APPLICATION NUMBER:
ANDA 79-205

Name: Ibuprofen Capsules (Liquid Filled), 200 mg

Sponsor: Marksans Pharma Limited

Approval Date: June 26, 2009
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## Reviews / Information Included in this Review

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APPLICATION NUMBER:
ANDA 79-205

APPROVAL LETTER
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
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.
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
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)
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.

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- Do not take more than directed
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- 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)
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:
- Ask your doctor before use if you are pregnant, under a doctor’s care for a serious condition, age 60 or over.
- 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

Each capsule contains:
- potassium 20 mg

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

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

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:
- Ask your doctor before use if you are pregnant, under a doctor’s care for a serious condition, age 60 or over.
- 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.
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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

Each capsule contains:
- potassium 20 mg

Do Not Use if seal under bottle cap imprinted with "SEALED FOR YOUR PROTECTION" is broken or missing.
**Ibuprofen Capsules, 200 mg (NSAID)**

**Pan Re ever / Fever Reducer (NSAID)**

**Liquid Filled Capsules**

**32 Softgels**

**Marksans**

**Drug Facts**

*Active ingredient (in each capsule)*

- Ibuprofen (NSAID) *equivalent to Pain reliever/fever reducer*

**Uses**

- Temporary relief of pain associated with:
  - Headache
  - Toothache
  - Menstrual cramps
  - Backache
  - Arthritis
  - PMS

**Directions**

- Do not exceed 6 capsules in 24 hours, unless directed by a doctor. If pain or fever does not respond to 1 capsule, 2 capsules may be used.

**Other information**

- Each capsule contains:
  - Potassium 20 mg
  - Each capsule contains 200 mg ibuprofen (NSAID) *equivalent to Pain reliever/fever reducer*

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

**Warnings**

- May cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
  - Facial swelling
  - Hives
  - Rash
  - Difficulty breathing or swelling of the mouth, throat, or tongue

**Precautions**

- Do not exceed 6 capsules in 24 hours, unless directed by a doctor. If pain or fever does not respond to 1 capsule, 2 capsules may be used.

- May cause complications during delivery. Do not use if pregnant or breast-feeding.

**Drug Facts**

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

**Other information**

- Do not exceed 6 capsules in 24 hours, unless directed by a doctor. If pain or fever does not respond to 1 capsule, 2 capsules may be used.

- May cause complications during delivery. Do not use if pregnant or breast-feeding.

**Warnings**

- May cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
  - Facial swelling
  - Hives
  - Rash
  - Difficulty breathing or swelling of the mouth, throat, or tongue

**Precautions**

- Do not exceed 6 capsules in 24 hours, unless directed by a doctor. If pain or fever does not respond to 1 capsule, 2 capsules may be used.
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

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**

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:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Pharmacopeial reference</th>
<th>mg / capsule</th>
<th>% per capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDICAMENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>Ibuprofen</td>
<td>USP</td>
<td>200.00</td>
<td>(b) (4)</td>
<td>Active ingredient</td>
</tr>
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</table>

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.
<table>
<thead>
<tr>
<th>Counts</th>
<th>Primary Package Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 capsules</td>
<td>(b)(4)</td>
<td>Smallest pack</td>
</tr>
<tr>
<td>600 capsules</td>
<td>(b)(4)</td>
<td>Largest pack</td>
</tr>
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8. Patent Information

**Patent Data – NDA 20-402**

<table>
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<tr>
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<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>There are no unexpired patents for this product in the Orange Book Database.</td>
<td>N/A</td>
<td>None</td>
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</table>

**Exclusivity Data – NDA 20-402**

<table>
<thead>
<tr>
<th>Code</th>
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<tr>
<td>None</td>
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<td>N/A</td>
<td>None</td>
</tr>
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Date of Review: 6/23/09    Date of Submission: 6/3/09
Primary Reviewer: Jim Barlow
Team Leader: Koung Lee
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.

