— container and then add a 100 count in a 100cc container or 12 count in a 20cc container all using the identical HDPE containers and closure systems.

Answer:

The intent of the question was to assure that OGD's reading of 21CFR314.70(d)(8) coincided with LNK's understanding, which is that if at least one size of a container closure system is approved for marketing, other sizes of that identical container closure system can be marketed without prior approval and upon notification in the next annual report. It is understood that cGMP requirements must be met.

We believe our understanding of OGD's position, as recorded above, accurately reflects our telephone conversation. If you believe this document contains any misunderstanding, or that further clarification is needed, we would much appreciate your comments in that regard and would ask that you call me at (516) 543-3787 to further discuss these matters.

Sincerely,

Pankaj S. Chudgar
Vice President

PSC/dju

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

March 5, 1998

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: ANDA 75-010/MAJOR AMENDMENT; Response to your communication of July 22, 1997

Product: Ibuprofen Tablets USP, 200mg

Dear Mr. Sporn:

We wish to amend our abbreviated new drug application 75-010 to fully respond to all of the deficiencies listed in Mr. James Wilson's facsimile transmission of July 22, 1997. This amendment sequentially lists each of OGD's comments followed by our response. The numbering for exhibits corresponds to the number of the response.

We trust we have satisfactorily responded to your comments. Please call me if you have any questions or need additional information.

Sincerely,

Joseph J. Mollica, Sr.
President

JJM/dju
Enc.
file: fdaltr.731

FACSIMILE AMENDMENT

AUG 6 1998

ANDA 75-010

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: LNK International, Inc. PHONE: 516-435-3500

ATTN: Joseph Mollica FAX: 516-~~543-2040~~ 435-3542

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Tablets USP, 200 mg (brown).

Reference is also made to your amendment dated March 5, 1998.

Attached are 2 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\faxfax.frm

AUG 6 1998

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The deficiencies presented below represent FACSIMILE Deficiencies.

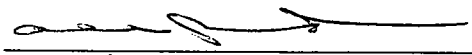
A. Deficiencies:

Since you do not wish to market the product in the 12's (40cc container/33mm closure) and the ——— container/—— closure) packaging, please withdraw labeling for these package sizes.

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

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

Sincerely yours,



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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

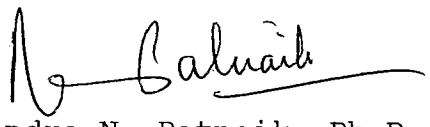
The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23 (5th supplement):

> The dissolution testing should be conducted in 900 mL of pH 7.2 phosphate buffer, using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

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,



Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

August 10, 1998

FACSIMILE AMENDMENT

Mr. Mark Anderson
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 75-010 -- Ibuprofen Tablets USP, 200mg. Brown

Dear Mr. Anderson:

We are in receipt of your facsimile deficiencies dated August 6, 1998 in regard to the above referenced abbreviated new drug application.

Enclosed please find our response to the minor deficiencies stated in the facsimile.

Sincerely,

Pankaj S. Chudgar
Vice President

PSC/dju
Enc.

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

August 14, 1998

NDA ORIG AMENDMENT

FA

Mr. James Barlow
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
7500 Standish Place
Rockville, Maryland 20855

Reference ANDA #75-010 -- Ibuprofen 200mg Brown Round and Capsule Shaped Tablets

Dear Mr. Barlow:

Enclosed please find our response to your fax communication regarding labeling deficiencies dated 8/3/98.

OGD Comment:

1. CONTAINER - 12's, — & 1000's

   a. "Please assure that the statement of identify (established name and pharmacological category) appear most prominently on the principal display panel. We refer you to 21 CFR 201.61 (c) for guidance.

LNK Response:

The established name and pharmacological category now appear most prominently on the principal display pan as stated in 21 CFR 201.61 (c). See enclosed final labeling for sizes 12's, — and 1000's as Attachment 1.

OGD Comment

   b. "Capsule shaped tablets (Active ingredients) - Revise to read as follows:

   "Each tablet contains ...."or "Each capsule-shaped tablet contains ....".

LNK Response:

We have revised capsule shaped tablets under active ingredients and it reads as follows:

"Each tablet contains .....". See enclosed final labeling as Attachment 1.

RECEIVED

AUG 17 1998

GENERIC DRUGS

Reference ANDA #75-010 -- Ibuprofen 200mg Brown Round and Capsule Shaped Tablets

OGD Comment:

2. CARTON - 12's & —

"Refer to comments under CONTAINER."

