CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 79-205

Name: Ibuprofen Capsules (Liquid Filled), 200 mg

Sponsor: Marksans Pharma Limited

Approval Date: June 26, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

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Microbiology Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-205

Pharmgen LLC
U.S. Agent for: Marksans Pharma Limited
Attention: Nilkanth J. Patel
Vice President, Regulatory Affairs
1919 Middle Country Road, Suite 206
Centereach, NY 11720

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 11, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ibuprofen Capsules (Liquid Filled), 200 mg.

Reference is also made to your amendments dated February, 14, April 11 (2 submissions), August 4, September 11, October 6, and November 10, 2008; and June 3, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Ibuprofen Capsules (Liquid Filled), 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Advil Liqui-Gels, 200 mg, of Wyeth Consumer Healthcare. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA 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,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
6/26/2009 02:07:26 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

LABELING

NDC 25000-133-13

Ibuprofen Capsules, 200 mg

Pain Reliever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

600 Softgels**

Marksans

Drug Facts

Active ingredient (in each capsule) — Purpose

Solubilized ibuprofen equal to
200 mg ibuprofen (NSAID)* ..... Pain reliever/Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include :

- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

LOT :

EXP :

N 3 25000 133 B 9

Size : 140 x 80 mm

Drug Facts (Continued)

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems

Drug Facts (Continued)

- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

Drug Facts (Continued)

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Drug Facts (Continued)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

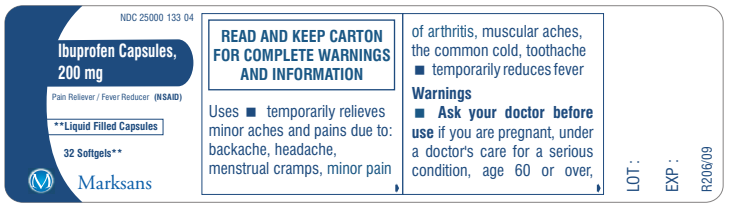
Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India

Mfg. Lic. No. : GO/Drugs/515

R306/09



Size : 95 x 26 mm

taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include: asthma (wheezing), blisters, facial swelling, hives, rash,

shock, skin reddening. If an allergic reaction occurs, stop use and seek medical help right away. **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer.
■ This product may cause **stomach bleeding.**

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.
Directions ■ do not take more than directed ■ the smallest effective dose should be used
■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
■ if pain or fever does not respond to 1 capsule, 2 capsules may be used
■ do not exceed 6 capsules in 24 hours, unless directed by a doctor.
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Manufactured by:
Marksans Pharma Ltd.
Verna, Goa - 403 722, India

EXP :

LOT :

Drug Facts (Continued)

- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use
- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are
- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

Drug Facts (Continued)

When using this product
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Stop use and ask a doctor if
- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Drug Facts (Continued)

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use. Keep carton.
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

R3606/09

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India
Mfg. Lic. No. : GO/Drugs/515

NDC 25000-133-04

Ibuprofen Capsules, 200 mg

Pain Reliever / Fever Reducer (NSAID)

**Liquid Filled Capsules

32 Softgels**

Marksans

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.

Drug Facts

Active ingredient (in each capsule)	Purpose
Solubilized ibuprofen equal to 200 mg ibuprofen (NSAID)* (present as the free acid and potassium salt)	Pain reliever/ Fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include :
- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :
- are age 60 or older
- have had stomach ulcers or bleeding problems

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

LABELING REVIEWS

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

ANDA Number: 79-205
Dates of Submission: **June 3, 2009**
Applicant's Name: Marksans Pharma Limited
Established Name: Ibuprofen Capsules, 200 mg

Approval Summary:

1. **Do you have copies of final printed labels and labeling?** Yes

2. **CONTAINER** – Bottles of 32 and 600 count **(for the 200 mg strength capsules)**
   Satisfactory in **final print** as of the June 3, 2009 electronic submission

3. **CARTON – 32 count bottles ONLY**
   Satisfactory in **final print** as of the June 3, 2009 electronic submission

4. **Revisions needed post-approval:** Yes

   a. Carton/Container: Front Panel
      Revise to read as follows – (add and asterisk)

      Pain Reliever/Fever Reducer (NSAID)*

   b. 32 count Container (only)
      Increase the prominence of the established name

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil Liqui-Gels®
NDA Number: N 20-402
NDA Drug Name: Advil Liqui-Gels®
NDA Firm: Wyeth Consumer Healthcare; Approved May 19, 2009. (NDA-20-402/S-025)
Date of Approval of NDA Insert and supplement: Approved May 19, 2009; NDA N 20-402/S-025
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Advil Liqui-Gels®

FOR THE RECORD:

1. MODEL LABELING
   Wyeth Consumer Healthcare. (ANDA 20-402/S-025), Approved May 19, 2009).

2. INACTIVE INGREDIENTS
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components.**
   (per chemistry review)

DRUG PRODUCT: Satisfactory

P.2.1 Components of the Drug Product

The quantitative composition and function of each component in the drug product is as listed:

S. No.	Ingredients	Pharmacopeial reference	mg / capsule	% per capsule	Function
MEDICAMENT					
01	Ibuprofen	USP	200.00	(b) (4)	Active ingredient

(b) (4)

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   USP: Preserve in tight, light-resistant container.
   RLD: Store at 20 to 25°C(68 to 77°F); avoid excessive heat above 40°C (104°F).
   ANDA: Same as RLD

4. PACKAGING CONFIGURATIONS
   NDA: 20s, 40s, 80s, 120s, 160s, 240s count bottles as well as 2-count capsule front and back pouch labels with 2-count pouch dispenser (50 x 2-count pouches).
   ANDA: Bottles of 32 and 600 **count**

5. The tablet/capsule imprintings have been accurately described as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).
   - Sea green to light green color oblong shaped soft gelatin capsules containing colorless to pale yellow colored, transparent, viscous liquid.

6. Manufacturing will be done by
   M/s. MARKSANS PHARMA LIMITED
   Plot No. L-82, L-83,
   Verna Industrial Estate,
   Verna, Goa – 403 722, INDIA.

7. CONTAINER/CLOSURE
   Container Closure System
   The firm will market commercial packs in white, opaque, round, (b) (4)
   with counts-32 and 600 capsules.

Counts	Primary Package Type	Comment
32 capsules	(b) (4)	Smallest pack
600 capsules	(b) (4)	Largest pack

8. Patent Information

Patent Data – NDA 20-402

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 20-402

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

Date of Review: 6/23/09 Date of Submission: 6/3/09
Primary Reviewer: Jim Barlow Date:

Team Leader: Koung Lee Date:

NDC 25000-133-13

Ibuprofen Capsules, 200 mg

Pain Reliever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

600 Softgels**

Marksans

Drug Facts

Active ingredient (in each capsule) — Purpose

Solubilized ibuprofen equal to
200 mg ibuprofen (NSAID)* ..... Pain reliever/Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include :

- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

LOT :

EXP :

N 3 25000 133 B 9

Size : 140 x 80 mm

Drug Facts (Continued)

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems

Drug Facts (Continued)

- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

Drug Facts (Continued)

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Drug Facts (Continued)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

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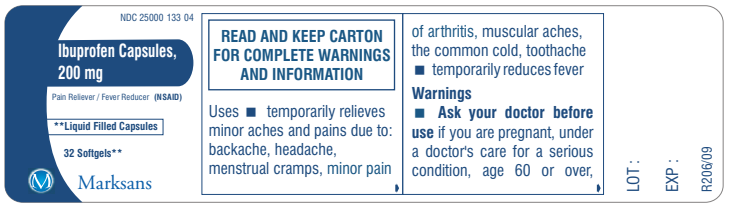
Mfg. Lic. No. : GO/Drugs/515

R306/09



Size : 95 x 26 mm

taking any other drug or have stomach problems.
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shock, skin reddening. If an allergic reaction occurs, stop use and seek medical help right away. **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer.
■ This product may cause **stomach bleeding.**

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.
Directions ■ do not take more than directed ■ the smallest effective dose should be used
■ do not take longer than 10 days, unless directed by a doctor

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Manufactured for :
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Manufactured by:
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Verna, Goa - 403 722, India

NDC 25000-133-04

Ibuprofen Capsules, 200 mg

Pa n Re ever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

32 Softgels**

Marksans

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.

Drug Facts

Active ingredient (in each capsule)	***Purpose***
Solubilized ibuprofen equal to 200 mg ibuprofen (NSAID)*	Pain reliever/ Fever reducer

(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

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- have had stomach ulcers or bleeding problems

Drug Facts (Continued)

- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use
- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
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Ask a doctor or pharmacist before use if you are
- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

Drug Facts (Continued)

When using this product
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Stop use and ask a doctor if
- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
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- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Drug Facts (Continued)

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use. Keep carton.
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

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Mfg. Lic. No. : GO/Drugs/515

N 3 25000 13304 7

LOT :

EXP :

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
6/24/2009 10:51:58 AM
LABELING REVIEWER

Koung Lee
6/24/2009 02:23:16 PM
LABELING REVIEWER
For Wm Peter Rickman

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

ANDA Number: 79-205
Dates of Submission: **August 4, 2008**
Applicant's Name: Marksans Pharma Limited
Established Name: Ibuprofen Capsules, 200 mg

Approval Summary:

1. **Do you have copies of final printed labels and labeling?** Yes

2. **CONTAINER** – Bottles of 32 **count (for the 200 mg strength capsules)**
   Satisfactory in **final print** as of the August 30, 2007 electronic submission

3. **CONTAINER** – Bottles of 600 **count (for the 200 mg strength capsules)**
   Satisfactory in **final print** as of the August 4, 2008 electronic submission

4. **CARTON – 32 count bottles ONLY**
   Satisfactory in **final print** as of the August 4, 2008 electronic submission

5. **Patent Data – NDA 20-402**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 20-402

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

6. **Revisions needed post-approval:** None

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil Liqui-Gels®
NDA Number: N 20-402
NDA Drug Name: Advil Liqui-Gels®
NDA Firm: Wyeth Consumer Healthcare; Approved June 12, 2008. (NDA-20-402/S-024)
Date of Approval of NDA Insert and supplement: Approved June 12, 2008; NDA N 20-402/S-024
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Advil Liqui-Gels®

FOR THE RECORD:

1. MODEL LABELING
   Wyeth Consumer Healthcare. (ANDA 20-402/S-024), Approved June 12, 2008).
2. INACTIVE INGREDIENTS
   *The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** DRUG PRODUCT [Name, Dosage form]*

P.1 Description and Composition of the Drug Product [name, dosage form]

P.2 Pharmaceutical Development [name, dosage form]

P.2.1 Components of the Drug Product

What are the components and composition of the final product? What is the function of each excipient?

The quantitative composition and function of each component in the drug product is listed.

S. No.	Ingredients	Pharmacopeial reference	mg / capsule	% per capsule	Function
MEDICAMENT					
01	Ibuprofen	USP	200.00	(b) (4)	Active ingredient

(b) (4)

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   USP: Preserve in tight, light-resistant container.
   RLD: Store at 20 to 25°C(68 to 77°F) avoid excessive heat above 40°C (104°F).
   ANDA: Same as RLD
4. PACKAGING CONFIGURATIONS
   ANDA: Bottles of 32 and 600 **count**
5. The tablet/capsule imprintings have been accurately described as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule,

effective 9/13/95).

6. Manufacturing will be done by
   US Agent:
   Nilkanth Patel
   Pharmgen LLC
   1919 Middle Country Road, Suite 206
   Centereach, NY 11720
7. CONTAINER/CLOSURE
   Container Closure System
   The firm will market commercial packs in (b) (4)
   with counts-32 and 600 capsules. (b) (4) bottle packs shall be packaged in outer shipper. In addition, it will ship bulk capsules in double (b) (4) bags, placed in (b) (4) container (b) (4) for repacking purpose.
   The largest and smallest packaging proposed for Ibuprofen capsules are:

Counts	**Primary Package Type**	**Comment**
32 capsules	(b) (4)	Smallest pack
600 capsules	(b) (4)	Largest pack

Date of Review: 9/10/08 Date of Submission: 8/4/08
Primary Reviewer: Jim Barlow Date:

Team Leader: John Grace Date:

NDC 25000-133-13

Ibuprofen Capsules 200 mg

Pain Reliever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

600 Softgels**

Marksans

Drug Facts

Active ingredient (in each capsule) ***Purpose***

Solubilized ibuprofen equal to
200 mg ibuprofen (NSAID)* ..... Pain reliever/Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.

Symptoms may include :

- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

LOT :

EXP :

N 3 25000 13313 9

Size : 140 x 80 mm

Drug Facts (Continued)

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- asthma

Drug Facts (Continued)

- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a

Drug Facts (Continued)

doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene

Drug Facts (Continued)

glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India

Mfg. Lic. No. : GO/Drugs/515

R208/08

EXP :

LOT :

Drug Facts (Continued)

- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

Drug Facts (Continued)

- take with food or milk if stomach upset occurs
- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

NDC 25000-133-04

Ibuprofen Capsules 200 mg

Pain Reliever / Fever Reducer (NSAID)

**Liquid Filled Capsules

32 Softgels**

Marksans

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.

Drug Facts

Active ingredient (in each capsule)	Purpose
Solubilized ibuprofen equal to 200 mg ibuprofen (NSAID)* (present as the free acid and potassium salt)	Pain reliever/ Fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.

Symptoms may include :

- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :

- are age 60 or older
- have had stomach ulcers or bleeding problems

Drug Facts (Continued)

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use. Keep carton.
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

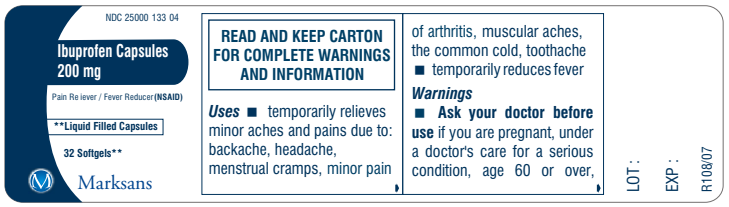
Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

R20808

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India
Mfg. Lic. No. : GO/Drugs/515



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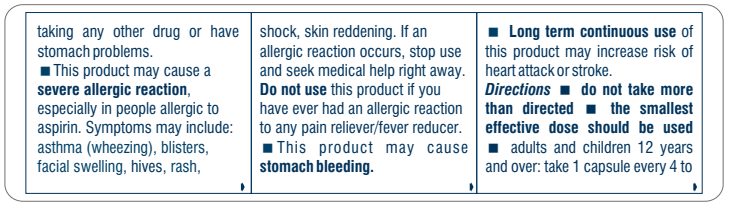

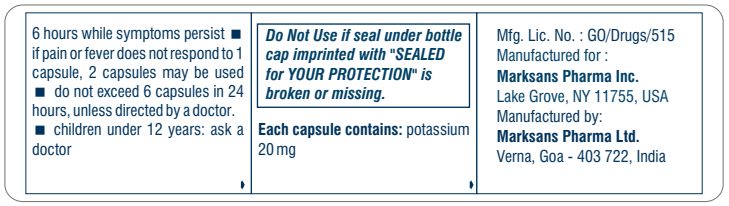

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/s/

James Barlow
9/10/2008 02:27:21 PM
LABELING REVIEWER

John Grace
9/11/2008 11:19:55 AM
LABELING REVIEWER

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

ANDA Number: 79-205
Dates of Submission: **August 30, 2007**
Applicant's Name: Marksans Pharma Limited
Established Name: Ibuprofen Capsules, 200 mg

Approval Summary:

1. Do you have copies of final printed labels and labeling? Yes

2. CONTAINER – Bottles of 32 and 600 **count (for the 200 mg strength capsules)**

Satisfactory in **final print** as of the August 30, 2007 electronic submission

3. CARTON – 32 count bottles ONLY
Satisfactory in **final print** as of the August 30, 2007 electronic submission

4. Patent Data – NDA 20-402

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 20-402

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

5. Revisions needed post-approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil Liqui-Gels®
NDA Number: N 20-402
NDA Drug Name: Advil Liqui-Gels®
NDA Firm: Wyeth Consumer Healthcare; Approved April 28, 2006. (NDA-20-402/S-016)
Date of Approval of NDA Insert and supplement: Approved April 28, 2006; NDA N 20-402/S-016
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Advil Liqui-Gels®

FOR THE RECORD:

1. MODEL LABELING
   Wyeth Consumer Healthcare. (ANDA 20-402/S-016), Approved April 28, 2006).
2. INACTIVE INGREDIENTS
   *The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** DRUG PRODUCT [Name, Dosage form]*

P.1 Description and Composition of the Drug Product [name, dosage form]

P.2 Pharmaceutical Development [name, dosage form]

P.2.1 Components of the Drug Product

What are the components and composition of the final product? What is the function of each excipient?

The quantitative composition and function of each component in the drug product is listed.

S. No.	Ingredients	Pharmacopeial reference	mg / capsule	% per capsule	Function
MEDICAMENT					
01	Ibuprofen	USP	200.00	(b) (4)	Active ingredient

(b) (4)

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   USP: Preserve in tight, light-resistant container.
   RLD: Store at 20 to 25°C(68 to 77°F) avoid excessive heat above 40°C (104°F).
   ANDA: Same as RLD
4. PACKAGING CONFIGURATIONS
   ANDA: Bottles of 32 and 600 **count**
5. The tablet/capsule imprintings have been accurately described as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

6. Manufacturing will be done by
   US Agent:
   Nilkanth Patel
   Pharmgen LLC
   1919 Middle Country Road, Suite 206
   Centereach, NY 11720
7. CONTAINER/CLOSURE
   Container Closure System
   The firm will market commercial packs in (b) (4)
   with counts-32 and 600 capsules. (b) (4) bottle packs shall be packaged in outer shipper. In addition, it will ship bulk capsules in double (b) (4) bags, placed in (b) (4) container (b) (4) for repacking purpose.
   The largest and smallest packaging proposed for Ibuprofen capsules are:

Counts	**Primary Package Type**	**Comment**
32 capsules	(b) (4)	Smallest pack
600 capsules	(b) (4)	Largest pack

Date of Review: 6/5/08 Date of Submission: 8/30/07
Primary Reviewer: Jim Barlow Date:

Team Leader: John Grace Date:

NDC 25000-133-13

Ibuprofen Capsules 200 mg

Pain Reliever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

600 Softgels**

Marksans

Drug Facts

Active ingredient (in each capsule) *Purpose*

Solubilized ibuprofen equal to
200 mg ibuprofen (NSAID)* ..... Pain reliever/Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - backache
  - headache
  - menstrual cramps
  - minor pain of arthritis
  - muscular aches
  - the common cold
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include :

- asthma (wheezing)
- blisters
- facial swelling
- hives
- rash
- shock
- skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

LOT :

EXP :

R108/07

N 3 25000 13313 9

Size : 140 x 80 mm

Drug Facts (Continued)

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you :

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- taken a diuretic

Drug Facts (Continued)

- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a

Drug Facts (Continued)

doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene

Drug Facts (Continued)

glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

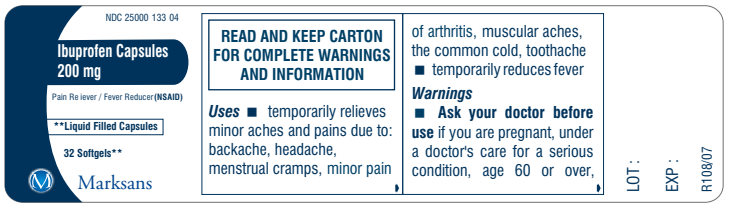
Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India

Mfg. Lic. No. : GO/Drugs/515

R10&07



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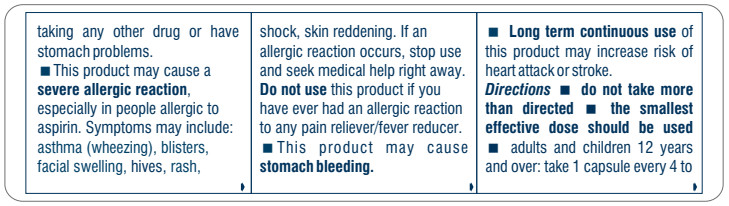

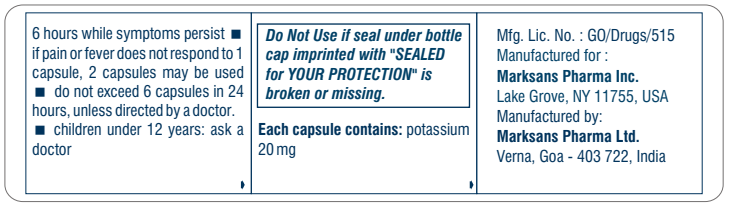

LOT :

EXP :

Drug Facts (Continued)

- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer ■ right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs

Drug Facts (Continued)

- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor.
- children under 12 years: ask a doctor

NDC 25000-133-04

Ibuprofen Capsules 200 mg

Pa n Re ever / Fever Reducer **(NSAID)**

****Liquid Filled Capsules**

32 Softgels**

Marksans

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION.