Pain Reliever / Fever Reducer (NSAID)

**Liquid Filled Capsules**

Ibuprofen Capsules, 200 mg

600 Softgels**

Marksans

NDC 25000-133-13
### 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
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
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)
<table>
<thead>
<tr>
<th><strong>Uses</strong></th>
<th><strong>Warnings</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporarily relieves minor aches and pains due to: backache, headache, menstrual cramps, minor pain of arthritis, muscular aches, the common cold, toothache.</td>
<td>Ask your doctor before use if you are pregnant, under a doctor’s care for a serious condition, age 60 or over.</td>
</tr>
<tr>
<td>Temporarily reduces fever.</td>
<td></td>
</tr>
</tbody>
</table>

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

**Side Effects**
- This product may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: hives, asthma (wheezing), blisters, facial swelling, rashes, 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.

**Dosage**
- 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.

**Each capsule contains:**
- Potassium 20 mg

**Manufacturers:**
- Marksans Pharma Ltd., Verna, Goa - 403 722, India
- Marksans Pharma Inc., Lake Green, NY 11755, USA

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

**Read and Keep Carton for Complete Warnings and Information**

**Do Not Use if seal under bottle cap imprinted with “SEALED FOR YOUR PROTECTION” is broken or missing.”**
**Drug Facts**

**Ibuprofen Capsules, 200 mg**

**NSAID**

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

**Liquid Filled Capsules**

**32 Softgels**

**Marksans**

**Warnings**

- **Ibuprofen** may temporarily decrease the number of white blood cells and platelets, which may increase the risk of infection or bleeding. If you develop fever, sore throat, persistent cough, rash, bruising, or bleeding problems, contact your doctor.

**Inactive Ingredients**

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

**Other Information**

- **Drug Facts** Continued

**Directions**

- **Use**
  - For children 6 to 11 years: do not exceed 2 capsules every 6 hours, 1 capsule every 4 to 6 hours. 
  - For children under 6 years: ask a doctor.

- **Do not use**
  - If you are allergic to ibuprofen or other NSAIDs.
  - If you have had stomach ulcers or bleeding problems.
  - If you have had heart disease, stroke, or heart attack.
  - If you have high blood pressure, kidney disease, or liver disease.
  - If you have asthma, diabetes, gout, or lupus.
  - If you have peptic ulcer or bleeding.

- **Do not exceed**
  - 6 capsules in 24 hours, unless directed by a doctor.

**When using this product**

- Do not exceed the recommended dose. 
- Do not use more than 10 days, unless directed by a doctor.

**Complete Warnings and Information**

- **Side Effects**
  - May temporarily cause stomach upset, heartburn, rash, skin reddening, facial swelling, hives, facial swelling, skin rashes, uterine contractions, miscarriage, stillbirth, or premature delivery. 

**Pregnancy and Breastfeeding**

- **If pregnant or breast-feeding**
  - Ask a doctor before use. 
  - Do not use if you are taking a blood thinning (anticoagulant) or steroid drug.

**Interactions**

- **Do not take**
  - Other drugs containing an NSAID (prescription or non-prescription) 
  - Other drugs containing aspirin, ibuprofen, naproxen, or others 
  - Blood thinning (anticoagulant) or steroid drug

**Overdose**

- **In case of overdose, get medical help or contact a Poison Control Center right away.**

**Storage**

- Store at 20 to 25°C (68 to 77°F).
- Avoid excessive heat above 40°C (104°F).

**Manufactured by**

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

**NDC 25000-133-04**
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>There are no unexpired patents for this product in the Orange Book Database.</td>
<td>N/A</td>
<td>None</td>
</tr>
</tbody>
</table>

Exclusivity Data – NDA 20-402

<table>
<thead>
<tr>
<th>Code</th>
<th>Reference</th>
<th>Expiration</th>
<th>Labeling Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>There is no unexpired exclusivity for this product in the Orange Book Database.</td>
<td>N/A</td>
<td>None</td>
</tr>
</tbody>
</table>

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
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.2.1 Components of the Drug Product