LNK Response:

We have revised the carton for 12's and — Please see Enclosed final labeling as Attachment 2.

OGD Comment:

3. CONSUMER LEAFLET LABELING

"Refer to the comment (b) under CONTAINER.

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

LNK Response:

As per the telephone conversation of August 7, 1998 between myself and you confirming that if all the information is present on the box, we do not need a consumer leaflet insert. Based on this conversation, we have OGD's authorization to withdraw the consumer leaflet insert from the application.

Sincerely,

Pankaj S. Chudgar
Vice President

file: ibuprofen\fdaresbr 898

FACSIMILE AMENDMENT

OCT 26 1998

ANDA 75-019

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: LNK International, Inc. PHONE: 516-435-3500

ATTN: Joseph Mollica, Sr. FAX: 516-543-2040

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 26, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Tablets USP, 200 mg (brown).

Reference is also made to your amendments dated March 5, August 10 and 14, 1998.

Attached are 3 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

CMC and labeling comments are attached

X:\new\ogdadmin\macros\faxfax.frm

OCT 26 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-010 APPLICANT: LNK International, Inc.

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The deficiencies presented below represent FASCIMILE Deficiencies.

Deficiencies:

As already informed in our previous telephone communications, you are required to submit stability data for both the round tablets and the capsule-shaped tablets in the smallest and the largest container closure system proposed for marketing.

Sincerely yours,

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

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

ANDA Number: 75-010 Date of Submission: August 10, 1998 and August 14, 1998.

Applicant's Name: LNK International, Inc.

Established Name: Ibuprofen Tablets USP, 200 mg (Brown round- and capsule-shaped tablets)

Labeling Deficiencies:

1. GENERAL

   We notice that there is a discrepancy between your submissions of August 10, 1998 and August 14, 1998 pertaining to the withdrawal and the resubmission of the labeling for the bottles of 12 and — count tablets and caplets. The following comments reflect a review of the August 14, 1998 submission which included the 12 and — count labels and labeling.

2. CONTAINER - Bottles of 12, — and 1000.

   Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and **clarity**. Please assure that these criteria are met prior to submission of final print. Also, you are required to submit 12 copies. We refer you to 21 CFR 314.94(a)(8)(ii) for guidance.

3. Carton - 12's and ——

   (See comment above.)

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

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

APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

October 30, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC ho
Fax

Attention: Mark Anderson, Project Manager

Facsimile Request

To Change Facsimile Amendment to Minor Amendment

RE: **ANDA # 75-010**
Ibuprofen Tablets USP, 200 mg (brown)

Dear Mr. Anderson:

Reference is made to the FDA Facsimile Amendment request dated October 26, 1998 and the phone conference dated October 29, 1998 concerning LNK's Abbreviated New Drug Application dated November 26, 1996 for **Ibuprofen Tablets USP, 200 mg. (brown)** and our amendments of March 5, August 10 and 14, 1998, LNK International provides a request to postpone review of this application until the stability data for the brown *capsule-shaped* tablet has reached the minimum 90 day accelerated to extend a 24 month expiration period as required.

Reviewer' requests dated October 26, 1998:

Chemistry Deficiencies:

As already informed in our previous telephone communications, you are required to submit stability data for both the round tablets and the capsule-shaped tablets in the smallest and largest container closure system proposed for marketing.

Labeling Deficiencies:

General

We notice that there is a discrepancy between your submission of August 10, 1998 and August 14, 1998 pertaining to the withdrawal and the resubmission of the labeling for the bottles of 12 and — count tablets and caplets. The following comment reflect a review of the August 14, 1998 submission, which included the 12 and — count labels and labeling.

Container - Bottles of 12, —and 1,000

Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color, and clarity. Please assure that these criteria are met prior to submission of final print. Also, you are required to submit 12 copies. We refer you to 21 CFR 314.94 (a) (8) (ii)

Carton - 12's and —

(See comment above.)

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

LNK appreciates and thanks you for the time taken to explain the alternatives to the filing of information on the brown *round* and *capsule-shaped* tablets. We will not file these at this time, based on the understanding that the lack of stability data for the *capsule-shaped* tablet may allow approval of the round tablet now and require a supplement for the capsule-shaped tablet, which could delay its approval for 180 days from the date of submission of that data. Also, we understand that the Minor Amendment submitted in January with full stability data for the *round* tablet and 90 day accelerated data for the *capsule-shaped* tablet, if acceptable could be approved within thirty days of receipt. LNK appreciates your guidance and has chosen to submit a Minor Amendment for both tablet forms the first week of January when the stability data for the *capsule-shaped* tablet is available.