Drug Facts

Active ingredient (in each capsule)	Purpose
Solubilized ibuprofen equal to 200 mg ibuprofen (NSAID)* ..... (present as the free acid and potassium salt)	Pain reliever/ Fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - ■backache ■headache ■menstrual cramps
  - ■minor pain of arthritis ■muscular aches
  - ■the common cold ■toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.

Symptoms may include :

■ asthma (wheezing) ■blisters ■facial swelling ■hives ■rash ■shock ■skin reddening

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you : ■are age 60 or older ■have had stomach ulcers or bleeding problems

Drug Facts (Continued)

Other information

- **each capsule contains**: potassium 20 mg
- read all warnings and directions before use. Keep carton.
- store at 20 to 25°C (68 to 77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients Ammonium Hydroxide, FD&C Green No. 3, Gelatin, Iron oxide black, Medium chain triglycerides, Polyethylene glycol, Propylene glycol, Potassium hydroxide, Purified water, Shellac, Sorbitol, Sorbitan monooleate.

Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

R110807

Manufactured for :
Marksans Pharma Inc.
Lake Grove, NY 11755, USA

Manufactured by:
Marksans Pharma Ltd.
Verna,Goa - 403 722, India
Mfg. Lic. No. : GO/Drugs/515

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
6/5/2008 03:11:36 PM
LABELING REVIEWER

John Grace
6/6/2008 12:10:03 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

CHEMISTRY REVIEWS

ANDA 79-205

Ibuprofen Capsules (liquid filled), 200 mg

Marksans Pharma Limited

Subhash C. Dhanesar, Ph.D.

Chemistry Division I

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A. Recommendation and Conclusion on Approvability 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

B. Description of How the Drug Product is Intended to be Used 6

C. Basis for Approvability or Not-Approval Recommendation 6

Chemistry Assessment **7**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] 7

P DRUG PRODUCT [Name, Dosage form] 9

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

Chemistry Review Data Sheet

1. ANDA 79-205

2. REVIEW #3

3. REVIEW DATE: November 24, 2008

4. REVIEWER: S. Dhanesar, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	August 30, 2007
Gratuitous Amendment	September 12, 2007
Gratuitous Amendment	December 11, 2007
Amendment (AB)	February 14, 2008
Amendment (AB)	April 11, 2008
Amendment (CMC)	March 11, 2008
Amendment (CMC)	April 16, 2008
Amendment (CMC)	April 21, 2008
Amendment (<467>) (AA)	May 22 and May 30, 2008 August 15, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	October 6, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Marksans Pharma Limited
Address:	601-622, 6th Floor, Chintamani Plaza Mohan Studio Compound Andheri-Kurla Road Andheri (East), Mumbai 400 099, India
Representative:	US Agent: Nilkanth Patel Pharmgen LLC 1919 Middle Country Road, Suite 206 Centereach, NY 11720
Telephone:	631-656-9753
Fax:	631-656-9754

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Ibuprofen Capsules (liquid filled), 200 mg

9. LEGAL BASIS FOR SUBMISSION: Advil® Liquid-Gels® from Wyeth

There are no unexpired patents or exclusivities for the drug product.

10. PHARMACOL. CATEGORY: Short term management of pain

11. DOSAGE FORM: Solid (Capsules)

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __x_OTC

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

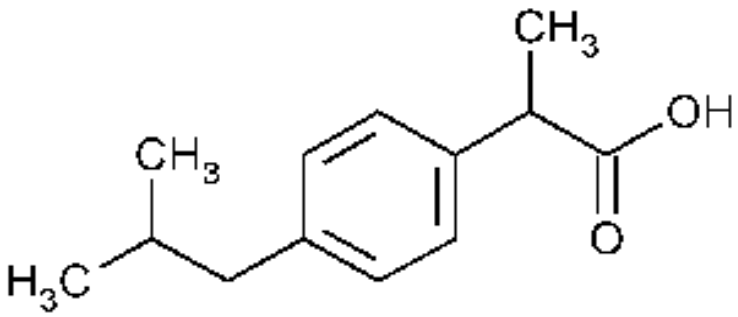
_____SPOTS product – Form Completed ___x___Not a SPOTS product

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

Benzene acetic acid, alpha-methyl-4-(2-methylpropyl), (±)-

(±)-*p*-Isobutylhydratropic acid

(±)-2-(*p*-Isobutylphenyl)propionic acid



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			Ibuprofen USP	3	Adequate	11-19-2008	R. Powers
(b) (4)				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-22-2008	
Methods Validation	Not required		
Labeling	Acceptable	06-25-2009	J. Barlow
Bioequivalence	Acceptable	05-29-2009	G. Johnson
EA	Granted		
Radiopharmaceutical	N/A		

Note: The firm did accept the DBE's dissolution conditions and specification. Clinical review is pending.

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 79-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The ANDA is approvable.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug product is an immediate release 200 mg Ibuprofen (liquid filled) soft gelatin capsules. (b) (4) .

The drug substance is Ibuprofen, USP. The maximum daily dose is 1200 mg.

B. Description of How the Drug Product is Intended to be Used
The drug product is sold over the counter and is used as directed in the package insert or as directed by a physician.

C. Basis for Approval Recommendation
The ANDA is approvable.

16 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Subhash Dhanesar
6/26/2009 03:12:11 PM
CHEMIST

Albert Mueller
6/26/2009 04:26:43 PM
CHEMIST

Dat Doan
6/29/2009 09:34:34 AM
CSO

ANDA 79-205

Ibuprofen Capsules (liquid filled), 200 mg

Marksans Pharma Limited

Subhash C. Dhanesar, Ph.D.

Chemistry Division I

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

B. Description of How the Drug Product is Intended to be Used 6

C. Basis for Approvability or Not-Approval Recommendation 6

Chemistry Assessment **7**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] 7

P DRUG PRODUCT [Name, Dosage form] 9

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

Chemistry Review Data Sheet

1. ANDA 79-205

2. REVIEW #2

3. REVIEW DATE: May 13, 2008/August 15, 2008

4. REVIEWER: S. Dhanesar, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	August 30, 2007
Gratuitous Amendment	September 12, 2007
Gratuitous Amendment	December 11, 2007
Amendment (AB)	February 14, 2008
Amendment (AB)	April 11, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	March 11, 2008
Amendment (CMC)	April 16, 2008
Amendment (CMC)	April 21, 2008
Amendment (<467>) (AA)	May 22 and May 30, 2008
	August 15, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Marksans Pharma Limited
Address:	601-622, 6th Floor, Chintamani Plaza Mohan Studio Compound Andheri-Kurla Road Andheri (East), Mumbai 400 099, India
Representative:	US Agent: Nilkanth Patel Pharmgen LLC 1919 Middle Country Road, Suite 206 Centereach, NY 11720
Telephone:	631-656-9753
Fax:	631-656-9754

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Ibuprofen Capsules (liquid filled), 200 mg

9. LEGAL BASIS FOR SUBMISSION: Advil® Liquid-Gels® from Wyeth

There are no unexpired patents or exclusivities for the drug product.

10. PHARMACOL. CATEGORY: Short term management of pain

11. DOSAGE FORM: Solid (Capsules)

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __x_OTC

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

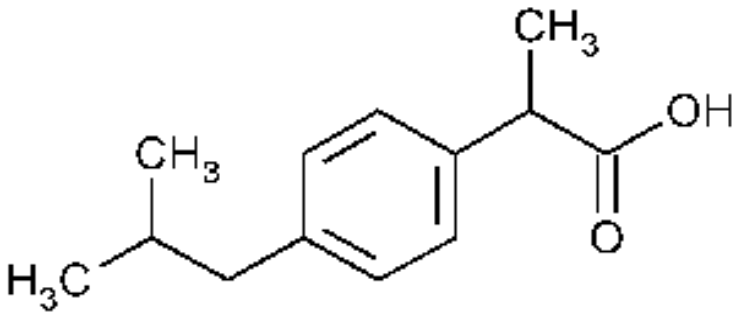
_____SPOTS product – Form Completed ___x___Not a SPOTS product

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

Benzene acetic acid, alpha-methyl-4-(2-methylpropyl), (±)-

(±)-*p*-Isobutylhydratropic acid

(±)-2-(*p*-Isobutylphenyl)propionic acid



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			Ibuprofen USP	3	Inadequate	08-13-2008	R. Powers
(b) (4)				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	deficient	9/2/08	Z. Williams
Methods Validation	Not required		
Labeling	Acceptable	06-05-2008	J. Barlow
Bioequivalence	Pending		
EA	Granted		
Radiopharmaceutical	N/A		

Note: The firm did accept the DBE's dissolution conditions and specification. Clinical review is pending.

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 79-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable due to pending EER and Bioequivalence (clinical) reviews. CMC is deficient. Labeling is acceptable. The dissolution conditions and specification recommended by DBE was accepted by the firm. The firm amended the CMC portion of the ANDA on April 21, 2008 to revise the testing specifications for the drug product and provided gratuitous amendment dated August 15, 2008 for USP<467> update.

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

II. Summary of Chemistry Assessments

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

The drug product is an immediate release 200 mg Ibuprofen (liquid filled) soft gelatin capsules. (b) (4)

The drug substance is Ibuprofen, USP. The maximum daily dose is 1200 mg.

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

The drug product is sold over the counter and is used as directed in the package insert or as directed by a physician.

C. Basis for Not-Approval Recommendation

The ANDA is not approvable due to pending EER. Bioequivalence (clinical) and CMC reviews are deficient. Labeling is acceptable.

18 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Subhash Dhanesar
9/5/2008 11:35:42 AM
CHEMIST

Albert Mueller
9/5/2008 12:14:11 PM
CHEMIST

Dat Doan
9/5/2008 01:11:08 PM
CSO

ANDA 79-205

Ibuprofen Capsules (liquid filled), 200 mg

Marksans Pharma Limited

Subhash C. Dhanesar, Ph.D.

Chemistry Division I

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A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 7

C. Basis for Approvability or Not-Approval Recommendation 7

Chemistry Assessment **8**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] 8

P DRUG PRODUCT [Name, Dosage form] 17

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

III. List Of Deficiencies To Be Communicated 49

Chemistry Review Data Sheet

1. ANDA 79-205

2. REVIEW #: 1

3. REVIEW DATE: January 18, 2008

4. REVIEWER: S. Dhanesar, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 30, 2007
Gratuitous Amendment	September 12, 2007
Gratuitous Amendment	December 11, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Marksans Pharma Limited
Address:	601-622, 6th Floor, Chintamani Plaza Mohan Studio Compound Andheri-Kurla Road Andheri (East), Mumbai 400 099, India
Representative:	US Agent: Nilkanth Patel Pharmgen LLC 1919 Middle Country Road, Suite 206 Centereach, NY 11720
Telephone:	631-656-9753
Fax:	631-656-9754

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Ibuprofen Capsules (liquid filled), 200 mg

9. LEGAL BASIS FOR SUBMISSION: Advil® Liquid-Gels® from Wyeth

There are no unexpired patents or exclusivities for the drug product.

10. PHARMACOL. CATEGORY: Short term management of pain

11. DOSAGE FORM: Solid (Capsules)

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __x_OTC

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

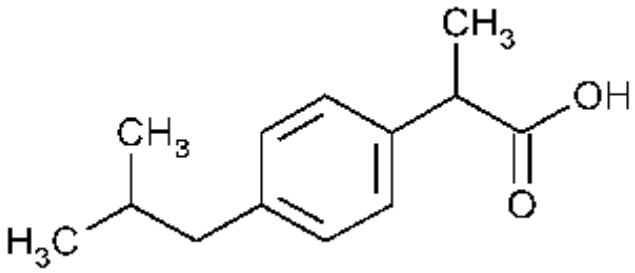
_____SPOTS product – Form Completed ___x___Not a SPOTS product

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

Benzene acetic acid, alpha-methyl-4-(2-methylpropyl), (±)-

(±)-*p*-Isobutylhydratropic acid

(±)-2-(*p*-Isobutylphenyl)propionic acid



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			Ibuprofen USP	3	Adequate	02-05-2008	R. Powers
			(b) (4)	4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Granted		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 79-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable due to pending EER, Bioequivalence and Labeling reviews and deficient CMC review.

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

II. Summary of Chemistry Assessments

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

The drug product is an immediate release 200 mg Ibuprofen (liquid filled) soft gelatin capsules.

The drug substance is Ibuprofen, USP. The maximum daily dose is 1200 mg.

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

The drug product is sold over the counter and is used as directed in the package insert or as directed by a physician.

C. Basis for Not-Approval Recommendation

The ANDA is not approvable due to pending EER, Bioequivalence and Labeling reviews and deficient CMC review.

45 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Subhash Dhanesar
2/13/2008 04:16:58 PM
CHEMIST

Albert Mueller
2/13/2008 04:33:53 PM
CHEMIST

Dat Doan
2/14/2008 12:11:25 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE ACCEPTABLE DSI INSPECTION REPORT REVIEW

ANDA No.	79-205
Drug Product Name	Ibuprofen Capsules
Strength	200 mg
Applicant Name	Marksans Pharma Limited
Date of Original Submission	August 30, 2007
Date of Report	May 29, 2009
Reviewer	Nam Chun, Pharm.D.

EXECUTIVE SUMMARY

Marksans Pharma Limited submitted ANDA 79-205 for Ibuprofen Capsules, 200 mg on August 30, 2007.

The bio review was completed and found acceptable on December 20, 2008 pending the outcome of a DSI inspection of the analytical and clinical sites, Accutest Research Laboratories, located at A-31TTC Industrial Area, Kopar Khairane, Navi-Mumbai, India.

The DSI inspection history for the sites is as follows:

- A "For Cause" inspection for ANDA (b) (4) was completed on 4/26/2005 and the outcome was VAI.
- A "Routine" inspection for ANDA (b) (4) was completed on 7/7/2004 and the outcome was VAI.

A new request for a "Routine" DSI re-inspection was requested for ANDA (b) (4) on June 2, 2008. ANDA 79-205 was added as a related ANDA to this request because both ANDAs shared the same study sites.

Per Bob West's request, since this application is ready for approval and the re-inspection of Accutest Research Laboratories has not yet been conducted, based upon prior satisfactory inspectional history of the sites, "the inspection link" to ANDA (b) (4) is hereby cancelled and the bio review of ANDA 79-205 is now acceptable. However, the study sites will be inspected at a later date as per our routine inspection request for ANDA (b) (4). (*Please see* attachment below for more information)

The bioequivalence section of the application is now complete and acceptable.

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing. The bioequivalence section of the application is acceptable.

ATTACHMENT:

From: Doan, Dat
Sent: Friday, May 22, 2009 1:30 PM
To: Solana-Sodeinde, Diana A
Subject: 79-205/Marksans/Ibuprofen

Hi Diana,

Concerning ANDA 79-205/Marksans/Ibuprofen

In the past you mentioned that this bio review is AC pending DSI. Can you give me a little more detail on the DSI (are they re-inspecting the site, what's holding it up?).

The firm is fairly new and getting this approved is a huge financial impact for them.

Thanks Diana,

Dat

From: Solana-Sodeinde, Diana A
Sent: Tuesday, May 26, 2009 11:44 AM
To: Doan, Dat
Subject: RE: 79-205/Marksans/Ibuprofen

Hi Dat

RE: Current status of ANDA 79-205

I just tried to call you but no answer.

The Bio review for ANDA 79205 has been completed thus far but NOT Approvable because of pending DSI results of ANDA (b) (4). These two applications share the same analytical and clinical sites located at Accutest Research Laboratories, A-31TTC Industrial Area, Kopar Khairane, Navi-Mumbai, India.

The DSI inspection history for the sites at the location mentioned above is listed below:

- A "For Cause" inspection for ANDA (b) (4) was completed on 4/26/2005and the outcome was VAI. (Expired since inspection occurred more than 3 years ago)
- A "Routine" inspection for ANDA (b) (4) was completed on 7/7/2004 and the outcome was VAI.(Expired since inspection occurred more than 3 years ago)

In summary, a new request for a "Routine" DSI inspection was entered for ANDA (b) (4) on 6/2/2008 while ANDA 79205 was indicated as a "Related ANDA," pending the outcome of DSI inspection of ANDA (b) (4). Completion of the inspection has been due since 12/1/2008. However, there is substantial delay probably due to the location of the sites (foreign country), especially in Mumbai, where there was a recent safety issue (terrorist attacks!) that affected the completion of most of the DSI inspections in India.

I am aware that the firms have been calling.

In fact I spoke to Mr. Miltan Patel (U.S. Agent for firm) and a Senior representative from the firm in India but unfortunately, since we are not allowed to give any information about DSI, all I can say is that the Bio status is "Under Review."

I hope this helps!

Thank you,

Diana (Lola) Solana-Sodeinde, Pharm. D.

From: Doan, Dat
Sent: Wednesday, May 27, 2009 8:23 AM
To: West, Robert L
Subject: FW: 79-205/Marksans/Ibuprofen

Message forwarded to Bob West

From: West, Robert L
Sent: Wednesday, May 27, 2009 8:32 AM
To: Doan, Dat; Solana-Sodeinde, Diana A
Subject: RE: 79-205/Marksans/Ibuprofen

Diana:

I recommend that if the reinspection of the Accutest Research Laboratories has not been scheduled, please complete the bio review based upon the satisfactory inspectional history of the sites.