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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Pharmacopeial reference</th>
<th>mg / capsule</th>
<th>% per capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Ibuprofen</td>
<td>USP</td>
<td>200.00</td>
<td>(b) (d)</td>
<td>Active ingredient</td>
</tr>
</tbody>
</table>

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 imprints have been accurately described as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule,
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
   with counts-32 and 600 capsules. Bottle packs shall be packaged in outer shipper. In addition, it
   will ship bulk capsules in double
   bags, placed in
   for repacking purpose.
   The largest and smallest packaging proposed for Ibuprofen capsules are:

<table>
<thead>
<tr>
<th>Counts</th>
<th>Primary Package Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 capsules</td>
<td>(b)(4)</td>
<td>Smallest pack</td>
</tr>
<tr>
<td>600 capsules</td>
<td>(b)(4)</td>
<td>Largest pack</td>
</tr>
</tbody>
</table>

---

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

Date of Submission: 8/4/08
Team Leader: John Grace
**Drug Facts**

**Active ingredient (in each capsule)**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Ibuprofen Capsules 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAID</strong></td>
<td>Pain Reliever / Fever Reducer (NSAID)</td>
</tr>
<tr>
<td><strong>Pain reliever</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fever reducer</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Muscular aches</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
</tr>
</tbody>
</table>

**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.

---

**Notes**

- NDC 25000-133-13
- **Liquid Filled Capsules**
- 600 Softgels**
- Marksans
**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

**Ask a doctor before use if you are**
- taking any other drug containing an NSAID (prescription or nonprescription)
- 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 doctor.
**Drug Facts (Continued)**

**doctor**

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

**Drug Facts (Continued)**

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

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.: G0/Drugs/515
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

Drug Facts (Continued)

- take a blood thinning (antiocoagulant) 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
- if you have ever had an allergic reaction to any pain reliever or fever reducer

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
- diabetes
- taken a diuretic
- reached age 60 or older
- took aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug
- using this product

When using this product
- avoid excessive heat above 40°C (104°F)
- store at 20 to 25°C (68 to 77°F)
- read all warnings and directions before use. Keep carton.

Directions
- 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

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

Warnings
- allergic alert: ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
- symptoms may include:
  - asthma (wheezing)
  - rash
  - dermatitis
  - facial swelling
  - hives
  - 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
- have had bleeding or stomach problems
- have had an allergic reaction to an NSAID in the past
- are age 60 or older
- are taking aspirin to prevent heart attack or stroke, because ibuprofen may decrease this benefit of aspirin

Inactive ingredients

Drug Facts (Continued)

- ibuprofen (in each capsule)
- ibuprofen (NSAID) (in each capsule) ................................... Fever reducer
- ibuprofen (NSAID) (in each capsule) ................................... Pain reliever
- ibuprofen (in each capsule) ................................... Fever reducer/fever reducer
- ibuprofen (prescription drug) ................................... Pain reliever/fever reducer

Active ingredient
- ibuprofen (prescription drug) (in each capsule)
- ibuprofen (NSAID) (in each capsule)

Purposes
- Fever reducer
- Pain reliever
- Fever reducer/fever reducer
- Pain reliever/fever reducer
- Pain reliever/fever reducer

Uses
- Fever reducer
- Pain reliever
- Fever reducer/fever reducer
- Pain reliever/fever reducer

Do not use if seal under bottle cap imprinted with "MARKSANS" is broken or missing.
Use: Temporarily relieves minor aches and pains due to: backache, headache, menstrual cramps, minor pain of arthritis, muscular aches, the common cold, toothache.

Warnings: Ask your doctor before use if you are pregnant, under a doctor's care for a serious condition, age 60 or over, 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.

Long term continuous use of this product may increase risk of heart attack or stroke.

Directions: Do not use if pain or fever does not respond to 1 capsule. 2 capsules may be used if pain or fever does not respond to 1 capsule. 2 capsules may be used if pain or fever does not respond to 1 capsule. Do not exceed 6 capsules in 24 hours, unless directed by a doctor. Children under 12 years: ask a doctor.

6 hours while symptoms persist: Each capsule contains: potassium 20 mg.