The response to the Facsimile Deficiency letter is complete and should be sufficient to warrant a MINOR AMENDMENT response and review of this Abbreviated New Drug Application in January. If there is a need for additional information or clarification, then please call me at (516) 435-3500 or fax (516) 543-2040.

Signed on behalf of LNK, International.

Sincerely,

Pankaj S. Chudgar
Vice President

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12/11/1998 LNK LETTER

FPI

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

December 21, 1998

DRUG AMENDMENT
N/A F

Mr. Mark Anderson
Office of Generic Drugs
FOOD AND DRUG ADMINISTRATION
7500 Standish Place
Rockville, MD 20855-2773

Labeling Facsimile Amendment

Reference ANDA #75-010 - Ibuprofen 200mg (USP) Brown Round & Capsule Shape Tablets

Dear Mr. Anderson:

LNK is submitting labeling, prior to the final minor amendment submission, based on the conference phone call of December 16. Your Office had suggested that the labeling could be submitted pending our stability to allow sufficient review time.

LNK will submit, on or about January 5, 1999, stability data and container closure information for Ibuprofen 200mg brown round tablets and brown capsule shaped tablets. We are submitting label and labeling for only those packaging configurations that will, on January 5th, be supported with stability data and will supplement or report in the annual report, as appropriate, for any other labeling. Currently, LNK is submitting 12, 100, 250 and 1,000 count labels and cartons where applicable for the brown round tablets and 12, 100 and 250 count labels and cartons where applicable for the brown capsule shape tablets.

LNK further acknowledges the Poison Prevention Packaging Act requirements for non-complying packaging. The Code (16 CFR 1700.5) allows for single size non-compliant packaging with appropriate Labeling statement, "Package No Child-Resistant". LNK has stability data for two non-compliant packaging sizes and will chose a size to be labeled with packaging statement and without. LNK will report this information in our annual report. LNK is requesting a waiver to have the 1000 count size labeled "This Package for Households Without Young Children" and an exemption from the OTC requirements.

ANDA #75-010 Continued

OGD Comments:

Labeling Deficiencies:

1. **GENERAL**

   We notice that there is a discrepancy between your submissions of August 10, 1998 and August 14, 1998 pertaining to the withdrawal and the resubmission of the labeling for the bottles of 12 and —count tablets and caplets. The following comments reflect a review of the August 14, 1998 submission which included the 12 and — count labels and labeling.

LNK Response:

Submission of August 10th was in response to the Facsimile Amendment dated August 6, 1998 in which we had informed you of our intention of withdrawing the 12 and —count packaging sizes for this product due to lack of available stability data, at that time. The submission of August 14, 1998 was in response to your fax letter dated August 3, 1998 from the Division of Labeling (Mr. Jim Barlow), which we did not receive when it was mailed to us earlier (date unknown). In this letter we were asked to submit labeling information for 12, —and 1000 count packaging sizes for this product. On receipt of this letter we sent the response to it on August 14th along with labeling information for 12, —and 1000 count tablets as requested, and also responded to other comments in that letter.

As mentioned in the initial comments of this letter, we are now in the process of completing stability studies for smallest and largest size of these container closure systems and will be submitting the stability data, along with all pertaining information, with another submission on or about January 5, 1999.

OGD Comments:

2. **CONTAINER - Bottles of 12,—and 1000**

   Please note that for computer generated labels to be acceptable as final print, they must be of actual size , color and clarity. Please assure that these criteria are met prior to submission of final print. Also, you are required to submit 12 copies. We refer you to 21 CFR 314.94 (a) (8) (ii) for guidance.

ANDA #75-010 Continued

LNK Response:

Enclosed please find 12 copies of each actual label and enlarged computer generated copies, where necessary, for the bottle sizes of 12, 100, 250 and 1000 count for Ibuprofen 200mg round brown film coated tablets and 12, 100, and 250 counts for the Ibuprofen 200mg capsule shape film coated brown tablets for all of which we have on-going stability studies as Exhibit #1.