Thank you,

Bob

I. Completed Assignment for 79205 ID: 8382

Reviewer: Solana-Sodeinde, Diana **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: DSI Inspection Report

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8382	8/30/2007	Other	DSI Inspection Report	1	1
				Bean Total:	1

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/s/

Diana Solana-Sodeinde
5/29/2009 03:33:22 PM
BIOPHARMACEUTICS

Lizzie Sanchez
5/29/2009 03:38:17 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	79205	
Drug Product Name	Ibuprofen Liquid Filled Capsules (OTC)	
Strength(s)	200 mg	
Applicant Name	Marksans Pharma Ltd.	
Address	601-622, Chintamani Plaza, Andheri Kurla Road, Andheri (East), Mumbai-400099, India	
Applicant's Point of Contact	Authorized U.S. Agent: Mr. Nikanth J. Patel, Vice President Pharmgen LLC, 1919 Middle Country Road, Suite #206 Centereach, NY 11720	
Contact's Telephone Number	631-656-9753	
Contact's Fax Number	631-656-9754	
Original Submission Date(s)	30 Aug 2007 and 22 April 2008 (dissolution acknowledgement)	
Submission Date(s) of Amendment(s) Under Review	11 Sept 2008 submission of corrected SAS fed and fasted data	
Reviewer	Zakia R. Williams Ph.D.	
Study Number (s)	US/07/023	US/07/024
Study Type (s)	Fasted (STF)	Fed (STP)
Strength (s)	200 mg	200 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Clinical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
Analytical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Analytical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
OUTCOME DECISION	**ACCEPTABLE**	

Review of a Study Amendment

1 EXECUTIVE SUMMARY

The current study amendment contains the results of the re-submitted SAS data for the fasted study, US/07/023 and fed study, US/07/024. On August 30, 2007, Marksans Pharma Ltd, submitted fasted and fed bioequivalence (BE) studies comparing its test product, Ibuprofen Capsules (Liquid Filled) 200 mg (OTC) to the corresponding reference product Wyeth Consumer Healthcare's Advil® Liquid-Gel® Capsules (Liquid Filled) 200 mg. That review was deemed incomplete for the fasted and fed studies due to deficiencies in the datasets. The firm responded in a Bioequivalence Amendment dated September 11, 2008 with clarifications on all the discrepancies identified by the reviewer concerning the datasets. The firm also submitted supportive documents.

The dissolution testing was reviewed previously (DFS N079205 N000 AB 14-Feb-2008). The firm's dissolution testing using the FDA-recommended method (900 mL of pH 7.2 phosphate buffer with basket at 150 rpm) is acceptable. The firm acknowledged its acceptance of the FDA-recommended specification of NLT (b)(4)% (Q) in 20 minutes in a Bioequivalence Amendment dated April 11, 2008.

The clinical and analytical sites were inspected on 3/14/2005, outcome VAI.

The application is now acceptable with no deficiencies.

Background[1]

On April 11, 2008, the firm submitted two (2) single dose, two-way crossover, *in vivo* BE studies under fed (1) and fasted (1) conditions comparing its test product, Ibuprofen Liquid Filled Capsules (OTC), 200 mg, to the RLD product, Advil® Liquid-Gel® Capsules (OTC), 200 mg, in healthy adult subjects. The fed and fasted BE studies were incomplete due to the following reasons:

1. The fed BE study was deemed incomplete because the data in the paper copy was inconsistent with the data submitted in the electronic copy. In the electronic copy, the **treatment variable** was mislabeled for the following subjects: #3, #5, #7, #10, #12, #13, #16, #17, #19, #21 and #23. The treatment variable indicated that the respective subjects received the reference product in both periods. As a result, the data was analyzed according to the treatment variables listed in the paper copy, which showed those subjects receiving test product in period 1 and reference product in period II.

2. The fasted BE study was deemed incomplete because the data in the paper copy was inconsistent with the data submitted in the electronic copy. The plasma concentration data submitted in the paper copy **did not** correspond with the plasma concentration data submitted in the electronic copy. In the paper copy, the plasma concentration data of the test product is reported in the electronic copy as the reference product plasma concentration data. Similarly, the plasma concentration data reported in the paper copy of the reference product is listed in the electronic copy as the test product plasma concentration data.

In the firm's initial written response (9/11/08) to these deficiencies, the firm also submitted additional data regarding the drop-outs for the fed BE study. In their response, there was a statement requesting to "kindly note that subjects No. 5 and 19 were dropped out from the study" in period II for the fed BE study. The reviewer identified this additional information to be inconsistent with the data submitted in the original submission. On October 20, 2008, the DBE contacted the firm by telephone regarding clarification of the accurate number of dropout subjects stated in its Bioequivalence Amendment Query Reply. The firm submitted an electronic response

[1] Division of System Files v 2.0. ANDA 79-205. Bioequivalence Review. N 079205 N 000 30-Aug-2007.

to this deficiency on November 10, 2008. The telephone deficiency response is also included in this amendment review.

Note: See additional information in the original review: DFS N 079205 N 000 30-Aug-2007

DBE Deficiency Comment No. 01

The data submitted for the fed bioequivalence (BE) study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy correspond with the **concentration data** submitted in the SAS files; however, in the SAS files, the **treatment variable** *does not* correspond to the sequence or period for the following subjects: 3,5,7,10,12,13,16,17,19,21,23 in the paper copy. The SAS files show these subjects receiving the reference product in both period 1 and period 2. Please explain this discrepancy and resubmit the data for the fed BE study, US/07/024, with correct treatment, period, and sequence information.

Firm's Response:
Marksan Pharma Ltd. acknowledged the deficiency as a "transcription error". As a result, the firm re-submitted the SAS data file correctly identifying subjects receiving either test product or reference product in the "Treatment Administered' column for subjects: 3,5,7,10,12,13,16,17,19,21,23.

DBE Deficiency Comment No. 02

The data submitted for the fasted BE study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy do not correspond with the plasma concentration data submitted in the SAS files. Please explain this discrepancy and resubmit the data for the fasted BE study, US/07/023 distinguishing the correct plasma concentration data for the test and reference product.

Firm's Response:
Marksan Pharma Ltd. responded to the deficiency comment stating "it was verified and confirmed that the plasma concentration data in the paper copy with the data submitted in the SAS file **are consistent**". Therefore, the firm did not make any changes to the data.

Note: Upon further investigation, the reviewer noticed that there were two paper copies sent to the Agency from the firm: one which was scanned and sent in a file via the eCTD, and the other which was sent in the orange jackets. The reviewer identified and noticed the *plasma concentration data sent in the orange jackets did not* correspond to the plasma concentration data submitted in the scanned paper copy or in the SAS electronic copy, both sent via eCTD. To clarify which plasma concentration data was correct, the reviewer cross-referenced the analytical raw data from the chromatographic report, as well as the output data from the statistical analysis report to the data from the eCTD. Upon verification, the reviewer analyzed the data using the information sent via eCTD.

The firm's response to the deficiency stating that the data submitted in the SAS file was consistent with the data in the paper copy was accurate for the scanned paper copy sent via eCTD.

DBE Telephone Deficiency Comment

In your summary tables and bio-study data in the original ANDA (79-205) you identified 3 drop out subjects (# 4, #5, and #19) for fed study (US/07/024); however, in response to deficiency #1, you mentioned 2 drop out subjects (#5 and #19). Please provide written clarification.

Firm's Response:
As mentioned in the clinical study report and DBE table (Model Bioequivalence Data Summary Tables) total three subjects (4, 5 and 19) were dropped out due to personal reasons (as they did not report for period 2). Total 21 subjects completed clinical study and data from 21 subjects were considered for statistical conclusion. The earlier response to deficiency (query) received from OGD refers to transcriptional error for subjects having sequence AB, hence subjects with sequence AB only, were addressed in the response. Although subject number 4 was dropped out from the study (as mentioned in the clinical study report and DBE tables) it was not addressed in the earlier response as subject number 4 was having sequence BA.

Comments from the Reviewer:

Fasted BE Study No.US/07/023 (two-way crossover)

1. For the fasted Study No. US/07/023, the firm enrolled twenty four (24) healthy subjects (18 male and 6 female), but 23 healthy subjects completed the study (subject #23 dropped out). In each study period, 200 mg of the test product was administered to the subjects after an overnight fast. The data for the subjects that completed the study was used in BE statistical evaluations.

2. The 90% confidence intervals for log-transformed $LAUC_T$, $LAUC_\infty$, and LC_{max} are within the acceptable range of 80-125%.

3. The firm's responses to the deficiency comment for the fasting BE study is acceptable.

Fed BE Study No. US/07/024 (two-way crossover)

1. The firm enrolled twenty four (24) subjects, but 21 healthy subjects completed the study. In each study period, after an overnight fast of at least 10 hours, a high fat breakfast was given to each subject half an hour before dosing. The data for the subjects (excluding subjects nos. 04, 05, and 19) that completed the study was used in BE statistical evaluations.

2. The firm re-submitted the SAS data file correctly identifying subjects receiving either test product or reference product. The only change in the re-submitted SAS data was the treatment variable correctly corresponding to the sequence and period for each subject. The re-submitted plasma concentration submitted in the SAS data file was consistent with the initial submitted plasma concentration data in the paper copy. For

that reason, it was not necessary to re-analyze the data. The 90% confidence intervals for log-transformed $LAUC_T$, $LAUC_\infty$, and LC_{max} data are within the acceptable range of 80-125%.

3. The firm's responses to both deficiency comments for the fed BE study are acceptable.

Deficiency Comments:

None

Recommendations

1. The Division of Bioequivalence accepts the fasted BE study (US/07/023) conducted by Marksans Pharma Ltd., on its Ibuprofen Capsules (Liquid Filled) 200 mg (OTC) lot # FH7006 comparing it to Wyeth Consumer Healthcare Advil® LIQUI-GELS® 200 mg lot # B98587.

2. The Division of Bioequivalence accepts the fed BE study (US/07/024) conducted by Marksans Pharma Ltd., on its Ibuprofen Capsules (Liquid Filled) 200 mg (OTC) lot # FH7006 comparing it to Wyeth Consumer Healthcare Advil® LIQUI-GELS® 200 mg lot # B98587.

3. The firm successfully completed the *in vitro* dissolution testing on its test product, Ibuprofen Capsules (Liquid Filled), 200 mg and on April 11, 2008, it accepted and acknowledged the following FDA-recommended dissolution method and specification:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
USP Apparatus:	I (Basket)
Rotation Speed:	150 rpm

NLT (b)(4)% (Q) of the labeled amount of ibuprofen in the dosage form is dissolved in 20 minutes.

4. The firm should be informed of the above recommendations.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen (Liquid Filled) Capsules, 200 mg (OTC)

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

We acknowledge that you will conduct dissolution testing on your Ibuprofen Capsules (Liquid Filled) 200 mg (OTC) using the following FDA-recommended dissolution method and specification:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm

The test product should meet the following specification:

NLT (b)(4)% (Q) of the labeled amount of Ibuprofen in the dosage form is dissolved in 20 minutes.

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

Sincerely yours,

{See appended electronic signature page}

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

4.7 Outcome Page

ANDA: 79-205

Reviewer: Williams, Zakia **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Ibuprofen Amend liq 200 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6590	9/11/2008	Other	Study Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zakia R Williams
12/18/2008 02:06:23 PM
BIOPHARMACEUTICS

Glendolynn S Johnson
12/18/2008 04:04:41 PM
BIOPHARMACEUTICS
Signing for Yih Chain Huang

Hoainhon T. Nguyen
12/20/2008 09:42:06 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	79205		
Drug Product Name	Ibuprofen Liquid Filled Capsules (OTC)		
Strength(s)	200 mg		
Applicant Name	Marksans Pharma Ltd.		
Address	601-622, Chintamani Plaza, Andheri Kurla Road, Andheri (East), Mumbai-400099, India		
Applicant's Point of Contact	Authorized U.S. Agent: Mr. Nikanth J. Patel, Vice President Pharmgen LLC, 1919 Middle Country Road, Suite #206 Centereach, NY 11720		
Contact's Telephone Number	631-656-9753		
Contact's Fax Number	631-656-9754		
Original Submission Date(s)	30 Aug 2007		
Submission Date(s) of Amendment(s) Under Review	11Apr 2008 (dissolution acknowledgement)		
Reviewer	Zakia R. Williams Ph.D.		
Study Number (s)	US/07/023	US/07/024	
Study Type (s)	Fasted (STF)	Fed (STP)	
Strength (s)	200 mg	200 mg	
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31		
Clinical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA		
Analytical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31		
Analytical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA		
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

This application contains the results of fasted and fed bioequivalence (BE) studies comparing the test product Ibuprofen Capsules (Liquid Filled) 200 mg (OTC) by Marksans Pharma Ltd. to Advil® Liquid-Gel® Capsules (Liquid Filled), 200 mg (OTC) by Wyeth Consumer Healthcare. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy adult subjects. Statistical analysis of the pharmacokinetic (PK) parameters from plasma concentrations of ibuprofen demonstrated bioequivalence in both fasted and fed studies. The results are summarized in the tables below. However, both studies are incomplete due to discrepancies in the data presented between the electronic copy and the paper copy.

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study No.US/07/023					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	63.70	68.13	0.93	90.00	97.13
AUC∞ (hr *µg/ml)	65.65	69.98	0.94	90.61	97.14
Cmax (µg/ml)	24.93	26.47	0.94	86.85	102.15

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. US/07/024					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	52.64	54.90	0.96	92.99	98.85
AUC∞ (hr *µg/ml)	56.07	58.13	0.96	93.26	99.77
Cmax (µg/ml)	11.69	12.34	0.95	88.18	101.73

The dissolution testing was reviewed previously (DFS N079205 N000 AB 14-Feb-2008). The firm's dissolution testing using the FDA-recommended method (900 mL of pH 7.2 phosphate buffer with basket at 150 rpm) is acceptable. The firm acknowledged its acceptance of the FDA-recommended specification of NLT (b)(4)% (Q) in 20 minutes in a Bioequivalence Amendment dated April 11, 2008.

The firm submitted the study data in both electronic and paper copies. For the fed study, the plasma concentration data in the paper copy corresponds with the **concentration data** submitted in the electronic copy; however, the **treatment variable** *does not* correspond to the sequence or period for the following subjects: 3,5,7,10,12,13,16,17,19,21,23. See Deficiency Comment section 3.10. For the fasted study, the *plasma concentration data* in the paper copy **does not** corresponds with the *plasma concentration data* submitted in the electronic copy. Consequently, the correct corresponding concentration data of test and reference product is not known. See Deficiency Comment section 3.10.

The clinical and analytical sites were inspected on 3/14/2005, outcome VAI.

The application is incomplete due to discrepancies in the data submitted in both fasted and fed BE studies.

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4.7 Outcome Page 116

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Ibuprofen Capsules (Liquid Filled) (OTC), 200 mg
Reference Product	Advil® Liquid-Gel® Capsules (OTC), 200 mg
RLD Manufacturer	Wyeth Consumer Healthcare
NDA No.	020402
RLD Approval Date	20 April 1995
Indication	Used to 1. Relieve pain and inflammation 2. Reduce fever 3. Treat osteoarthritis, rheumatoid arthritis and menstrual cramps

3.2 PK/PD Information[1,2]

Bioavailability	The orally administered drug is approximately 80% absorbed from the gut. A linear dose-response is noted for single ibuprofen doses up to 800 mg. There is also a correlation between the reduction of fever and drug concentration over time.
Food Effect	Although the peak concentration is lower and time to peak concentration is slower if the drug is taken with food, the extent of ibuprofen absorption is not affected.
Tmax	1.15 hour (non-fasting); 0.7 hour (fasting)[2]
Metabolism	Ibuprofen is metabolized via hepatic oxidation by cytochrome P450 2C9 to two inactive metabolites.
Excretion	Ibuprofen is excreted in the urine, 50 - 60% as metabolites and approximately 10% as unchanged drug. Some biliary excretion may occur. Excretion is usually complete within 24 hours of oral administration.
Half-life	2.526 hour (single oral dose) [2]
Drug Specific Issues (if any)	The FDA pregnancy category is B during the first and second trimesters and D during the third trimester of pregnancy.

http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=303&sec=monphar

[2]Enterprisesearch- NDA 20-402; 200 mg (Ibuprofen) Liquigel Capsules. Submission Date: December 11, 1996

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2: Fasted and Fed

1.	**Type of study:**	Fasted
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	200 mg

	Subjects:	Normal healthy adult, human subjects
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	200 mg
	Subjects:	Normal healthy adult, human subjects
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Ibuprofen
Bioequivalence based on:	90% CI
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Control 07-0327 (Perrigo)
Summary of OGD or DBE History	There is no approved generic drug listed in the Orange Book (OTC section) for this product. Control Document History (b) (4) 07-0327 Perrigo 4/27/2007 (b) (4) ANDA History: (b) (4) 77-338 (Dr. Reddy) submitted 10/21/2004: The 90% CI on LCmax was 70.11% - 97.60%. The study was initiated on January 4, 2003, which met the FDA acceptance criteria in place at that time for FED bioequivalence studies. The CDER Guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies" was issued on December 2002. 78-682 (Banner) submitted 12/15/2006

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose Fasted	Yes	1
Single-dose fed	Yes	1
Steady-state	No	---
In vitro dissolution	Yes	1
Waiver requests	No	---
BCS Waivers	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	1 (Dissolution acknowledgment)

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Ibuprofen Capsules (Liquid Filled) 200 mg
Bioanalytical method validation report location	Volume II of V, (Appendix 16.7.3 of Bioanalytical Report), Pages 1 to 72
Analyte	Ibuprofen
Internal standard (IS)	(b) (4)
Method description	LC/MS/MS

Limit of quantification	0.251 µg/mL
Average recovery of drug (%)	105.75%
Average recovery of IS (%)	94.90%
Standard curve concentrations (units/mL)	0.251 µg/mL to 99.940 µg/mL
QC concentrations (units/mL)	LLOQQC: 0.251 µg/mL QC-1 (LQC): 0.753 µg/mL QC-2 (MQC): 40.177 µg/mL QC-3 (HQC): 77.842 µg/mL ULOQQC: 99.940 µg/mL
QC Intra day precision range (%)	LLOQQC: 6.36 % LQC: 4.66% MQC: 3.88% HQC: 6.02% ULOQQC: 6.71%
QC Intra day accuracy range (%)	LLOQQC: 93.56 % LQC: 99.34% MQC: 104.25% HQC: 101.45% ULOQQC: 104.79%
QC Inter day precision range (%)	LLOQQC: 9.70 % LQC: 4.89% MQC: 4.28% HQC: 6.07% ULOQQC: 6.71%
QC Inter day accuracy range (%)	LLOQQC: 98.86 % LQC: 99.71% MQC: 101.27% HQC: 97.76% ULOQQC: 99.79%
Carry Over Effect*	Mean % Interference: (see comment below) For Drug: 11.60% of LLOQ For IS: 0.05%
Bench-top stability (hrs)	8 hours @ room temperature
Stock solution stability (days)	24 hours @ room temperature, 17 days @ 2ºC -8ºC
Processed stability (hrs)	11 hours @ 4^0C
Freeze-thaw stability (cycles)	3 cycles
Long term stability (days)	16 days @ -20°C ± 5°C: In an amendment dated 14-Feb-2008, the firm submitted sufficient long-term stability data covering 51 days at -20º C for ibuprofen in the biological matrix.
Reinjection reproducibility	At least for 10 minutes
Dilution integrity	Two times and Four times (see comments below)
Selectivity	no significant interference peaks.
Matrix effect	LQC: 1.52% CV HQC: 5.05% CV For IS: 6.97% CV

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

Complete.