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


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>There are no unexpired patents for this product in the Orange Book Database.</td>
<td>N/A</td>
<td>None</td>
</tr>
</tbody>
</table>

Exclusivity Data – NDA 20-402

<table>
<thead>
<tr>
<th>Code</th>
<th>Reference</th>
<th>Expiration</th>
<th>Labeling Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>There is no unexpired exclusivity for this product in the Orange Book Database.</td>
<td>N/A</td>
<td>None</td>
</tr>
</tbody>
</table>

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®
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
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.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Pharmacopeial reference</th>
<th>mg / capsule</th>
<th>% per capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDICAMENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>Ibuprofen</td>
<td>USP</td>
<td>200.00</td>
<td></td>
<td>Active ingredient</td>
</tr>
</tbody>
</table>

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 imprints 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:

<table>
<thead>
<tr>
<th>Counts</th>
<th>Primary Package Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 capsules</td>
<td>(b)(4)</td>
<td>Smallest pack</td>
</tr>
<tr>
<td>600 capsules</td>
<td>(b)(4)</td>
<td>Largest pack</td>
</tr>
</tbody>
</table>

Date of Review: 6/5/08  Date of Submission: 8/30/07
Primary Reviewer: Jim Barlow  Date:
Team Leader: John Grace  Date:
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)
- rhinitis
- facial swelling
- hives
- shock
- skin reddening

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

NDC 25000-133-13

Ibuprofen Capsules 200 mg
Pain Reliever / Fever Reducer (NSAID)

**Liquid Filled Capsules**
600 Softgels**

Marksans
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)

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)


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

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

Do Not Use if seal under bottle cap imprinted with “SEALED FOR YOUR PROTECTION” is broken or missing.
NDC 25000 133 04
Pain Releiver / Fever Reducer
(NSAID)
**Liquid Filled Capsules**
32 Softgels
Ibuprofen Capsules 200 mg
Marksans
Size : 95 x 26 mm

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

Warnings
- Ask your doctor before use if you are pregnant, under a doctor’s care for a serious condition, age 60 or over,

- This product may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
  - hives, asthma (wheezing), blisters, facial swelling, 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.

- Long term continuous use of this product may increase risk of heart attack or stroke.

Directions
- do not take more than directed
- the smallest effective dose should be used
- 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

Each capsule contains: potassium 20 mg

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

Marksans Pharma Ltd.
Verna, Goa - 403 722, India

Marksans Pharma Inc.
Lake Grove, NY 11755, USA

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

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Mfg. for: Marksans Pharma Inc.

Size : 95 x 26 mm

Marked clear for YOUR PROTECTION
Drug Facts

Active ingredient
Solubilized Ibuprofen equal to 200 mg Ibuprofen (NSAID) * Pain reliever/fever reducer

Nonsteroidal anti-inflammatory drug

Uses
Temporarily relieves minor aches and pains due to:
- Headache
- Toothache
- The common cold
- Minor pain of arthritis

Purpose
Fever reducer

Directions
Do not use for more than 10 days, unless directed by a doctor (see Warnings)

*nonsteroidal anti-inflammatory drug

Warnings

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

Symptoms may include:
- Asthma (wheezing)
- Edema (swelling)
- Facial swelling
- Shock

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

**Liquid Filled Capsules**

32 Softgels**

Marksans

Marksans Pharma Ltd.

Verna, Goa - 403 722, India

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

Mfg. Date: 2007-01-01

Expiry Date: 2007-12-31

NDC: 25000-133-04

Drug Facts

Active ingredient
Solubilized Ibuprofen equal to 200 mg Ibuprofen (NSAID) * Pain reliever/fever reducer

Nonsteroidal anti-inflammatory drug

Uses
Temporarily relieves minor aches and pains due to:
- Headache
- Toothache
- The common cold

Purpose
Fever reducer

Directions
Do not use for more than 10 days, unless directed by a doctor (see Warnings)

*nonsteroidal anti-inflammatory drug

Warnings

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

Symptoms may include:
- Asthma (wheezing)
- Edema (swelling)
- Facial swelling
- Shock

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

**Liquid Filled Capsules**

32 Softgels**

Marksans

Marksans Pharma Ltd.