OGD Comments:

3. **Carton - 12's and 50's**

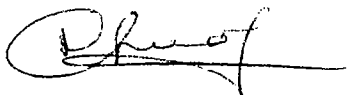
LNK Response:

Enclosed are 12 copies of computer generated box labels and enlarged copies where necessary, for 12 and 250 count package size for both Ibuprofen 200mg film coated brown round and capsule shape tablets as Exhibit #2.

Examining the previously submitted labels of 12 and 1000 count (response dated August 14, 1998) compared to the current proposed labels, shows no changes. Based on this information, we feel that a side-by-side comparison of these labels is not necessary.

Thank you for all your help and consideration.

Sincerely,



Pankaj S. Chudgar
Vice President

PSC/dju
Attachments

file: ibuprofn\facres.12

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

ANDA 75-010
Ibuprofen Tablets USP, 200 mg (brown)

January 4, 1999

Mr. Mark Anderson
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment

RE: ANDA # 75-010
Ibuprofen Tablets USP, 200 mg (brown)

Dear Mr. Anderson:

Reference is made to the FDA Facsimile Amendment request dated October 26, 1998 concerning LNK's Abbreviated New Drug Application dated November 26, 1996 for Ibuprofen Tablets USP, 200 mg. (brown) and our amendments of October 28 and December 21, 1998 and our phone conference of December 16, 1998, LNK International provides a complete response as recommended in the phone conference: (1) a labeling submission submitted December 21, (2) today's submission including stability and container information, and (3) this cover letter clearly identifying the two submission and titled a MINOR AMENDMENT. To facilitate review, LNK identifies ANDA 75-139, Ibuprofen Tablets USP, 200 mg. (white) as a companion ANDA to this application and the pending approval and Biowaiver of that ANDA has been delayed based on the Bioequivalence Study in this ANDA.

The reviewer's deficiencies are transcribed in bold lettering followed immediately by LNK's response in normal type and supported by numbered attachments as needed.

A. **Chemistry Deficiencies**:

1. **As already informed in our previous telephone communications, you are required to submit stability data for both the round tablets and the capsule-shaped tablets in the smallest and largest container closure system proposed for marketing.**

The stability data for the ***round tablets*** from the (12's) Snap Cap, to the (250's) Snap Cap container closure system, 12's (Screw Cap) to the 1000's (Screw Cap) and

ANDA 75-010
Ibuprofen Tablets USP, 200 mg (brown)

100's in a 90cc square bottle, all proposed for marketing are provided in Exhibit 1, Exhibit 2, Exhibit 3, Exhibit 4 and Exhibit 5 respectively. The stability data for the ***capsule-shaped tablets*** from the (12's) Snap Cap to the (250's) Snap Cap and 100 count in a 90cc square bottle container closure system proposed for marketing are provided in Exhibits 6, 7 and 8 respectively. In addition, we are submitting the container closure information for all container closure systems.

The stability data for the capsule shape tablets, 12 count screw cap container is provided as Exhibit 9. This stability data is submitted for the 2 month time point because the three month time station will not be available until the third week of January. LNK will submit the three month data as soon as it is available. We hope that this will not delay the approval of the two ANDAs. Alternatively, LNK would be willing to submit information in the annual report for the 12 count, Non- CRC system or if the Office prefers, LNK would be willing to withdraw this packaging system and supplement for the system later. The most crucial goal of this amendment is to obtain the approvals for ANDA 75-139 and ANDA 75-010.

The following stability information can be found in Exhibits noted:

Exhibit #	Shape	Count	Closure Type	Stability Lot	Accelerated	Room Temperature
1	RoundTablets	12's	Snap Cap	P18658	90 days	3 months
2	RoundTablets	250's	Snap Cap	P18658	90 days	3 months
3	RoundTablets	12's	Screw Cap	P18658	90 days	3 months
4	RoundTablets	1000's	Screw Cap	R&D 728	90 days	2 years
5	RoundTablets	100's	Easy Off	P18658	90 days	3 months
6	Capsule Shape Tablets	12's	Snap Cap	P19515	90 days	3 months
7	Capsule Shape Tablets	250's	Snap Cap	P19515	90 days	3 months
8	Capsule Shape Tablets	100's	Easy Off	P19515	90 days	3 months
9	Capsule Shape Tablets	12's	Screw Cap	P19515	60 days	---

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1/4/1999 LNK LETTER

ANDA 75-010
Ibuprofen Tablets USP, 200 mg (brown)