1. Carryover effect of the analyte was measured in terms of interference at the retention time of analyte in blank sample (47.5) injected after ULOQ sample compared against the mean response obtained in the processed LLOQ sample (410). Thus, the mean interference of the analyte (ibuprofen) is 47.5/410 = 11.6% of LLOQ.

2. The dilution integrity stock solutions (DQC) prepared was 1.7 times the ULOQ working solution concentration. A spiked sample of ibuprofen in plasma was prepared to 2 and 4 dilutions of the original concentration and analyzed against a calibration curve. The precision (%CV) for both dilutions 2 and 4 was 2.62% and 3.0% respectively and accuracy for both dilutions was 103.07% and 100.93%, respectively. It should be noted that no dilution is needed for study samples.

3. The pre-study method validation is **complete**.

3.6 In Vivo Studies

Table 1 Summary of all in vivo Bioequivalence Studies**

Study Ref. No.	Study Design	Study Objective	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters +/-SD (% CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} § (hr)	AUC_{0-t} (ngxhr/mL)	AUC_{∞} (ngxhr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
US/07/023	Single-dose, open label, two period, two treatment, two sequence, randomized, crossover study	* The objective of this study is to demonstrate bioequivalence between Test Product and Reference Product	**Test product:** Ibuprofen soft gelatin capsules 200 mg [Batch # FH7006]	23 Healthy human (18M/5F) Subjects 25.87 ± 5.50 (18-37)	25.36 ± 4.93 (19.48)	0.75 (0.50-1.25)	66.66 ± 21.57 (32.38)	68.95 ± 23.53 (34.15)	1.94 ± 0.53 (27.28)	0.38 ± 0.09 (22.93)	Volume I, File 1 of 2, Section 5.3, Page No. 1-44
			Reference product: Advil® Liqui-Gels® Solubilized Ibuprofen Capsules, 200 mg [Batch # B98587]		27.08 ± 5.93 (21.92)	0.50 (0.25-1.75)	71.92 ± 26.68 (37.08)	73.99 ± 28.00 (37.83)	1.97 ± 0.63 (31.74)	0.38 ± 0.10 (25.39)	Volume I, File 1 of 2, Section 5.3, Page No. 1-44

**This table was submitted by the firm in the EDR with the units expressed as ng/mL. This may be a typographical error while the correct unit is µg/mL

Study Ref. No.	Study Design	Study Objective	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters +/-SD (% CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} § (hr)	AUC_{0-t} (ngxhr/mL)	AUC_{∞} (ngxhr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
US/07/024	Single-dose, open label, two period, two treatment, two sequence, randomized, crossover study	* The objective of this study is to demonstrate bioequivalence between Test Product and Reference Product	Test product: Ibuprofen Soft Gelatin Capsules 200 mg p.o [Batch # FH7006]	21 Healthy human (!5M/6F) Subjects 26.90 ± 5.93 (19-36)	12.08 ± 3.26 (27.12)	2.50 (0.75-6.00)	54.81 ± 15.22 (27.82)	58.42 ± 16.66 (28.56)	2.27 ± 0.57 (24.94)	0.32 ± 0.08 (25.14)	Volume I, File 1 of 2, Section 5.3, Page No. 1-45
			Reference product: Advil® LIQUI-GELS® Solubilized Ibuprofen Capsules 200 mg p.o [Batch # B98587]		12.91 ± 3.72 (29.04)	3.00 (1.25-4.00)	57.05 ± 15.71 (27.59)	60.40 ± 16.82 (27.89)	2.20 ± 0.55 (24.73)	0.33 ± 0.08 (23.72)	Volume I, File 1 of 2, Section 5.3, Page No. 1-45

**This table was submitted by the firm in the EDR with the units expressed as ng/mL. This may be a typographical error while the correct unit is µg/mL

Table 2 Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study No.US/07/023					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	63.70	68.13	0.93	90.00	97.13
AUC∞ (hr *µg/ml)	65.65	69.98	0.94	90.61	97.14
Cmax (µg/ml)	24.93	26.47	0.94	86.85	102.15

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. US/07/024					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	52.64	54.90	0.96	92.99	98.85
AUC∞ (hr *µg/ml)	56.07	58.13	0.96	93.26	99.77
Cmax (µg/ml)	11.69	12.34	0.95	88.18	101.73

Table 3. Reanalysis of Study Samples

Ibuprofen Capsules (liquid filled) 1 x 200 mg Fasted Study No US/07/023								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**%of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	**0**	**0**	**00**	**0.00**	**0**	**0**	**0**	**0.00**

Ibuprofen Capsules (liquid filled) 1 x 200 mg Fed Study No US/07/024								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**%of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.00	0.00	0	0	0.00	0.00
Reason B (Sample Repeated For Inconsistent Internal Standard Response)	1	0.0	0.14	0.00	1	0	0.14	0.00
Total	**1**	**0**	**0.14**	**0.00**	**1**	**0**	**0.14**	**0.00**

Did use of recalculated plasma concentration data change study outcome?

There were no samples reanalyzed for PK reasons.

Comments from the Reviewer:

Fasted BE Study No.US/07/023 (two-way crossover)

1. For the fasted Study No. US/07/023, the firm enrolled twenty four (24) healthy subjects (18 male and 6 female), but 23 healthy subjects completed the study (subject #23 dropped out). In each study period, 200 mg of the test product was administered to the subjects after an overnight fast. The data for the subjects that completed the study was used in BE statistical evaluations.

2. The 90% confidence intervals for log-transformed $LAUC_T$, $LAUC_\infty$, and LC_{max} are within the acceptable range of 80-125%. However, the fasted study is incomplete since the data in the paper copy and the electronic copy are not consistent.

3. Two subjects (# 20 for Test and #8 for Reference) had first measurable concentrations Cmax at the 0.25 hour. According to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Product,* a study data should be considered and accepted when the firm has taken collection of early time points between 5 and 15 minutes after dosing followed by additional sample collection in the first hour after dosing. Therefore, the data from subjects #8 and #20 were included in the statistical analysis.

Fed BE Study No.US/07/024 (two-way crossover)

1. The firm enrolled twenty four (24) subjects, but 21 healthy subjects completed the study. In each study period, after an overnight fast of at least 10 hours, a high fat breakfast was given to each subject half an hour before dosing. The data for the subjects (excluding subjects nos. 04, 05, and 19) that completed the study was used in BE statistical evaluations.

2. The 90% confidence intervals for log-transformed $LAUC_T$, $LAUC_\infty$, and LC_{max} data are within the acceptable range of 80-125%. However, the fed study is incomplete since the data in the paper copy and the electronic copy are not consistent.

3.7 Formulation

Location in appendix	Section 4.2, Page 42
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS N079205 N 000 30-Aug-2007 DFS N079205 N 000 AB 14-Feb-2008
Source of Method (USP, FDA or Firm)	FDA-recommended method
Medium	Phosphate buffer pH 7.2
Volume (mL)	900 mL
USP Apparatus type	USP 1 (Basket)
Rotation (rpm)	150
DBE-recommended specifications	Not less than (NLT) (b)(4)% (Q) in 20 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Single strength and High %CV at 5 and 10 minutes
Is method acceptable?	**COMPLETE (see comment below)**
If not then why?	

The dissolution testing was reviewed previously (DFS N079205 N000 AB 14-Feb-2008). The firm's dissolution testing using the FDA-recommended method (900 mL of pH 7.2 phosphate buffer with basket at 150 rpm) is acceptable. The firm acknowledged its acceptance of the FDA-recommenced specification of NLT (b)(4)% (Q) in 20 minutes in a Bioequivalence Amendment on April 11, 2008.

3.9 Waiver Request(s)

None

3.10 Deficiency Comments

1. The data submitted for the fed BE study are not consistent between the electronic and paper copies. The plasma concentration data submitted in the paper copy and electronic copy are consistent; however, in the electronic copy, the **treatment variable** *does not* correspond to the sequence or period for the following subjects: 3,5,7,10,12,13,16,17,19,21,23 in the paper copy. The electronic copy shows these subjects receiving reference product in both period 1 and period 2. The firm should explain this discrepancy and resubmit the data for the fed BE study, US/07/024 with correct treatment, period, and sequence information.

2. The data submitted for the fasted BE study are not consistent between the electronic and paper copies. The plasma concentration data submitted in the paper copy **does not** correspond with the plasma concentration data submitted in the electronic copy. In the paper copy, the plasma concentration data of the test product is reported in the electronic copy as the reference product plasma concentration data. Similarly, the plasma concentration data reported in the paper copy of the reference product is listed in the electronic copy as the test product plasma concentration data. The firm should explain the discrepancy and resubmit the data for the fasted BE study, US/07/023 with correct plasma concentration data for each treatment.

3.11 Recommendations

1. The fasted BE study, US/07/023, conducted by Marksans Pharma Ltd. on its Ibuprofen Soft Gelatin Capsules 200 mg comparing it to Wyeth Consumer Healthcare Advil® LIQUI-GELS® 200 mg is complete. However, the fasted study is incomplete since the data in the paper copy and the electronic copy are not consistent.

2. The fed BE study, US/07/024, conducted by Marksans Pharma Ltd. on its Ibuprofen Soft Gelatin Capsules 200 mg comparing it to Wyeth Consumer Healthcare Advil® LIQUI-GELS® 200 mg is complete. However, the fed study is incomplete since the data in the paper copy and the electronic copy are not consistent.

3. The firm's in vitro dissolution testing on its test product, Ibuprofen Capsules (Liquid Filled), 200 mg is complete upon its acceptance and acknowledgment of the following FDA-recommended dissolution method and specification

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
USP Apparatus:	I (Basket)
Rotation Speed:	150 rpm

NLT (b)(4)% (Q) of the labeled amount of ibuprofen in the dosage form is dissolved in 20 minutes.

4. On 4/11/2008, the firm submitted a bioequivalence amendment in the electronic copy stating that "Marksans Pharma Ltd. acknowledges and commits to accept FDA-recommended dissolution method instead of previously submitted in-house dissolution method and specification NLT (b) (4)% in (b) (4) minutes for this drug product".

3.12 Comments for Other OGD Disciplines

Discipline	Comment

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasted Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	US/07/023
Study Title	A randomized, single dose, open label, bioequivalence study of Ibuprofen Soft Gelatin Capsules 200 mg in normal, healthy, adult, human subjects under fasted condition.
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA. Tel.: +91 22 27780718 Telefax: +91 22 27780721
Clinical Investigator	**Dr. Suhas Khandave M.D. (Pharmacology)**
Dosing Dates	12/June/2007 19/June/2007
Analytical Sites	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA. Tel.: +91 22 27780718 Telefax: +91 22 27780721
Analysis Date	Date of Initiation of Subject Analysis: 23rd July 2007 Date of Completion of Subject analysis: 27th July 2007
Analytical Director	(b) (4)
Storage Period of Biostudy Samples No. of days from the first day of sample collection to the last day of sample analysis.	45 day. In an amendment, dated 14-Feb-2008 the firm submitted sufficient long-term stability data covering 51 days at -20º C for ibuprofen in the biological matrix.

Table 5. Product information

Product	Test	Reference
Treatment ID	**A**	**B**
Product Name	Ibuprofen Soft Gelatin Capsules 200 mg	Advil® LIQUI-GELS® Solubilized Ibuprofen Capsules 200 mg
Manufacturer	Marksans Pharma Limited, Goa, India	Distributed by: Wyeth Consumer Healthcare, Madison, NJ 07940, Made in USA. By arrangements with R.P. Scherer Corp.
Batch/Lot No.	FH7006	B98587
Manufacture Date	April 2007	----------
Expiration Date	----------	August 2008
Strength	200 mg	200 mg
Dosage Form	Soft gelatin capsules	Soft gelatin capsules
Bio-batch Size	(b) (4) Capsules*	----------
Production Batch Size	(b) (4) Capsules	----------
Potency	(b) (4)% 198.6 mg/Capsule	(b) (4)% 198.8 mg/Capsule
Content Uniformity (mean, %CV)	(b) (4) (98.0%-100.6%)	(b) (4)% (94.2%-103.7%)
Dose Administered	A single oral dose of test formulation Ibuprofen capsules 200 mg in each period with 240 mL of water	A single oral dose of reference formulation Advil® LIQUI-GELS® 200 mg in each period with 240 mL of water
Route of Administration	Oral	Oral

*As presented in the submission. This number may be a typographical error.

Table 6. Study Design, Single-Dose Fasted Bioequivalence Study

Number of Subjects	24 healthy, adult , human subjects (18 male and 6 female) enrolled; 23 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB:1, 4, 5, 8, 9, 11, 13, 15, 17,19, 22, 24, BA:2, 3, 6, 7, 10, 12, 14, 16, 18, 20, 21, 23
Blood Sampling Times	Pre-dose samples were collected within 60 minutes before scheduled dosing time and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00 hours post dose

Blood Volume Collected/Sample	Samples were collected through an indwelling cannula placed in a forearm vein or by direct vein puncture. A total of 17 blood samples (6 mL each) were collected from 0 hour pre-dose to 24 hours post dose during each period. Samples were collected in BD Vacutainer® containing K2 EDTA 10.8 mg
Blood Sample Processing/Storage	Post collection, study blood samples were centrifuged at 10º C and spun at 3500 rpm for 10 minutes. Plasma was dispensed in vials in two aliquots one as analytical sample and the other as control sample. All plasma samples were stored upright at -20ºC ± 5ºC.
IRB Approval	Yes June 2, 2007
Informed Consent	Yes, December 16, 2006
Length of Fasted	Overnight fast of at least 10 hours prior to dosing and 4 hours post-dose in each period
Length of Confinement	Subjects were confined at 12 hours prior to dosing until after the 24 hour post dose.
Safety Monitoring	Safety was evaluated by monitoring clinical adverse events during each period. The investigator measured vital signs, including auxiliary temperature, blood pressure, pulse and respiration rate.

Comments on Study Design:

The study design is complete.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasted Bioequivalence Study, Study No.US/07/023			
		Treatment Groups	
		Test Product N = 23	Reference Product N =23
Age (years)	Mean ± SD	25.87 ± 5.50	25.87 ± 5.50
	Range	18-37	18-37
Age Groups	< 18	Nil	Nil
	18 – 39	23 (100%)	23 (100%)
	40 – 64	Nil	Nil
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	18 (78.26%)	18 (78.26%)
	Female	5 (21.74%)	5 (21.74%)
Race	Asian	23 (100%)	23 (100%)
	Black	Nil	Nil
	Caucasian	Nil	Nil

	Hispanic Other	Nil Nil	Nil Nil
BMI (Kg/m^2)	Mean ± SD Range	On Protocol basis Subject were enrolled according to Life Insurance Corporation Chart	On Protocol basis Subject were enrolled according to Life Insurance Corporation Chart
Other factors	-	Nil	Nil

Table 8. Dropout Information, Fasted Bioequivalence Study

Study No. US/07/023				
Subject No	**Reason for dropout/withdrawn replacement**	**Period**	**Replaced?**	**Replaced with**
23	Dropped out in period I due to personal reasons; having sequence (BA)	I	Not Applicable	Not Applicable

Table 9. Study Adverse Events, Fasted Bioequivalence Study

Body system/Adverse Event	Reported Incidence by Treatment Groups	
	Fast Bioequivalence Study No.:US/07/023	
	Test n (%)	Reference n (%)
Body System/ Adverse Events	**Adverse Events**	
	Test n (%)	**Reference n (%)**
Central Nervous System		
Headache	1 (50.0%)	0 (0.0%)
Gastrointestinal System		
Burning sensation (Epigastric region)	0 (0.0%)	1 (50.0%)
Total	**1 (50.0%)**	**1 (50.0%)**

Table 10. Protocol Deviations, Fasted Bioequivalence Study

Study No. US/07/023		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Deviation in scheduled time in blood sample collection	6	2

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fasted BE study.

2. The blood sampling time point deviations (ranging from 3 to 17 minutes) were noted but the original scheduled time points were used for the calculation of all of the pharmacokinetic parameters. The time point deviations were not close to Tmax.

3. No concomitant medication was given prior to the study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasted Bioequivalence Study

Bioequivalence Study No. : US/07/023 Ibuprofen Capsules (Liquid Filled) 200 mg								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	0.251	0.502	2.009	10.044	30.133	60.265	80.353	99.940
Inter day Precision (%CV)	2.53	5.08	2.31	1.59	2.02	1.66	1.45	2.43
Inter day Accuracy (% Actual)	100.36	98.28	103.12	103.20	97.99	95.88	99.62	101.47

Linearity (Range of r Values)	(r > 0.98) 0.9984-0.9997
Linearity Range (µg//mL)	0.251 to 99.940
Sensitivity/LOQ (µg//mL)	0.251

Bioequivalence Study No.: US/07/023 **Ibuprofen Capsules (Liquid Filled) 200 mg**						
Parameter	**Quality Control Samples**					
	LLOQ QC	**LQC**	**MQC_01**	**MQC_02**	**HQC**	**ULOQ QC**
Concentration (µg /mL)	NA	0.753	25.110	40.177	77.842	NA
Inter day Precision (%CV)	NA	6.37	5.93	5.90	5.40	NA
Inter day Accuracy (%Actual)	NA	100.28	108.46	105.18	100.88	NA

Comments on Study Assay Validation:

1. Initially, the firm had only one MQC of 40.177 µg/mL, between the LQC and HQC. The firm introduced a second MQC_02 with a nominal concentration of 25.110 µg/mL after reviewing data of the first three batches. The highest concentration of the study samples was 40.737 µg/mL; therefore, HQC was not relevant.