Verna, Goa - 403 722, India

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

Mfg. Date: 2007-01-01

Expiry Date: 2007-12-31

NDC: 25000-133-04

Drug Facts

Active ingredient
Solubilized Ibuprofen equal to 200 mg Ibuprofen (NSAID) * Pain reliever/fever reducer

Nonsteroidal anti-inflammatory drug

Uses
Temporarily relieves minor aches and pains due to:
- Headache
- Toothache
- The common cold

Purpose
Fever reducer

Directions
Do not use for more than 10 days, unless directed by a doctor (see Warnings)

*nonsteroidal anti-inflammatory drug

Warnings

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

Symptoms may include:
- Asthma (wheezing)
- Edema (swelling)
- Facial swelling
- Shock

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

**Liquid Filled Capsules**

32 Softgels**

Marksans

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Verna, Goa - 403 722, India

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

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NDC: 25000-133-04

Drug Facts

Active ingredient
Solubilized Ibuprofen equal to 200 mg Ibuprofen (NSAID) * Pain reliever/fever reducer

Nonsteroidal anti-inflammatory drug

Uses
Temporarily relieves minor aches and pains due to:
- Headache
- Toothache
- The common cold

Purpose
Fever reducer

Directions
Do not use for more than 10 days, unless directed by a doctor (see Warnings)

*nonsteroidal anti-inflammatory drug

Warnings

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

Symptoms may include:
- Asthma (wheezing)
- Edema (swelling)
- Facial swelling
- Shock

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

**Liquid Filled Capsules**

32 Softgels**

Marksans

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Verna, Goa - 403 722, India

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

Mfg. Date: 2007-01-01

Expiry Date: 2007-12-31

NDC: 25000-133-04

Drug Facts

Active ingredient
Solubilized Ibuprofen equal to 200 mg Ibuprofen (NSAID) * Pain reliever/fever reducer

Nonsteroidal anti-inflammatory drug

Uses
Temporarily relieves minor aches and pains due to:
- Headache
- Toothache
- The common cold

Purpose
Fever reducer

Directions
Do not use for more than 10 days, unless directed by a doctor (see Warnings)

*nonsteroidal anti-inflammatory drug

Warnings

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

Symptoms may include:
- Asthma (wheezing)
- Edema (swelling)
- Facial swelling
- Shock

If an allergic reaction occurs, stop use and seek medical help right away.
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
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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   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk  
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II. Summary of Chemistry Assessments.........................................................................................6  
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Chemistry Assessment .............................................................................................7  

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

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7. NAME & ADDRESS OF APPLICANT:

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<th>Name:</th>
<th>Marksans Pharma Limited</th>
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</table>
| Address:             | 601-622, 6th Floor, Chintamani Plaza  
Andheri-Kurla Road  
Andheri (East), Mumbai 400 099, India |
| Representative:      | Nilkanth Patel        |
| US Agent:            | Pharmgen LLC          |
| Telephone:           | 631-656-9753          |
| Fax:                 | 631-656-9754          |

8. DRUG PRODUCT NAME/CODE/TYPE:
Executive Summary Section

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

\[
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17. RELATED/SUPPORTING DOCUMENTS:

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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:

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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  ___ 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.
   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.
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
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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   A APPENDICES ................................................................................................9
   R REGIONAL INFORMATION ..........................................................................9

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   B. Environmental Assessment Or Claim Of Categorical Exclusion ..................9
Chemistry Review Data Sheet

1. ANDA 79-205

2. REVIEW #2


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

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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: 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:
Executive Summary Section

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

\[ \text{Chemical Structure} \]

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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:

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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  __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.