2. **Container - Bottles of 12, —and 1,000**

Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color, and clarity. Please assure that these criteria are met prior to submission of final print. Also, you are required to submit 12 copies. We refer you to 21 CFR 314.94 (a) (8) (ii)

3. **Carton - 12's and — (See comment above.)**

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

The Office had recommended, in the phone conference, that the Labeling portion of this deficiency letter could be submitted prior to the stability information. LNK submitted on December 21, 1998, the following Labels and Labeling:

Shape	Actual Label Copies (12 Each)	Computer Generated Box Labels (12 Each)	Count
ROUND TABLETS	√	√	12
	√	*	100
	√	√	250
	√	*	1000
CAPSULE-SHAPE TABLETS	√	√	12
	√	*	100
	√	√	250

*No box (carton) required as all the information is printed on the bottle label.

ANDA 75-010
Ibuprofen Tablets USP, 200 mg (brown)

The response to the Minor Deficiency letter is complete and sufficient to warrant an Approval of this Abbreviated New Drug Application. If there is a need for additional information or clarification, then please call me at (516) 543-3787 or fax (516) 543-2040.

Signed on behalf of LNK, International.

Sincerely,

Pankaj S. Chudgar
Vice President

PSC/dju
Attachments
file: Ibuprofn\fdaamd.199

APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

January 19, 1999

Mr. Mark Anderson
Office of Generic Drugs
FOOD AND DRUG ADMINISTRATION
7500 Standish Place
Rockville, MD 20855-2773

Re: MINOR TELEPHONE AMENDMENT
ANDA 75-010
IBUPROFEN 200mg FILM COATED
BROWN ROUND & CAPSULE SHAPE TABLETS

Dear Mr. Anderson:

With reference to the phone conversation of this afternoon regarding the above mentioned ANDA #75-010 for Ibuprofen 200mg Brown Film Coated Tablets, enclosed please find our responses to the additional information you requested along with the required attachments.

1. Copies of complete batch records for Ibuprofen 200mg Brown Film Coated round tablets for lot #P18658 and Ibuprofen 200mg Brown Capsule Shape Tablets lot #P19515 as Exhibit #1. These two batches were manufactured using raw material supplied by ——————— and using the same equipment, procedures and controls. These batches were fully packaged as indicated in the batch record.

2. Bulk Stability Data for Ibuprofen 200mg brown Film Coated Round Tablets for Lot #P13517B is enclosed as Exhibit #2 along with specifications for the ——

3. 90 days accelerated and three month ambient Stability Data for Ibuprofen 200mg Brown Film Coated Capsule Shape Tablets lot #P19515 in 12 count using 50cc bottle with screw cap as Exhibit #3.

4. USP testing data (<661>) and (<671>), container/closure test, for 50cc HDPE bottles enclosed as Exhibit #4.

Thank you, very much, for your help and consideration in this matter and we hope this response to the Minor Telephone Amendment is complete and sufficient to warrant an Approval of the above Abbreviated New Drug Application. If there is a need for any clarification, please call me at (516) 543-3787 or fax (516) 543-2040.

Signed on behalf of LNK International, Inc.

Sincerely,

Pankaj S. Chudgar
Vice President

PSC/dju
Attachments

file:ibuprofn\fdaltr.119

APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

February 10, 1999

Mr. Mark Anderson
Office Of Generic Drugs
FOOD AND DRUG ADMINISTRATION
7500 Standish Place
Rockville, MD 20855-2773

NDA ONE AMENDMENT

MINOR TELEPHONE AMENDMENT

Reference: ANDA # 75-139 Ibuprofen 200mg White Film Coated Round and Capsule Shaped Tablets

ANDA # 75-010 Ibuprofen 200mg Brown Film Coated Round and Capsule Shaped Tablets

Dear Mr. Anderson:

Enclosed please find revised copies of Stability Protocol for the above mentioned products. Effective immediately, we are revising our ambient stability storage conditions to 25°C to 30°C with ambient relative humidity for all our products.

This response to the Minor Telephone Amendment is complete and sufficient to warrant an Approval of these Abbreviated New Drug Applications. If there is a need for additional information or clarification, then please call me at (516) 543-3787 or fax (516) 543-2040.

Signed on behalf of LNK, International.

Sincerely,

Pankaj S. Chudgar
Vice President

RECEIVED

FEB 11 1999

GENERIC DRUGS

PSC/dju
Enc.
File: ibuprofn\fdaltr.210