2. The accuracy and precision parameters of the QC's and standard curves were all acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially 12,13, 14, 15,16

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ARL/AL/SOP/069/02	27/01/07	STANDARD OPERATING PROCEDURE FOR REPEAT ANALYSIS

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	NA
Does the reviewer agree with the outcome of the repeat assays?	NA
If no, reason for disagreement	NA

Summary/Conclusions, Study Assays:

The bioanalytical method is acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18

Fasted Bioequivalence Study, Study No.US/07/023									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr * µg/ml)	66.613	32.38	42.55	116.10	71.941	37.08	43.72	145.68	0.93
AUC∞ (hr *µg/ml)	68.919	34.15	43.71	128.69	74.021	37.83	44.83	147.22	0.93
Cmax (µg/ml)	25.298	19.48	16.73	40.67	27.040	21.92	17.23	40.74	0.94
Tmax* (hr)	0.750	.	0.50	1.25	0.500	.	0.25	1.75	1.50
Kel (hr^{-1})	0.379	22.80	0.20	0.56	0.379	25.44	0.18	0.55	1.00
T1/2 (hr)	1.937	27.29	1.23	3.51	1.971	31.75	1.26	3.78	0.98

- Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study No.US/07/023					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	63.70	68.13	.95	90.00	97.12
AUC∞ (hr *µg/ml)	65.66	69.98	.94	90.62	97.14
Cmax (µg/ml)	24.93	26.47	.94	86.85	102.15

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study No.US/07/023					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
				Lower	**Upper**
AUC0-t (hr *µg/ml)	63.70	68.13	0.93	90.00	97.13
AUC∞ (hr *µg/ml)	65.65	69.98	0.94	90.61	97.14
Cmax (µg/ml)	24.93	26.47	0.94	86.85	102.15

Table 17. Additional Study Information, Fasted Study No.US/07/023

Root mean square error, AUC0-t	0.0750	
Root mean square error, AUC∞	0.0685	
Root mean square error, Cmax	0.1598	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	23	23
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax*	1	1
Were the subjects dosed as more than one group?	No	No

*The arithmetic table does not accurately reflect the Cmax value of the Test product of subject 20 because the data were not properly submitted electronically. See deficiency comment in section 3.10

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	23	0.97	0.90	0 99
Reference	23	0.97	0.92	0 99

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm and reviewer used the data from the 23 healthy, adult male and female subjects completing the fasted BE study statistical evaluations.

2. The 90% CI for the least squares geometric means of lnAUCt, lnAUC∞, and lnC_{max} of ibuprofen calculated by the reviewer agree with the firm's calculations.

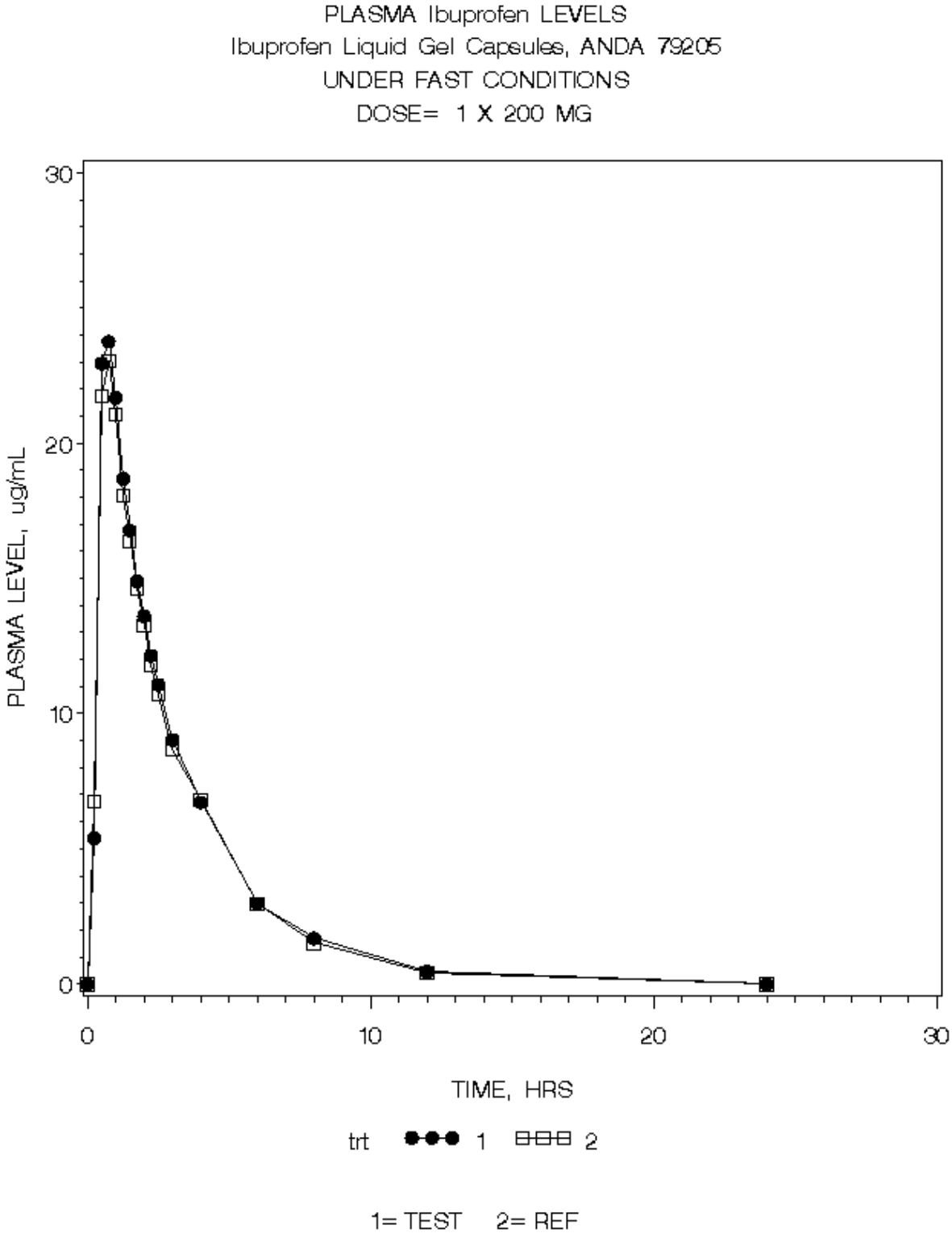
Summary and Conclusions, Single-Dose Fasted Bioequivalence Study:

The single-dose fasted bioequivalence study is incomplete due to discrepancies in the SAS dataset submitted in the electronic and paper copy. See Deficiency Comment section 3.10

Table 18. Mean Plasma Concentrations, Single-Dose Fasted Bioequivalence Study

Ibuprofen Capsules (Liquid Filled) 200 mg					
Time (hr)	Test (n= 23)		Reference (n=23)		T/R Ratio
	Mean (µg//mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	5.40	130.76	6.77	141.28	0.80
0.50	22.96	41.07	21.76	40.03	1.06
0.75	23.76	19.27	23.04	23.61	1.03
1.00	21.68	21.05	21.05	21.17	1.03
1.25	18.69	19.87	18.08	18.87	1.03
1.50	16.78	24.29	16.38	20.96	1.02
1.75	14.90	26.77	14.64	23.15	1.02
2.00	13.61	31.19	13.28	26.87	1.02
2.25	12.15	33.47	11.78	27.38	1.03
2.50	11.08	36.89	10.72	30.92	1.03
3.00	9.04	38.27	8.69	32.22	1.04
4.00	6.72	47.46	6.80	48.41	0.99
6.00	2.98	61.87	2.96	59.16	1.01
8.00	1.69	83.59	1.52	81.79	1.11
12.00	0.47	140.65	0.40	156.91	1.17
24.00	0.01	479.58	0.00	.	.

Figure 1. Mean Plasma Concentrations, Single-Dose Fasted Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	US/07/024
Study Title	A randomized, single dose, open label, bioequivalence study of Ibuprofen soft gelatin capsules 200 mg in normal, healthy, adult, human subjects under fed condition.
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA. Tel.: +91 22 27780718 Telefax: +91 22 27780721
Clinical Investigator	Dr. Suhas Khandave M.D. (Pharmacology)
Dosing Dates	22nd June 2007 01st July 2007
Analytical Sites	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA. Tel.: +91 22 27780718 Telefax: +91 22 27780721
Analysis Date	Date of Initiation of Subject Analysis: 24th July 2007 Date of Completion of Subject analysis: 28th July 2007
Analytical Director	(b) (4)
Storage Period of Biostudy Samples No. of days from the first day of sample collection to the last day of sample analysis.	36 days In an amendment, dated 14-Feb-2008 the firm submitted sufficient long-term stability data covering 51 days at -20º C for ibuprofen in the biological matrix.

Table 20. Product Information

Product	Test	Reference
Treatment ID	**A**	**B**
Product Name	Ibuprofen Soft Gelatin Capsules 200 mg	Advil® LIQUI-GELS® Solubilized Ibuprofen Capsules 200 mg
Manufacturer	Marksans Pharma Limited, Goa, India.	Distributed by: Wyeth Consumer Healthcare, Madison, NJ 07940, Made in USA. By arrangements with R.P. Scherer Corp.
Batch/Lot No.	FH7006	B98587
Manufacture Date	April 2007	----------
Expiration Date	----------	August 2008
Strength	200 mg	200 mg

Dosage Form	Soft gelatin capsules	Soft gelatin capsules
Bio-batch Size	(b) (4) **Capsules***	----------
Production Batch Size	(b) (4) Capsules	----------
Potency	(b) (4)% 198.6 mg/Capsule	(b) (4)% 198.8 mg/Capsule
Content Uniformity	(b) (4)% (98.0%-100.6%)	(b) (4)% (94.2%-103.7%)
Dose Administered	A single oral dose of test formulation Ibuprofen capsules 200 mg in each period with 240 mL of water	A single oral dose of reference formulation Advil® LIQUI-GELS® 200 mg in each period with 240 mL of water
Route of Administration	Oral	Oral

*As presented in the submission. This number may be a typographical error

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	24 healthy, adult , human subjects (18 male and 6 female) enrolled 21 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	9 days
Randomization Scheme	AB:1,3,5,7,10,12,13,16,17,19,21,23 BA:2,4,6,8,9,11,14,15,18,20,22,24
Blood Sampling Times	Pre-dose samples were collected within 60 minutes before scheduled dosing time and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00 hours post dose
Blood Volume Collected/Sample	Samples were collected through an indwelling cannula placed in a forearm vein or by direct vein puncture. A total of 17 blood samples (6 mL each) were collected from 0 hour pre-dose to 24 hours post dose during each period. Samples were collected in BD Vacutainer® containing K2 EDTA 10.8 mg
Blood Sample Processing/Storage	Post collection, study blood samples were centrifuged at 10º C and spun at 3500 rpm for 10 minutes. Plasma was dispensed in vials two in aliquots one as analytical sample and the other as control sample. All plasma samples were stored upright at -20ºC ± 5ºC.
IRB Approval	Yes June 2, 2007
Informed Consent	Yes, December 16, 2006
Length of Fast Before Meal	Overnight fast of at least 10 hours prior to the high fat breakfast given half an hour before dosing.
Length of Confinement	Subjects were confined at 12 hours prior to dosing until after the 24 hour post dose.
Safety Monitoring	Safety was evaluated by monitoring clinical adverse events during each period. The investigator measured vital signs, including auxiliary temperature, blood pressure, pulse and respiration rate.

Standard FDA Meal Used?	No
If No, then meal components and composition is listed in the tables below	

Composition of Meal Used in Fed Bioequivalence Study US/07/024		
Composition	**Percent of total cal**	**cal**
	Test Meal	**Test Meal**
Fat	55	531
Carbohydrate	27	260
Protein	18	168
Total	100	959

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study

APPENDIX B
MEALS FOR EACH STUDY PERIOD

Food-item	Conventional Measure	Ingredients	CHO (g)	Protein (g)	Fat (g)	Energy (calories)
HIGH-FAT BREAKFAST						
Milk	2 cups	Whole milk	24	16	16	300
		Almond	0	0	5	45
		Sugar	5	0	0	20
Paneer Paratha	1 (~100g)	Wheat flour	22	3	0	105
		Paneer	0	7	5	75
Curds	1 cup	Beaten curds	12	8	8	150
Green chutney		Coriander leaves + mint leaves + green chillies	NA	NA	NA	NA
Cheese Singles	2 slices	Cheese	2	8	10	130
Cashew	10 pieces	Cashew	0	0	5	45
	2 tsp	Ghee	0	0	10	90
Total			**65**	**42**	59	**960**
Total calories			260	168	531	
Percent			27	**18**	55	
LUNCH						
Phulkas	2 nos. (30g each)	Wheat flour (kneaded)	30	4	0	140
Rice	1cup	Rice	30	4	0	140
Patli-Dal	1 cup	Dal	13	4	0	70
		Onion	5	0	0	20
Methi vegetable	1 cup cooked	Onion	5	0	0	20
		Methi leaves	15	2	0	70
		Tomato chopped				
Tomato-cucumber salad	1 cup	Tomato + cucumber (chopped)				
	3 tsp	Cooking oil	0	0	15	135
Total			**98**	**14**	**15**	**595**
SNACK						
Dahi Vada	3 pieces	Maida vadas	23	4	0	105
		Curd (whole - milk)	6	4	4	75
		Sugar	10	0	0	40
Whole milk	½ cup	Whole milk	6	4	4	75
Fruit	1 no.	Banana	15	0	0	60
		Oil	0	0	5	45
Total			**60**	**12**	13	**400**

DINNER						
Chapatti	2 nos. (30 g each)	Wheat flour (kneaded)	30	4	0	140
Steamed Rice	1 cup	Rice	30	4	0	140
Patli Dal	1 cup	Dal	13	4	0	70
		Onion	4	1	0	20
Curd	½ cup	Curd (skim milk)	6	4	4	75
Cooked Vegetable	1 cup	Spinach leaves	15	2	0	70
		Onion	4	1	0	20
Tomato-cucumber salad	1 cup	Tomato + cucumber (chopped)				
Fruit	1 no	1 banana	15	0	0	60
	2 tsp	Cooking oil	0	0	10	90
Total			**117**	**20**	**14**	**685**

Abbreviations use:- tsp: teaspoon, tbsp: tablespoon, NA: Not Applicable

Nutritive Value of the Day's Menu:-				
Description	CHO (g)	Protein (g)	Fat (g)	Energy (calories)
BREAKFAST	65	42	59	960
LUNCH	98	14	15	595
EVENING SNACK	60	12	13	400
DINNER	117	20	14	685
TOTAL	**340**	**88**	**101**	**2640**
Calories	**1360**	**352**	**909**	
Percent Contributed	**52**	**13**	**35**	

Comments on Study Design:

The study design is acceptable

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. US/07/024			
		Treatment Groups	
		Test Product N = 21	Reference Product N = 21
Age (years)	Mean ± SD	26.90 ± 5.93	26.90 ± 5.93
	Range	19-36	19-36
Age Groups	< 18	Nil	Nil
	18 – 40	21 (100%)	21 (100%)
	41 – 64	Nil	Nil
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	15 (71.43%)	15 (71.43%)
	Female	6 (28.57%)	6 (28.57%)
Race	Asian	21 (100%)	21 (100%)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI	Mean ± SD Range	On Protocol basis Subject were enrolled according to Life Insurance Corporation Chart	On Protocol basis Subject were enrolled according to Life Insurance Corporation Chart
Other Factors		Nil	Nil

Table 23. Dropout Information, Fed Bioequivalence Study

Study No.US/07/024				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
04	Dropped out in period II due to personal reasons; having sequence (BA)	II	Not Applicable	Not Applicable
05	Dropped out in period II due to personal reasons; having sequence (AB)	II	Not Applicable	Not Applicable
19	Dropped out in period II due to personal reasons; having sequence (AB)	II	Not Applicable	Not Applicable

Table 24. Study Adverse Events, Fed Bioequivalence Study

Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. US/07/024	
	Test Product (A)	Reference Product (B)
Central Nervous System		
Giddiness	0 (0.0%)	1 (14.286 %)
Gastrointestinal System		
Pain in abdomen	0 (0.0%)	1 (14.286 %)
Musculoskeletal System		
Backache	0 (0.0%)	1 (14.286 %)
Body As Whole		
Pain in Claves*	1 (14.286 %)	0 (0.0%)
Burn over dorsal aspects of left foot	1 (14.286 %)	0 (0.0%)
Fever with chills	0 (0.0%)	1 (14.286 %)
Body ache	0 (0.0%)	1 (14.286 %)
Total	**2 (28.57 %)**	**5 (71.43 %)**

*As submitted by firm. This may be a typographical error for Calves.

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No:US/07/024		
Type	**Subject (Test)**	**Subject (Reference)**
Deviation in scheduled time in blood sample collection	1	3

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No SAE's were reported during the fed BE study.

2. The blood sampling time point deviations (ranging from 3 to 6 minutes) were noted but the original scheduled time points were used for the calculation of all of the pharmacokinetic parameters. The time point deviations were not close to Tmax.

3. No scheduled concomitant medication was given prior to the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. :US/07/024 Ibuprofen Capsules (Liquid Filled) 200 mg								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	0.251	0.502	2.009	10.044	30.133	60.265	80.353	99.940
Inter day Precision (%CV)	2.53	5.08	2.31	1.59	2.02	1.66	1.45	2.43
Inter day Accuracy (% Actual)	100.36	98.28	103.12	103.20	97.99	95.88	99.62	101.47
Linearity (Range of Values)	(r > 0.98) 0.9984-0.9997							
Linearity Range (µg/mL)	0.251 to 99.940							
Sensitivity/LOQ (µg/mL)	0.251							

Bioequivalence Study No.: US/07/024 Analyte Name: Ibuprofen							
Parameter	**Quality Control Samples**						
	LLOQ QC	**LQC**	**MQC_03**	**MQC_01**	**MQC_02**	**HQC**	**ULOQ QC**
Concentration (µg /mL)	NA	0.753	12.557	25.114	40.183	77.855	NA
Inter day Precision (%CV)	NA	5.92	5.23	4.55	4.50	5.28	NA
Inter day Accuracy (%Actual)	NA	97.14	91.84	96.67	103.54	105.20	NA

Comments on Study Assay Validation:

1. The firm introduced a third MQC_03 with a nominal concentration of 12.557 µg/mL after reviewing data of first three batches with MQC_01 and MQC *02* with nominal concentrations of 25.114 µg/mL and 40.183 µg/mL, respectively. The highest concentration of the study samples was 22.24 µg/mL; therefore, MQC_02 and HQC were not relevant.

2. The accuracy and precision parameters of the QC's and standard curves were all acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes

Were chromatograms serially or randomly selected?	Serially 12,13, 14, 15,16

Comments on Chromatograms:

Acceptable

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ARL/AL/SOP/069/02	27/01/07	STANDARD OPERATING PROCEDURE FOR REPEAT ANALYSIS

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	NA

Summary/Conclusions, Study Assays:

1. The 90% CI for the least squares geometric means of lnAUCt, lnAUC∞, and lnC_{max} of Ibuprofen calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

2. The single-dose fed bioequivalence study is incomplete due to discrepancies in the SAS dataset submitted in the electronic and the paper copy. See Deficiency Comment section 3.10

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Fed Bioequivalence Study, Study No.US/07/024									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr*µg/m)	54.694	27.82	30.47	79.21	56.923	27.59	32.60	84.24	0.96
AUC∞ (hr*µg/m)	58.342	28.56	30.97	86.96	60.312	27.89	34.58	92.01	0.97
Cmax (µg/ml)	12.013	27.11	5.57	21.12	12.811	29.03	5.26	22.24	0.94
Tmax* (hr)	2.500	.	0.75	6.00	3.000	.	1.25	4.00	0.83
Kel (hr^{-1})	0.322	24.81	0.18	0.53	0.331	23.83	0.21	0.47	0.97

T1/2 (hr)	2.284	24.93	1.31	3.93	2.207	24.75	1.46	3.33	1.03

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No.US/07/024					
Parameter	Test	Reference	Ratio	90% C.I.	
				Lower	Upper
AUC0-t (hr * µg/ml)	52.71	54.85	0.96	92.90	99.41
AUCi (hr * µg/ml)	56.13	58.09	0.97	93.24	100.14
Cmax (hr * µg/ml)	11.67	12.36	0.94	87.98	101.26

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Ibuprofen Capsules (Liquid Filled) 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. US/07/024					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
				Lower	Upper
AUC0-t (hr * µg/ml)	52.64	54.90	0.96	92.99	98.85
AUCi (hr * µg/ml)	56.07	58.13	0.96	93.26	99.77
Cmax (hr * µg/ml)	11.69	12.34	0.95	88.18	101.73

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.0572	
Root mean square error, AUC∞	0.0631	
Root mean square error, Cmax	0.1338	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	21	21
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	21	0.94	0.80	0.98
Reference	21	0.94	0.88	0.99

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm and reviewer used data from the 21 healthy, adult subjects completing the fed BE study statistical evaluations.