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.
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
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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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:

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7. NAME & ADDRESS OF APPLICANT:

Name: Marksans Pharma Limited

601-622, 6th Floor, Chintamani Plaza

Mohan Studio Compound

Andheri-Kurla Road

Andheri (East), Mumbai 400 099, India

US Agent:

Nilkanth Patel

Pharmgen LLC

1919 Middle Country Road, Suite 206

Centereach, NY 11720

Representative:

Telephone: 631-656-9753

Fax: 631-656-9754

8. DRUG PRODUCT NAME/CODE/TYP:

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

   ![Chemical Structure](image)
17. RELATED/SUPPORTING DOCUMENTS:

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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:

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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 Ibupfen (liquid filled) soft gelatin capsules.

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

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

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/s/
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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
APPLICATION NUMBER:
ANDA 79-205

BIOEQUIVALENCE REVIEWS
**EXECUTIVE SUMMARY**


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-31 TTC 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.
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

---

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 . 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 was completed on 4/26/2005 and the outcome was VAI. (Expired since inspection occurred more than 3 years ago)
• A "Routine" inspection for ANDA 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 on 6/2/2008 while ANDA 79205 was indicated as a "Related ANDA," pending the outcome of DSI inspection of ANDA . 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. Milton 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.
Message forwarded to Bob West

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

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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
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 80% (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**

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 I 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.

---

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 LAUCₜ, LAUCₜ, and LCₘₐₓ 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 \( \text{LAUC}_T, \text{LAUC}_{\infty}, \) and \( \text{LC}_{\text{max}} \) 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 \( \text{[b]} \) % (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 40% (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

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/s/
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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

<table>
<thead>
<tr>
<th>ANDA No.</th>
<th>79205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product Name</td>
<td>Ibuprofen Liquid Filled Capsules (OTC)</td>
</tr>
<tr>
<td>Strength(s)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Applicant Name</td>
<td>Marksans Pharma Ltd.</td>
</tr>
<tr>
<td>Address</td>
<td>601-622, Chintamani Plaza, Andheri Kurla Road, Andheri (East), Mumbai-400099, India</td>
</tr>
<tr>
<td>Applicant’s Point of Contact</td>
<td>Authorized U.S. Agent: Mr. Nikanth J. Patel, Vice President Pharmgen LLC, 1919 Middle Country Road, Suite #206 Centereach, NY 11720</td>
</tr>
<tr>
<td>Contact’s Telephone Number</td>
<td>631-656-9753</td>
</tr>
<tr>
<td>Contact’s Fax Number</td>
<td>631-656-9754</td>
</tr>
<tr>
<td>Original Submission Date(s)</td>
<td>30 Aug 2007</td>
</tr>
<tr>
<td>Submission Date(s) of Amendment(s) Under Review</td>
<td>11 Apr 2008 (dissolution acknowledgement)</td>
</tr>
<tr>
<td>Reviewer</td>
<td>Zakia R. Williams Ph.D.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Number(s)</th>
<th>US/07/023</th>
<th>US/07/024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Type(s)</td>
<td>Fasted (STF)</td>
<td>Fed (STP)</td>
</tr>
<tr>
<td>Strength(s)</td>
<td>200 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>Accutest Research Laboratories (I) Pvt. Ltd., A-31</td>
<td></td>
</tr>
<tr>
<td>Clinical Site Address</td>
<td>M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA</td>
<td></td>
</tr>
<tr>
<td>Analytical Site</td>
<td>Accutest Research Laboratories (I) Pvt. Ltd., A-31</td>
<td></td>
</tr>
<tr>
<td>Analytical Site Address</td>
<td>M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA</td>
<td></td>
</tr>
<tr>
<td>OUTCOME DECISION</td>
<td>INCOMPLETE</td>
<td></td>
</tr>
</tbody>
</table>

---
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.