2. The 90% CI for the least squares geometric means of lnAUCt, lnAUC∞, and lnC_{max} of ibuprofen calculated by the reviewer agree with the firm's calculations

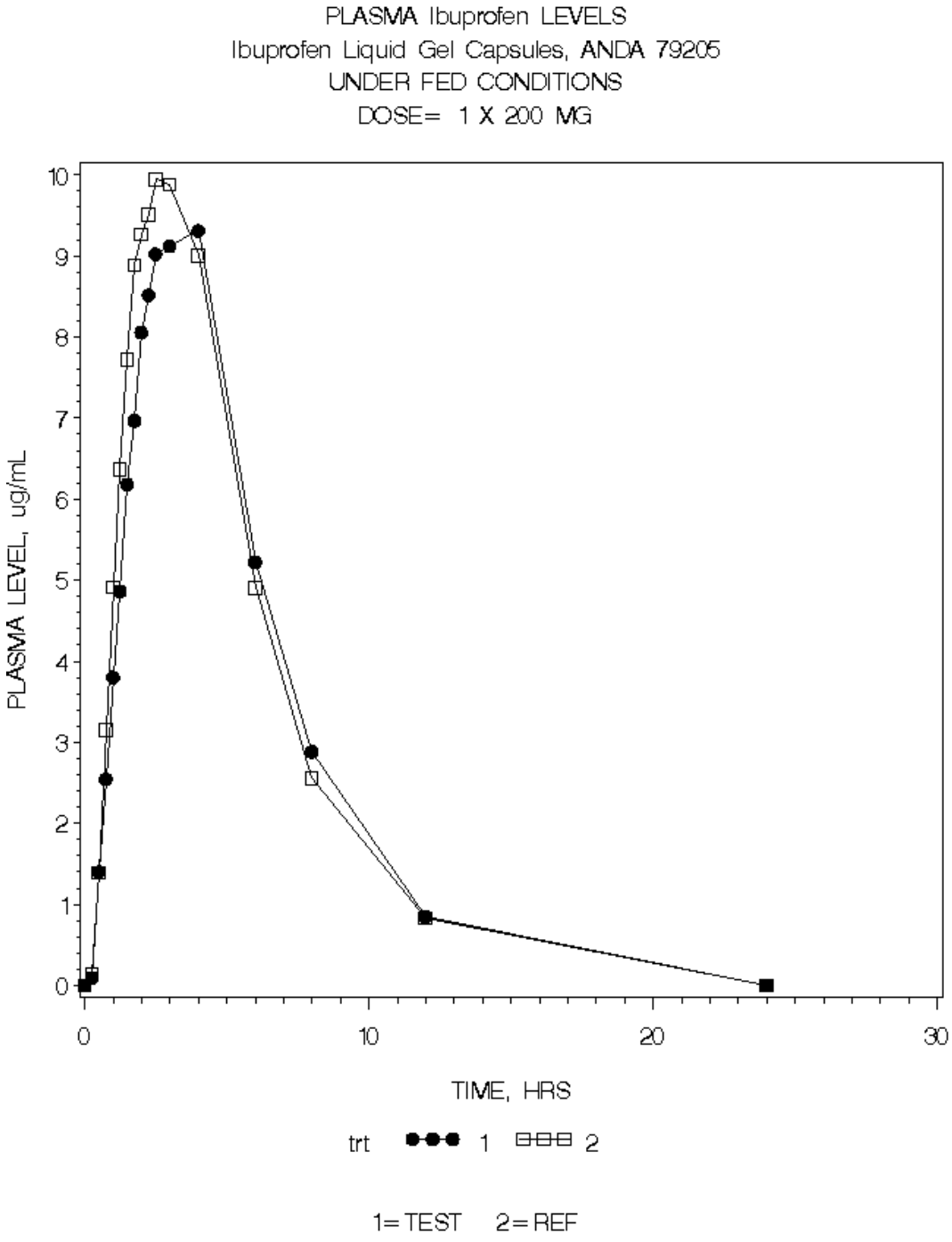
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is incomplete due to discrepancies in the SAS dataset submitted in the EDR and paper copy. See Deficiency Comment section 3.10

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Ibuprofen Capsules (Liquid Filled) 200 mg					
Time (hr)	Test (n=21)		Reference (n=21)		Ratio (T/R)
	Mean (µg/mL)	CV%	Mean (µg/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.25	0.10	307.19	0.14	211.96	0.69
0.50	1.40	173.51	1.40	89.36	1.01
0.75	2.55	123.23	3.16	74.23	0.81
1.00	3.80	106.92	4.91	72.14	0.77
1.25	4.87	88.41	6.37	65.48	0.76
1.50	6.19	73.84	7.73	62.84	0.80
1.75	6.97	67.24	8.89	58.69	0.78
2.00	8.06	54.06	9.27	46.31	0.87
2.25	8.52	47.11	9.51	40.19	0.90
2.50	9.03	41.00	9.95	33.18	0.91
3.00	9.12	32.20	9.89	32.71	0.92
4.00	9.31	33.10	9.00	35.56	1.03
6.00	5.22	46.47	4.91	46.29	1.06
8.00	2.89	57.91	2.56	58.99	1.13
12.00	0.85	74.02	0.84	75.99	1.02
24.00	0.00	.	0.00	.	.

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

S. No.	Ingredients	Pharmacopoeia reference	mg / capsule	% per capsule	Function
MEDICAMENT					
01	Ibuprofen	USP	200.00	(b) (4)	Active ingredient

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Acceptable 1. All of the excipients are within the IIG limits 2. The color additive FD&C green No. 3 is (b) (4)% per capsule, less than the 0.1% requirement, therefore its amount is insignificant. 3. (b) (4) hence insignificant.

4.3 Dissolution Data

The firm's proposed specification shown below in the table is not acceptable (see dissolution review in DFS N079205 N 000 AB 14-Feb-2008). The firm has acknowledged and accepted the DBE-recommended dissolution specification of NLT (b)(4)% (Q) in 20 minutes in the Bioequivalence Amendment dated April 11, 2008. See Recommendation section 3.11

Dissolution Conditions	**Apparatus:**	USP Type I
	Speed of Rotation:	150 rpm
	Medium:	Phosphate buffer pH 7.2
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b)(4)% of the labeled amount is dissolved in (b)(4)minutes	
Dissolution Testing Site (Name, Address)	Marksans Pharma Ltd.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**				**Study Report Location**
						5	**10**	**20**	**30**	
Study Report #: MV/AMV/DP/FH/017	Report date: 14th August 2007	Marksans Pharma Ltd.'s Ibuprofen Capsules, 200 mg (liquid filled) Lot # FH7006	200 mg Capsule	12	Mean (%)	2.5	75.9	94.0	94.3	Module 5.3.1.3
					Range (%)	(1.2 to 5.9)	(29.0 to 90.1)	(87.2 to 97.0)	(91.3 to 98.1)	
					%CV	62.6	24.1	2.7	2.1	
Study Report #: MV/AMV/DP/FH/017	Report date: 14th August 2007	Wyeth Consumer Healthcare's Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg) Lot # B98587	200 mg Capsule	12	Mean (%)	3.6	72.2	100.6	100.1	Module 5.3.1.3
					Range (%)	(2.0 to 6.6)	(19.9 to 97.5)	(99.1 to 102.4)	(99.1 to 101.7)	
					%CV	37.3	39.0	1.0	0.7	

4.4 Detailed Regulatory History (If Applicable)

4.5 Consult Reviews

70 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

BIOEQUIVALENCE DEFICIENCIES

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen (Liquid Filled) Capsules, 200 mg (OTC)

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

1. The data submitted for the fed bioequivalence (BE) study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy correspond with the **concentration data** submitted in the SAS files; however, in the SAS files, the **treatment variable** *does not* correspond to the sequence or period for the following subjects: 3,5,7,10,12,13,16,17,19,21,23 in the paper copy. The SAS files show these subjects receiving the reference product in both period 1 and period 2. Please explain this discrepancy and resubmit the data for the fed BE study, US/07/024, with correct treatment, period, and sequence information.

2. The data submitted for the fasted BE study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy do not correspond with the plasma concentration data submitted in the SAS files. Please explain this discrepancy and resubmit the data for the fasted BE study, US/07/023 distinguishing the correct plasma concentration data for the test and reference product.

Sincerely yours,

{See appended electronic signature page}

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

4.7 Outcome Page

ANDA: 79-205

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

Reviewer: Williams, Zakia **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Ibuprofen liqui-gel 200 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5829	8/30/2007	Bioequivalence Study	Fasted Study	1	1
5829	8/30/2007	Bioequivalence Study	Fed Study	1	1
5829	2/14/2008	Other	Dissolution Amendment	0	0
5829	4/11/2008	Dissolution Data	Dissolution Acknowledgement	0	0
				Bean Total:	2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zakia R Williams
9/2/2008 11:51:02 AM
BIOPHARMACEUTICS

Yih Chain Huang
9/2/2008 12:41:29 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
9/2/2008 02:48:28 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Divison of Bioequivalence I

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	79-205	
Drug Product Name	Ibuprofen Capsules (Liquid Filled)	
Strength (s)	200 mg	
Applicant Name	Marksans Pharma Ltd.	
Address	601-622, Chintamani Plaza, Andheri Kurla Road, Andheri (East), Mumbai-400099, India	
Applicant's Point of Contact	Authorized U.S. Agent: Mr. Nikanth J. Patel, Vice President Pharmgen LLC, 1919 Middle Country Road, Suite #206 Centereach, NY 11720	
Contact's Phone Number	631-656-9753	
Contact's Fax Number	631-656-9754	
Submission Date(s)	30 Aug 2007	
Amendment Date(s)	14 Feb 2008	
First Generic	No	
Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	US/07/023	US/07/024
Study Type (s)	Fasting (STF)	Fed (STP)
Strength(s)	200 mg	200 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Clinical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
Analytical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Analytical Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

Review of a dissolution amendment. This is the **second** review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted dissolution testing using its proposed dissolution method and the FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable at S_1 level. The firm proposed specification of not less than (b) (4) (Q) in (b) (4) minutes differs from the FDA-recommended specification [NLT (b) (4)% (Q) in 20 minutes]. The firm should acknowledge the FDA-recommended method and specification.

The firm provided sufficient long-term stability data for ibuprofen in the biological matrix.

The DBE will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

A. FDA-Recommended Dissolution Method

USP Apparatus I (Basket) at 150 rpm in 900 mL of Phosphate buffer, pH 7.2

Dissolution Conditions	**Apparatus:**	USP Type I
	Speed of Rotation:	150 rpm
	Medium:	Phosphate buffer pH 7.2
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b)(4)% of the labeled amount is dissolved in (b)(4)minutes	
Dissolution Testing Site (Name, Address)	Marksans Pharma Ltd.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**				**Study Report Location**
						5	**10**	**20**	**30**	
Study Report #: MV/AMV/DP/FH/017	Report date: 14th August 2007	Marksans Pharma Ltd.'s Ibuprofen Capsules, 200 mg (liquid filled) Lot # FH7006	200 mg Capsule	12	Mean (%)	2.5	75.9	94.0	94.3	Module 5.3.1.3
					Range (%)	(1.2 to 5.9)	(29.0 to 90.1)	(87.2 to 97.0)	(91.3 to 98.1)	
					%CV	62.6	24.1	2.7	2.1	
Study Report #: MV/AMV/DP/FH/017	Report date: 14th August 2007	Wyeth Consumer Healthcare's Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg) Lot # B98587	200 mg Capsule	12	Mean (%)	3.6	72.2	100.6	100.1	Module 5.3.1.3
					Range (%)	(2.0 to 6.6)	(19.9 to 97.5)	(99.1 to 102.4)	(99.1 to 101.7)	
					%CV	37.3	39.0	1.0	0.7	

B. Firm's Proposed Dissolution Method

USP Apparatus I (Basket) at (b) (4) rpm in 900 mL of Phosphate buffer, pH 7.2 + (b) (4)

Dissolution Conditions	**Apparatus:**	USP Type I
	Speed of Rotation:	(b) (4) rpm
	Medium:	Phosphate buffer pH 7.2 + (b) (4)
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % of the labeled amount is dissolved in (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Marksans Pharma Ltd.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report #: MV/AMV/DP/FH/011	Report date: 3rd May 2007	Marksans Pharma Ltd.'s Ibuprofen Capsules, 200 mg Lot # FH7006	200 mg Capsule	12	Mean (%)	1.69	41.35	93.33	95.72	96.17	95.88	92.69	Module 5.3.1.3
					Range (%)	(0.9-2.2)	(8.9-85.3)	(90.2-95.6)	(92.9-102.9)	(92.8-102.7)	(92.2-105.0)	(89.6-97.1)	
					%CV	21.5	55.3	1.5	2.6	2.5	3.4	2.8	
Study Report #: MV/AMV/DP/FH/011	Report date: 3rd May 2007	Wyeth Consumer Healthcare's Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg) Lot # B98587	200 mg Capsule	12	Mean (%)	2.43	45.55	98.13	99.32	100.77	101.03	101.02	Module 5.3.1.3
					Range (%)	(1.4-5.9)	(5.7-87.6)	(92.9-100.8)	(98.1-103.4)	(98.1-106.1)	(97.8-107.5)	(97.1-108.1)	
					%CV	50.4	66.4	2.0	1.4	2.5	3.1	3.4	

II. COMMENTS:

1. Currently, there is no USP method for Ibuprofen Capsules (Liquid filled). The dissolution method and specification for the over-the-counter product, Advil® Liqui-Gel® Capsules, 200 mg are proposed by the innovator firm, Wyeth Consumer Healthcare.

   (NOT TO BE RELEASED UNDER FOIA)

Location of NDA Dissolution Review	Internal databases: FDA Enterprise Search, N 020402 REV 14-May-1999 Division of System Files v 2.0. ANDA 078082 Review bioequivalence Biopharmaceutics N 078082 N 000 22-Dec-2005.
Source of Method (USP, FDA or Firm)	FDA (020402)
Medium	Phosphate buffer, pH 7.2
Volume (mL)	900
USP Apparatus type	I (Basket)
Rotation (rpm)	150
Dissolution specification	Not less than (NLT) (b) (4)% (Q) in 20 minutes

2. The firm conducted dissolution testing using its proposed dissolution method and the FDA-recommended dissolution method. The difference between the two (2) methods was the dissolution medium and rotation speed of the USP apparatus I. The firm proposed using (b) (4) Whereas, the dissolution medium for the FDA-recommended method is Phosphate Buffer, pH 7.2 and the rotation speed of the USP Apparatus I (Basket) is 150 rpm.

	Firm's dissolution method	FDA-recommended method
Medium	Phosphate buffer, pH 7.2 (b) (4)	Phosphate buffer, pH 7.2
Volume (mL)	900	900
USP Apparatus type	I (Basket)	I (Basket)
Rotation (rpm)	(b) (4)	150
Specification	Not less than (NLT) (b) (4)% (Q) in (b) (4) minutes	Not less than (NLT) (b) (4)% (Q) in 20 minutes

3. The firm's dissolution testing on its Ibuprofen Capsules (Liquid filled), 200 mg, lot # FH7006 and the reference product, Advil® Liqui-Gel® Capsules, 200 mg, lot # B98587 using the FDA-recommended method is acceptable, Table 2-A. The firm dissolution testing using its proposed method is not acceptable, see Table 2-B.

4. The firm's proposed specification of NLT (b)(4)% (Q) in (b)(4) minutes differs from the FDA-recommended specification of NLT (b)(4)% (Q) in 20 minutes. However, the firm's test product still met the FDA-recommended specification at the S_1 level.

5. In this amendment, the firm submitted its dissolution testing data using the FDA-recommended method in the recommended DBE common-technical document (CTD) format.

6. In this amendment, the firm submitted sufficient long-term stability data covering 51 days at -20°C for ibuprofen in the biological matrix.

7. As previously, stated in the original dissolution review the firm provided the SAS datasets (.xpt format) for its BE studies.

8. No Division of Scientific Investigations (DSI) inspections are pending or necessary.

III. DEFICIENCY COMMENT

The firm's proposed specification is not acceptable. The firm should acknowledge and accept the FDA-recommended dissolution method and specification for its test product, Ibuprofen Capsules, 200 mg

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30, and 45 minutes
Specification:	NLT (b)(4)% (Q) in 20 minutes

IV. RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Marksans Pharma Ltd., on its Ibuprofen Capsules (Liquid filled), 200 mg, lot # FH7006 is acceptable.

2. The firm should acknowledge and accept the FDA-recommended dissolution method and specification for its test product, Ibuprofen Capsules (Liquid Filled).

The firm should be informed of the above deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen Capsules (Liquid Filled), 200 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

Based on the dissolution testing data submitted for your Ibuprofen Capsules (Liquid Filled), your proposed specification of not less than (NLT) (b)(4)% Q in (b)(4) minutes is not acceptable. Please provide your acknowledgment and acceptance of the following FDA-recommended dissolution method and specification:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30 and 45 minutes

The test product should meet the following specification:

NLT (b)(4)**%** (Q) of the labeled amount of ibuprofen in the dosage form should be dissolved in **20 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

ANDA: 79-205

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4917	8/30/2007	Dissolution Data	Dissolution Review	0	0
4917	2/14/2008	Dissolution Data	Dissolution Amendment	0	0
				Bean Total:	0

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

April Braddy
2/28/2008 08:53:02 AM
BIOPHARMACEUTICS

Moheb H. Makary
2/28/2008 08:56:06 AM
BIOPHARMACEUTICS

Barbara Davit
2/29/2008 04:52:47 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	79-205	
Drug Product Name	Ibuprofen Capsules (Liquid Filled)	
Strength (s)	200 mg	
Applicant Name	Marksans Pharma Ltd.	
Address	601-622, Chintamani Plaza, Andheri Kurla Road, Andheri (East), Mumbai-400099, India	
Applicant's Point of Contact	Authorized U.S. Agent: Mr. Nikanth J. Patel, Vice President Pharmgen LLC, 1919 Middle Country Road, Suite #206 Centereach, NY 11720	
Contact's Phone Number	631-656-9753	
Contact's Fax Number	631-656-9754	
Submission Date(s)	30 Aug 2007	
First Generic	No	
Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	US/07/023	US/07/024
Study Type (s)	Fasting (STF)	Fed (STP)
Strength(s)	200 mg	200 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Clinical Site Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
Analytical Site	Accutest Research Laboratories (I) Pvt. Ltd., A-31	
Analytical Address	M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA	
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted dissolution testing using its proposed dissolution method. Therefore, the firm should conduct and submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended method: USP Apparatus I (Basket) @ 150 rpm in Phosphate buffer, pH 7.2 (900 mL) at 37˚C ± 0.5˚C.

In addition, the firm should submit sufficient long-term stability data for ibuprofen in the biological matrix covering at least 46 days.

The DBE will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☐	☒	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP Type I
	Speed of Rotation:	(b) (4) rpm
	Medium:	Phosphate buffer pH 7.2 + (b) (4)
	Volume:	900 mL
	Temperature:	37°C ±0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % of the labeled amount is dissolved (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Marksans Pharma Ltd.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report #: MV/AMV/DP/FH/011	Report date: 3rd May 2007	Marksans Pharma Ltd.'s Ibuprofen Capsules, 200 mg Lot # FH7006	200 mg Capsule	12	Mean (%)	1.69	41.35	93.33	95.72	96.17	95.88	92.69	Module 5.3.1.3
					Range (%)	(0.9-2.2)	(8.9-85.3)	(90.2-95.6)	(92.9-102.9)	(92.8-102.7)	(92.2-105.0)	(89.6-97.1)	
					%CV	21.5	55.3	1.5	2.6	2.5	3.4	2.8	
Study Report #: MV/AMV/DP/FH/011	Report date: 3rd May 2007	Wyeth Consumer Healthcare's Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg) Lot # B98587	200 mg Capsule	12	Mean (%)	2.43	45.55	98.13	99.32	100.77	101.03	101.02	Module 5.3.1.3
					Range (%)	(1.4-5.9)	(5.7-87.6)	(92.9-100.8)	(98.1-103.4)	(98.1-106.1)	(97.8-107.5)	(97.1-108.1)	
					%CV	50.4	66.4	2.0	1.4	2.5	3.1	3.4	

II. COMMENTS:

1. Currently, there is no USP method for Ibuprofen Capsules (Liquid filled). The dissolution method and specification for the over-the-counter product, Advil® Liqui-Gel® Capsules, 200 mg are proposed by the innovator firm, Wyeth Consumer Healthcare.

   (NOT TO BE RELEASED UNDER FOIA)

Location of NDA Dissolution Review	Internal databases: FDA Enterprise Search, N 020402 REV 14-May-1999 Division of System Files v 2.0. ANDA 078082 Review bioequivalence Biopharmaceutics N 078082 N 000 22-Dec-2005.
Source of Method (USP, FDA or Firm)	FDA (020402)
Medium	Phosphate buffer, pH 7.2
Volume (mL)	900
USP Apparatus type	I (Basket)
Rotation (rpm)	150
Dissolution specification	Not less than (NLT) (b)(4)% (Q) in 20 minutes

2. The firm's dissolution testing on its Ibuprofen Capsules (Liquid filled), 200 mg, lot # FH7006 and the reference product, Advil® Liqui-Gel® Capsules, 200 mg, lot # B98587 using its proposed method is not acceptable, see Table 2. The firm should conduct dissolution testing using the FDA-recommended dissolution method.

3. The firm provided the sixteen (16) bioequivalence (BE) summary tables in pdf and/or word format.

4. The firm provided the SAS datasets (.xpt format) for its BE studies.

5. The long-term stability data provided by the firm of 16 days at -20 ± 5 ºC is not sufficient to cover the maximum storage time for the ibuprofen human plasma samples.

   - For the fasting BE study No. US/07/023, the time from the first sample collection until the last sample was analyzed was 46 days (12 Jun 2007 to 27 Jul 2007).

   - For the fed BE study No. US/07/024, the time from the first sample collection until the last sample was analyzed was 37 days (22 Jun 2007 to 28 Jul 2007).

6. No Division of Scientific Investigations (DSI) inspections are pending or necessary.

III. DEFICIENCY COMMENTS:

1. The firm did not conduct its dissolution testing using the FDA-recommended dissolution method. The FDA-recommended dissolution method is as follows:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30, and 45 minutes

2. The firm did not provide sufficient long term stability data for ibuprofen in the biological matrix (human plasma).

IV. RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Marksans Pharma Ltd., on its Ibuprofen Capsules (Liquid filled), 200 mg, lot # FH7006 is incomplete for the reason provided in deficiency comment No. 1.

   The firm should conduct and submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended dissolution method:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30, and 45 minutes

2. The firm should submit sufficient long-term stability data for ibuprofen in the biological matrix (human plasma) covering at least 46 days.

The firm should be informed of the above deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCES

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen Capsules (Liquid Filled), 200 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. Please submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended method:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30 and 45 minutes

Please submit the comparative dissolution results which should include the individual capsule data as well as the mean, range, %CV at each time point for the 12 capsules tested and dates of dissolution testing. Also, please resubmit the dissolution testing data summary table with the above data.

2. The long-term stability data you provided is not sufficient to cover the storage period of the study samples for the BE studies you submitted. Please provide the data to support the long-term storage stability of ibuprofen in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed which was at least 46 days.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

ANDA: 79-205

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4579	8/30/2007	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

April Braddy
1/28/2008 09:05:22 AM
BIOPHARMACEUTICS

Moheb H. Makary
1/28/2008 09:28:10 AM
BIOPHARMACEUTICS

Barbara Davit
1/31/2008 03:38:32 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-205

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 79-205 Applicant Marksans Pharma Limited
Drug Ibuprofen Capsules (liquid filled), 200 mg Strength(s)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 27 May 2009 Date 6/26/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Advil Liqui- NDA# 20-402
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 9/4/2007, BOS=Advil Liquid Gels NDA 20-402, PI cert provided. ANDA ack for filing on 9/4/2007(LO dated 11/16/2007). There are no remaining patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.

2. Project Manager, Dat Doan Team1 Review Support Branch Date 5/27/09 Date _____
Initials dd Initials _____

Original Rec'd date 8/11/07
Date Acceptable for Filing 8/14/07
Patent Certification (type) I
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 2/11/09
Date of Office Bio Review
Date of Labeling Approv. Sum 9/11/08
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:bio AC 5/29/09, labeling ac 6/25/09

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date_____ Date 6/26/09
Name/Initials_____ Name/Initials rlw/for
Comments:

From: Lee, Koung U
Sent: Friday, June 26, 2009 10:08 AM
To: Doan, Dat; Barlow, James T
Cc: West, Robert L
Subject: RE: 79-205/Marksans/Ibuprofen

Dat,

I concur. I'm also concurring for Jim.

Thanks.

Koung

From: Doan, Dat
Sent: Friday, June 26, 2009 9:39 AM
To: Lee, Koung U; Barlow, James T
Cc: West, Robert L
Subject: 79-205/Marksans/Ibuprofen
Importance: High

HI Koung, Jim:

Can I please get your endorsements for ANDA 79-205/Marksans/Ibuprofen?

<< File: 79205.ap.labeling.summary.pdf >>
<< File: 79205.ap.letter.DOC >>

Thanks,

Dat

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 6/26/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents currently listed in the "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date6/2/09

Chemistry Div. I II OR III Initials RMP
Comments:Satisfactory for AP.

6. Frank Holcombe **First Generics Only** Date 6/26/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. Banner Pharmacaps ANDA 78-682 for this drug product was approved on 3/24/09.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Advil LiquiGels 200 mg
Wyeth Consumer Healthcare NDA 20-402

8. Peter Rickman Date 6/26/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐ Comments: Bioequivalence studies (fasting and non-fasting) found acceptable. In-vitro dissolution testing also found acceptable. Bio study sites have acceptable DSI inspection histories - see memo in DFS endorsed 5/29/09. Office-level bio endorsed 12/20/08.

Final-printed labeling (FPL) found acceptable for approval 6/24/09.

CMC found acceptable for approval (Chemistry Review #3).

OR

8. Robert L. West Date 6/26/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 12/22/08 (Verified 6/26/09). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler — Date 6/26/09
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan — Date6/26/09
Review Support Branch — Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:20pm Time notified of approval by phone
2:21pm Time approval letter faxed

FDA Notification:
6/26/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/26/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 079205

****** Compliance Recommendations ******

App No	Doc Seq No	Date	OC Recommendation
079205	000	12/22/2008	ACCEPTABLE

****** EER Table ******

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
	MARKSANS PHARMA LIMITED	CSG	OC RECOMMENDATION	12/22/2008	AC	12/22/2008	None
	(b) (4)	CTL	OC	8/7/2008	AC	8/7/2008	None

			RECOMMENDATION					
	(b) (4)	CTL	OC RECOMMENDATION	5/29/2008	AC	5/29/2008	None	
(b) (4)	(b) (4)	CSN	OC RECOMMENDATION	11/21/2007	AC	11/21/2007	None	

COMIS TABLE:

Comis Application Table Data for Application No: 079205

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form | *COMIS Pool Reviewers* | ES DFS Files Only | ES - All Files | EDR | Cycles

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Drug Name: IBUPROFEN

Potency: 200 MG Dosage Form: CAP APPL Type: N

Applicant: MARKSANS PHARMA

Status Code: PN Status Date: 10/7/2008 Clock Date: 9/4/2007 USP: N Org: 600

Therapeutic Drug Class: ACUTE PAIN, NON-OPIOID

Patent Certification: 1 Patent Expiration Date: PEPFAR: N

Incom Doc Type	Seq No	Supp Mod Type	Letter Date	Stamp Date	Decision Code	Decision_Date	Status code	Status Date	Priority Flag	Document ID-Click to see Assignment	Priority Date
N Volume Locator	000	MC	9/12/2007	9/13/2007	CL	9/13/2007				3156107	
N Volume Locator	000		8/30/2007	9/4/2007	NM	2/14/2008	PN	10/7/2008	1	3152151	10/7/2008
N Volume Locator	000	AC	12/11/2007	12/12/2007	NM	2/14/2008				3879832	
N Volume Locator	000	AB	2/14/2008	2/15/2008	OP	2/15/2008				3912257	
N Volume Locator	000	AM	3/11/2008	3/13/2008	NM	9/5/2008				3924178	

N ***Volume Locator***	000	AB	4/11/2008	4/15/2008	OP	4/15/2008				3940089	
N ***Volume Locator***	000	AM	4/16/2008	4/17/2008	NM	9/5/2008				3941437	
N ***Volume Locator***	000	AM	4/21/2008	4/23/2008	NM	9/5/2008				3943931	
N ***Volume Locator***	000	AM	5/22/2008	5/27/2008	NM	9/5/2008				3959798	
N ***Volume Locator***	000	AM	5/30/2008	6/2/2008	NM	9/5/2008				3962209	
N ***Volume Locator***	000	AF	8/4/2008	8/5/2008	OP	8/5/2008				3994510	
N ***Volume Locator***	000	AA	8/15/2008	8/18/2008	NM	9/5/2008				4001054	
N ***Volume Locator***	000	AB	9/11/2008	9/12/2008	OP	9/12/2008				4013394	
N ***Volume Locator***	000	AM	10/6/2008	10/7/2008	OP	10/7/2008				4024982	
N ***Volume Locator***	000	AB	11/10/2008	11/12/2008	OP	11/12/2008				4042651	
N ***Volume Locator***	000	AF	6/3/2009	6/4/2009	OP	6/4/2009				4145555	***Comis Document Table Data***

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020402 Product 001 in the OB_OTC list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: June 25, 2009

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/s/

Dat Doan

6/26/2009 02:29:35 PM

COMPLETE RESPONSE -- MINOR

ANDA 79-205

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Marksans Pharma Ltd. TEL: 631-656-9753

ATTN: Nikanth J. Patel FAX: 631-656-9754

FROM: Dat Doan FDA CONTACT PHONE: (240) 276-8573

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 30, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Capsules (Liquid Filled), 200 mg.

Reference is also made to your amendment dated March 11, April 16, April 21, May 22, May 30, and August 15, 2008.

SPECIAL INSTRUCTIONS: **please see attached**

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachment (1 page). 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 MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 79-205 APPLICANT: Marksans Pharma Limited

DRUG PRODUCT: Ibuprofen (Liquid Filled) Capsules, 200 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) for Ibuprofen USP is deficient. Please do not respond to your deficiencies until the DMF holder has informed you that they have responded to their deficiencies.

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

1. The bioequivalence information which you have provided has been found to be deficient. The deficiencies were sent to you under separate cover. Please respond to them as soon as possible.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

3. To facilitate the review process, all changes (chemistry/manufacturing/controls, labeling, bioequivalence, etc.) should be identified and itemized in your cover letter.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Albert Mueller

9/5/2008 01:27:47 PM

BIOEQUIVALENCY AMENDMENT

ANDA 79-205

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Marksans Pharma Ltd. TEL: 631-656-9753

ATTN: Nikanth J. Patel FAX: 631-656-9754

FROM: Beth Fabian-Fritsch FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on August 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Capsules (Liquid Filled), 200 mg.

Reference is also made to the amendments dated February 14, 2008 and April 11, 2008.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all 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. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.

This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen (Liquid Filled) Capsules, 200 mg (OTC)

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

1. The data submitted for the fed bioequivalence (BE) study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy correspond with the **concentration data** submitted in the SAS files; however, in the SAS files, the **treatment variable** *does not* correspond to the sequence or period for the following subjects: 3,5,7,10,12,13,16,17,19,21,23 in the paper copy. The SAS files show these subjects receiving the reference product in both period 1 and period 2. Please explain this discrepancy and resubmit the data for the fed BE study, US/07/024, with correct treatment, period, and sequence information.

2. The data submitted for the fasted BE study are not consistent between the electronic and paper copies. The plasma concentration data in the paper copy do not correspond with the plasma concentration data submitted in the SAS files. Please explain this discrepancy and resubmit the data for the fasted BE study, US/07/023 distinguishing the correct plasma concentration data for the test and reference product.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Dale Conner

9/3/2008 11:21:53 AM

BIOEQUIVALENCY AMENDMENT

ANDA 79-205

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Marksans Pharma Ltd. TEL: 631-656-9753

ATTN: Nikanth J. Patel FAX: 631-656-9754

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on August 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Capsules (Liquid Filled), 200 mg.

Reference is also made to your amendment dated February 14, 2008.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all 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. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen Capsules (Liquid Filled), 200 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

Based on the dissolution testing data submitted for your Ibuprofen Capsules (Liquid Filled), your proposed specification of not less than (NLT) (b) (4) % Q in (b) (4) minutes is not acceptable. Please provide your acknowledgment and acceptance of the following FDA-recommended dissolution method and specification:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30 and 45 minutes

The test product should meet the following specification:

NLT (b) (4) % (Q) of the labeled amount of ibuprofen in the dosage form should be dissolved in **20 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Barbara Davit
3/18/2008 06:10:16 PM
Signing for Dale P Conner

MINOR AMENDMENT

ANDA 79-205

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Marksans Pharma Ltd. TEL: 631-656-9753

ATTN: Nikanth J. Patel FAX: 631-656-9754

FROM: Dat Doan PROJECT MANAGER: (240) 276-8573

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 30, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Capsules (Liquid Filled), 200 mg.

SPECIAL INSTRUCTIONS: **please see attached**

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (__**1**__ page). 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 MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR 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 you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 79-205 APPLICANT: Marksans Pharma Limited

DRUG PRODUCT: Ibuprofen (Liquid Filled) Capsules, 200 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please establish a specification for the relative amounts of ibuprofen potassium salt and free ibuprofen in your drug product. Please include the validated methods with data for these two new tests.

2. Please revise the limits for "Any Individual Impurity" and for (b) (4) in the API to comply with the ICH Q3A(R) recommended limits for a maximum daily dose of 1200 mg. Also please reduce your API total impurities limit to reflect your test results.

3. Please revise your drug product release and stability (b) (4) to NMT (b) (4)% to comply with the ICH Q3B(R) recommended limit for a maximum daily dose of 1200 mg for the drug product.

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

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

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

3. The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies.

4. To facilitate the review process, all changes (chemistry/manufacturing/controls, labeling, bioequivalence, etc.) should be identified and itemized in your cover letter.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Albert Mueller

2/14/2008 02:03:59 PM

BIOEQUIVALENCY AMENDMENT

ANDA 79-205

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Marksans Pharma Ltd. TEL: 631-656-9753

ATTN: Nikanth J. Patel FAX: 631-656-9754

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on August 30, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Capsules (Liquid Filled), 200 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all 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. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCES

ANDA: 79-205

APPLICANT: Marksans Pharma Ltd.

DRUG PRODUCT: Ibuprofen Capsules (Liquid Filled), 200 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. Please submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended method:

Medium:	Phosphate buffer, pH 7.2
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	150 rpm
Sampling times:	5, 10, 15, 20, 30 and 45 minutes

Please submit the comparative dissolution results which should include the individual capsule data as well as the mean, range, %CV at each time point for the 12 capsules tested and dates of dissolution testing. Also, please resubmit the dissolution testing data summary table with the above data.

2. The long-term stability data you provided is not sufficient to cover the storage period of the study samples for the BE studies you submitted. Please provide the data to support the long-term storage stability of ibuprofen in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed which was at least 46 days.

Sincerely yours,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Davit
2/1/2008 06:11:29 PM
Signing for Dale P Conner

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 79-205 **FIRM NAME**: MARKSANS PHARMA LIMITED (NEW FIRM)

PIV: NO **Electronic or Paper Submission: PAPER (CTD FORMAT)**

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: IBUPROFEN
DOSAGE FORM: CAPSULES, 200 MG (LIPUID FILLED)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Random Queue: 1
Chem Team Leader: Mueller, Albert PM: Dat Doan Labeling Reviewer: James Barlow

Letter Date: AUGUST 30, 2007 **Received Date**: SEPTEMBER 4, 2007

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 5030300 ACUTE PAIN, NON-OPIOID

Archival copy: PAPER (CTD FORMAT) **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Rebekah Granger **Date 11/14/2007**	**Recommendation:** ☐ **FILE** ☐ **REFUSE to RECEIVE**
ADDITIONAL COMMENTS REGARDING THE ANDA:	

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) OTC YES	☒
1.2	**Cover Letter** Dated: AUGUST 30, 2007 YES	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) 3. Expiration of Patent(s): N/A a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES **Patent and Exclusivity Search Results from query on Appl No 020402 Product 001 in the OB_OTC list.** --- ## Patent Data **There are no unexpired patents for this product in the Orange Book Database.** [Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.] ## Exclusivity Data **There is no unexpired exclusivity for this product.**	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒
1.12.11	**Basis for Submission** NDA# : 20-402 Ref Listed Drug: ADVIL LIQUI-GELS Firm: WYETH CONSUMER HEALTHCARE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such) **HOW SUPPLIED:** Bottles of 32 Capsules Bottles of 600 Capsules	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** YES **3.2.S.1.2 Structure** YES **3.2.S.1.3 General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES – DMF (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** Refer to DMF (b) (4)	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification** YES	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** Refer to DMF (b) (4)	☒
3.2.S.7	**Stability** Refer to DMF (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers (b) (4) **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** YES **3.2.P.3.5 Process Validation and/or Evaluation** YES 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) PROPOSED COMMERCIAL BATCH SIZE: (b) (4) Capsules	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** YES **3.2.P.4.3 Validation of Analytical Procedures** YES **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** YES **3.2.P.5.6 Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 24 MONTHS **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES – Lot #FH7006	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** Refer to DMF (b) (4) **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES – See Attached **3.2.R.1.P.2** **Information on Components** YES **3.2.R.2.P** **Comparability Protocols** YES **3.2.R.3.P** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

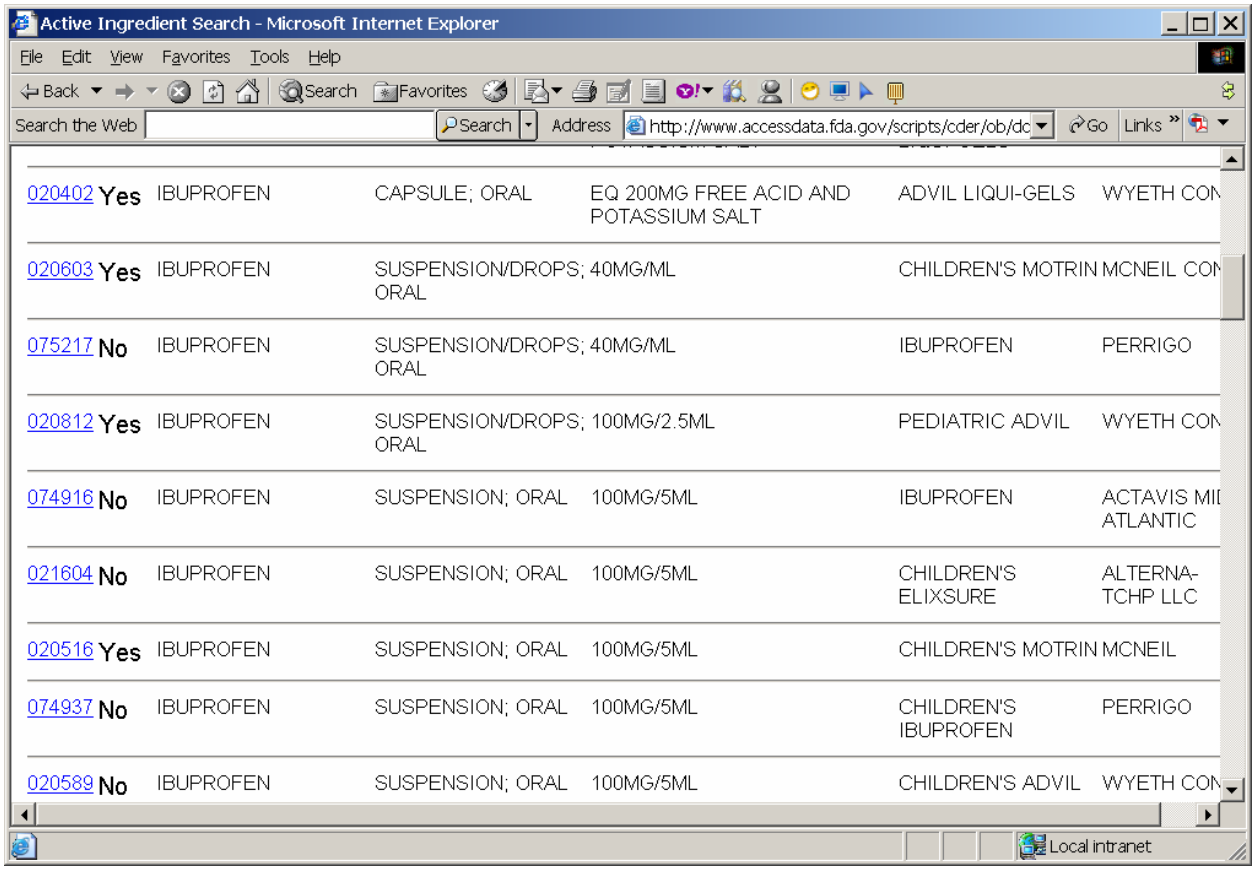
MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

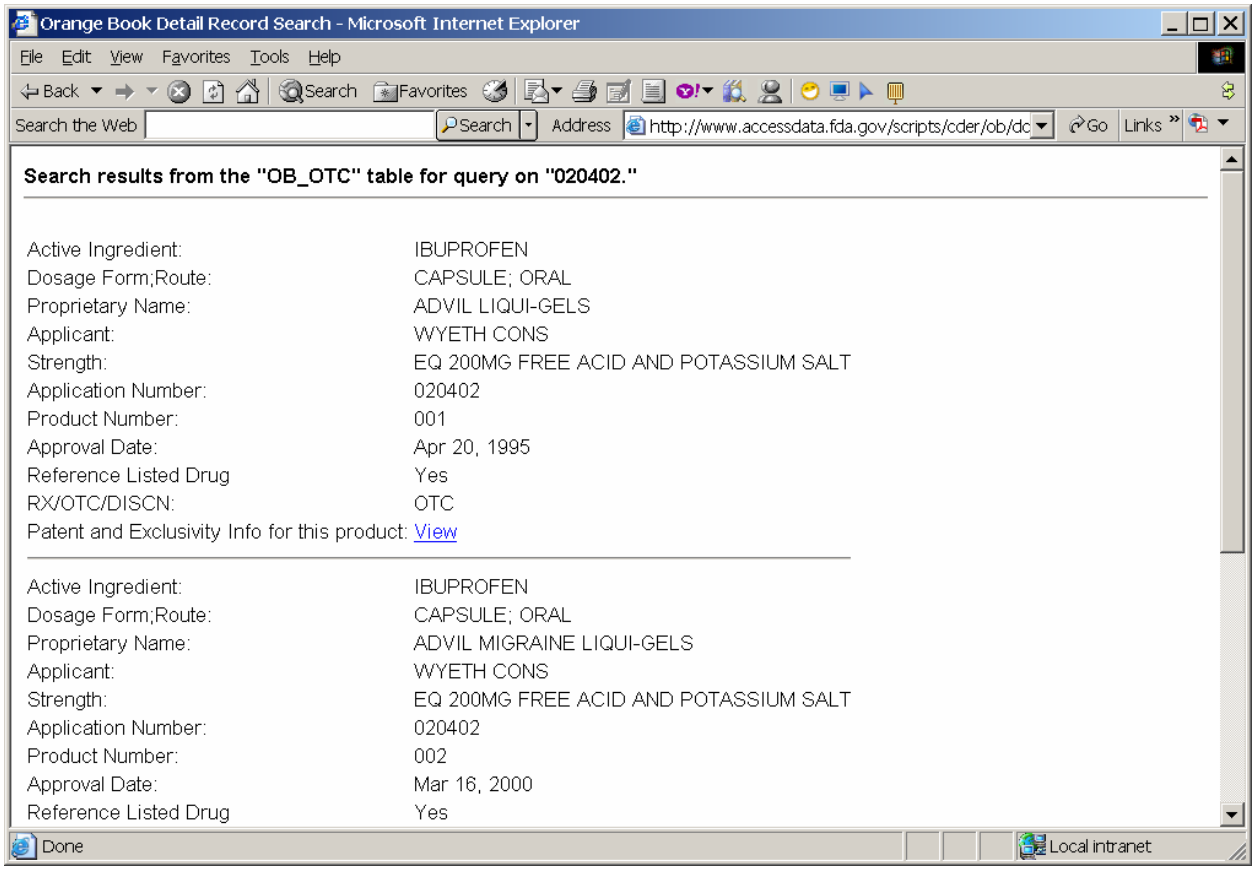
5.2	**Tabular Listing of Clinical Studies** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** RLD: B98587 ANDA: FH7006 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information YES Table 13. Protocol Deviations YES **5.3.1.3 In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study YES **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples YES Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES **5.3.7 Case Report Forms and Individual Patient Listing**	☒
5.4	**Literature References**	

	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES) (**i.e., fasting/fed/sprinkle) FASTING AND FED ON 200 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒

Updated 10/10/2006 C. Bina



020402	Yes	IBUPROFEN	CAPSULE; ORAL	EQ 200MG FREE ACID AND POTASSIUM SALT	ADVIL LIQUI-GELS	WYETH CON
020603	Yes	IBUPROFEN	SUSPENSION/DROPS; ORAL	40MG/ML	CHILDREN'S MOTRIN	MCNEIL CON
075217	No	IBUPROFEN	SUSPENSION/DROPS; ORAL	40MG/ML	IBUPROFEN	PERRIGO
020812	Yes	IBUPROFEN	SUSPENSION/DROPS; ORAL	100MG/2.5ML	PEDIATRIC ADVIL	WYETH CON
074916	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	IBUPROFEN	ACTAVIS MID ATLANTIC
021604	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ELIXSURE	ALTERNA-TCHP LLC
020516	Yes	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S MOTRIN	MCNEIL
074937	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S IBUPROFEN	PERRIGO
020589	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ADVIL	WYETH CON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File Edit View Favorites Tools Help
Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/dc Go Links
Search results from the "OB_OTC" table for query on "020402."
Active Ingredient: IBUPROFEN
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: ADVIL LIQUI-GELS
Applicant: WYETH CONS
Strength: EQ 200MG FREE ACID AND POTASSIUM SALT
Application Number: 020402
Product Number: 001
Approval Date: Apr 20, 1995
Reference Listed Drug Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: View
Active Ingredient: IBUPROFEN
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: ADVIL MIGRAINE LIQUI-GELS
Applicant: WYETH CONS
Strength: EQ 200MG FREE ACID AND POTASSIUM SALT
Application Number: 020402
Product Number: 002
Approval Date: Mar 16, 2000
Reference Listed Drug Yes
Done
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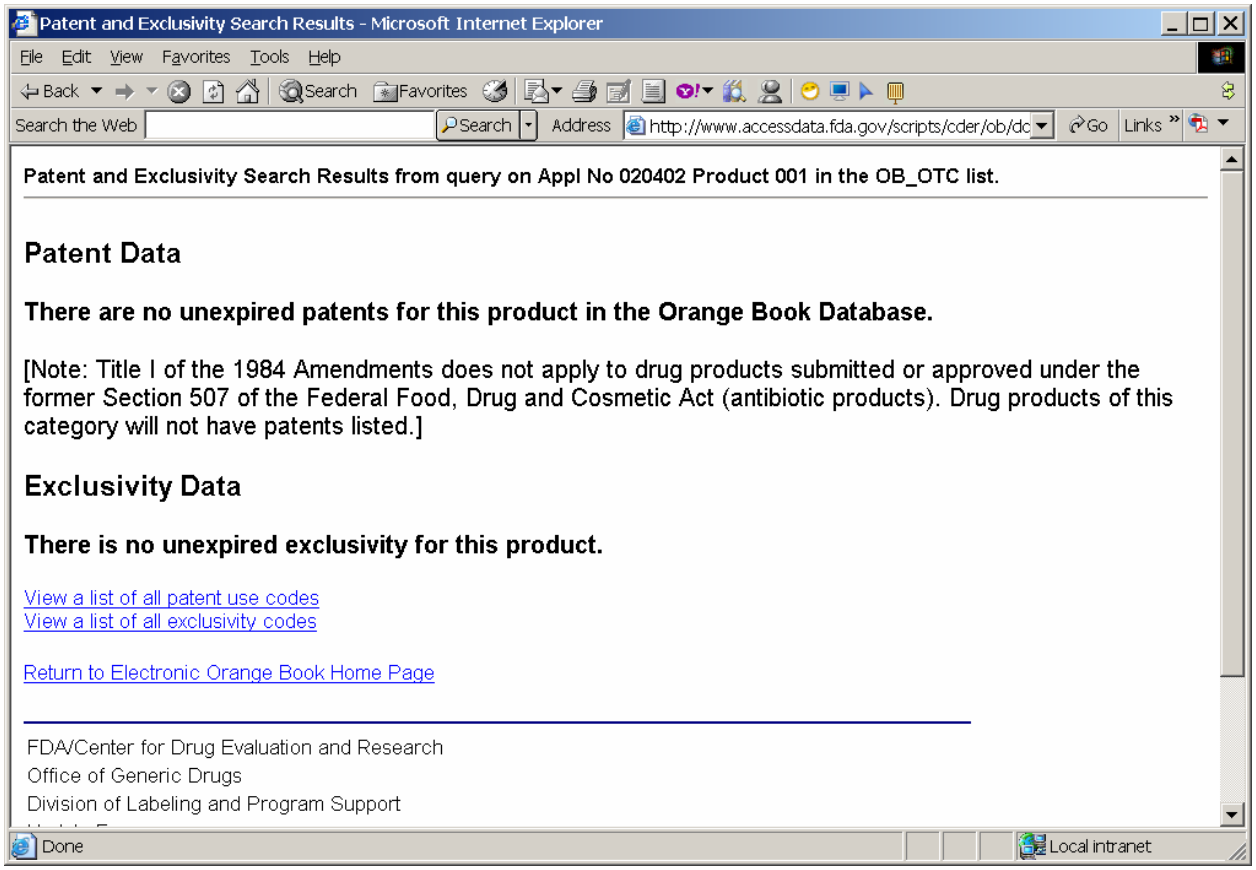
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Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
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Office of Generic Drugs
Division of Labeling and Program Support
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Table 3 Statistical Summary of the Comparative Bioavailability Data

Ibuprofen Soft Gelatin Capsules 200 mg Dose (1x 200mg Capsule) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study Code: US/07/023)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	63.70	68.13	93.50	90.00-97.12
AUC_{∞}	65.66	69.98	93.82	90.62-97.14
C_{max}	24.93	26.47	94.19	86.85-102.15

Ibuprofen Soft Gelatin Capsules 200 mg Dose (1x 200mg Capsule) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study Code: US/07/024)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	52.71	54.85	96.10	92.90-99.41 %
AUC_{∞}	56.13	58.09	96.63	93.24-100.14 %
C_{max}	11.67	12.36	94.39	87.98-101.26 %

Table 6 Formulation Data:

Ibuprofen Soft Gelatin Capsules, 200 mg:

The quantitative composition and function of each component in the drug product is listed.

S. No.	Ingredients	Pharmacopoeial reference	mg / capsule	% per capsule	Function
MEDICAMENT					
01	Ibuprofen	USP	200.00	(b) (4)	Active ingredient

(b) (4)

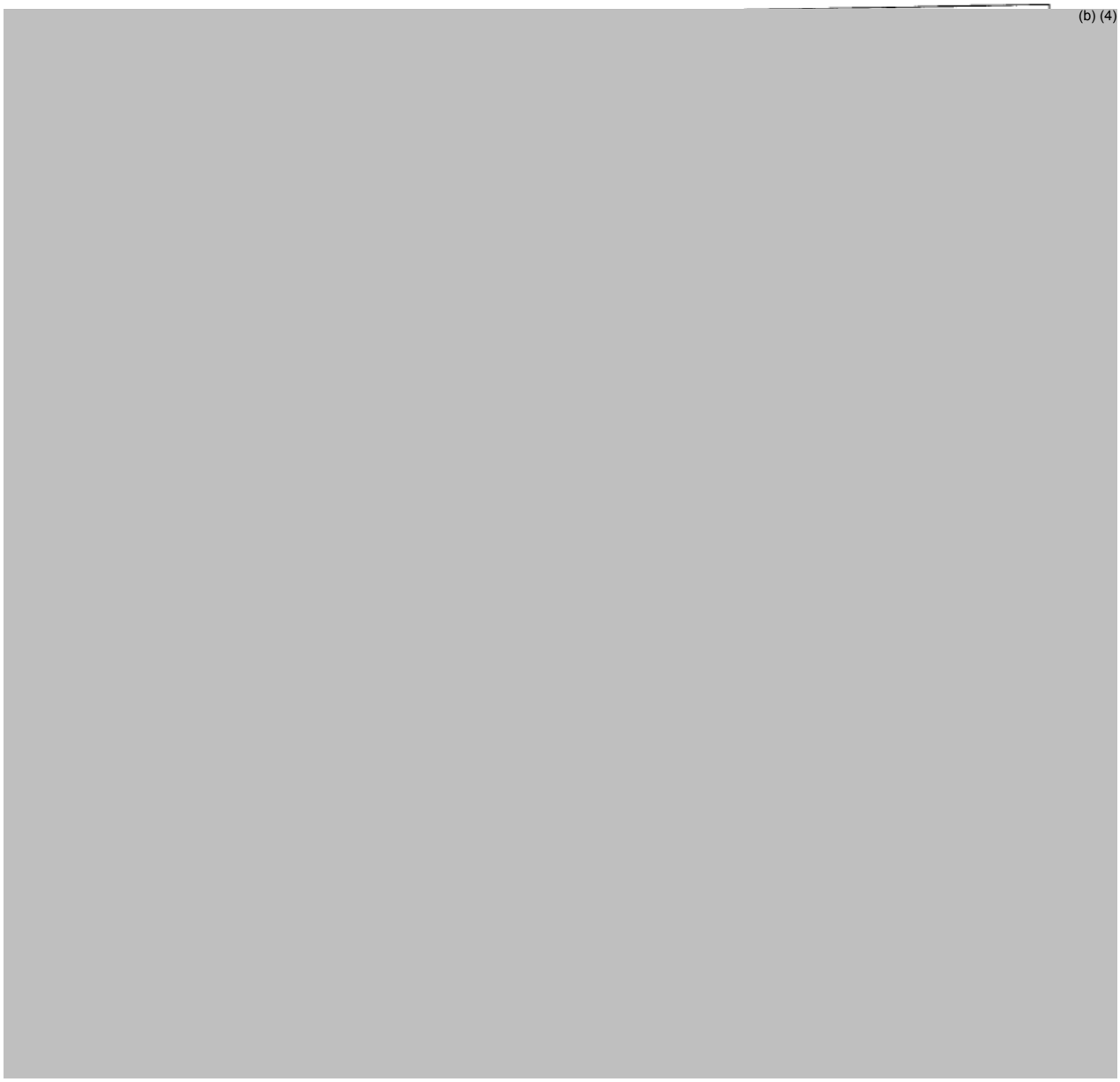
INACTIVE INGREDIENTS SEARCH FOR ANDA 79205

MARKSANS PHARMA LTD – IBUPROFEN CAPSULES, 200 MG

3.2.R.1.P.1 Batch Reconciliation

Batch Reconciliation for Ibuprofen Capsules, 200 mg

(b) (4)



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/s/

Martin Shimer

11/16/2007 09:22:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-205

Pharmgen LLC
US Agent for Marksans Pharma Limited
Attention: Nilkanth J Patel
1919 Middle Country Road
Suite #206
Centereach, NY 11720

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.

NAME OF DRUG: Ibuprofen Capsules, 200 mg

DATE OF APPLICATION: August 30, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 4, 2007

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:

Dat Doan
Project Manager
301-827-5807

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Martin Shimer
11/16/2007 09:21:51 AM
Signing for Wm Peter Rickman