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>AUC0-t (hr *µg/ml)</td>
<td>63.70</td>
<td>68.13</td>
<td>0.93</td>
<td>90.00 97.13</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>65.65</td>
<td>69.98</td>
<td>0.94</td>
<td>90.61 97.14</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>24.93</td>
<td>26.47</td>
<td>0.94</td>
<td>86.85 102.15</td>
</tr>
</tbody>
</table>

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 90% (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 correspond 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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3 SUBMISSION SUMMARY

3.1 Drug Product Information

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

3.2 PK/PD Information

<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Effect</td>
<td>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.</td>
</tr>
</tbody>
</table>
| Tmax                    | 1.15 hour (non-fasting); 0.7 hour (fasting)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Ibuprofen is metabolized via hepatic oxidation by cytochrome P450 2C9 to two inactive metabolites.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excretion</td>
<td>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.</td>
</tr>
</tbody>
</table>
| Half-life               | 2.526 hour (single oral dose)

3.3 OGD Recommendations for Drug Product

<table>
<thead>
<tr>
<th>Number of studies recommended:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2: Fasted and Fed</td>
</tr>
</tbody>
</table>

| 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:

### 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

- ANDA History:
  - 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

### Contents of Submission

<table>
<thead>
<tr>
<th>Study Types</th>
<th>Yes/No?</th>
<th>How many?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose Fasted</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Single-dose fed</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Steady-state</td>
<td>No</td>
<td>---</td>
</tr>
<tr>
<td>In vitro dissolution</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Waiver requests</td>
<td>No</td>
<td>---</td>
</tr>
<tr>
<td>BCS Waivers</td>
<td>No</td>
<td>---</td>
</tr>
<tr>
<td>Clinical Endpoints</td>
<td>No</td>
<td>---</td>
</tr>
<tr>
<td>Failed Studies</td>
<td>No</td>
<td>---</td>
</tr>
<tr>
<td>Amendments</td>
<td>Yes</td>
<td>1 (Dissolution acknowledgment)</td>
</tr>
</tbody>
</table>
### 3.5 Pre-Study Bioanalytical Method Validation

<table>
<thead>
<tr>
<th>Information Requested</th>
<th>Ibuprofen Capsules (Liquid Filled) 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioanalytical method validation report location</td>
<td>Volume II of V, (Appendix 16.7.3 of Bioanalytical Report), Pages 1 to 72</td>
</tr>
<tr>
<td>Analyte</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Internal standard (IS)</td>
<td>(b)(6)</td>
</tr>
<tr>
<td>Method description</td>
<td>LC/MS/MS</td>
</tr>
<tr>
<td><strong>Limit of quantification</strong></td>
<td>0.251 µg/mL</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Average recovery of drug (%)</strong></td>
<td>105.75%</td>
</tr>
<tr>
<td><strong>Average recovery of IS (%)</strong></td>
<td>94.90%</td>
</tr>
<tr>
<td><strong>Standard curve concentrations (units/mL)</strong></td>
<td>0.251 µg/mL to 99.940 µg/mL</td>
</tr>
</tbody>
</table>
| **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 @ 2°C-8°C |
| **Processed stability (hrs)** | 11 hours @ 4°C |
| **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 -20°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 |
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**

<table>
<thead>
<tr>
<th>Study Ref. No.</th>
<th>Study Design</th>
<th>Study Objective</th>
<th>Treatments (Dose, Dosage Form, Route) [Product ID]</th>
<th>Subjects (No. (M/F) Type Age: mean (Range))</th>
<th>Mean Parameters +/-SD (% CV)</th>
<th>Study Report Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>US/07/023</td>
<td>Single-dose, open label, two period, two treatment, two sequence, randomized, crossover study</td>
<td>* The objective of this study is to demonstrate bioequivalence between Test Product and Reference Product</td>
<td><strong>Test product:</strong> Ibuprofen soft gelatin capsules 200 mg [Batch # FH7006]</td>
<td>23 Healthy human (18M/5F) Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Reference product:</strong> Advil® Liqui-Gels® Solubilized Ibuprofen Capsules, 200 mg [Batch # B98587]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Subjects</strong></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>T&lt;sub&gt;max&lt;/sub&gt; § (hr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.36 ± 4.93 (19.48)</td>
<td>0.75 (0.50-1.25)</td>
</tr>
</tbody>
</table>

**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>
<thead>
<tr>
<th>Study Ref. No</th>
<th>Study Design</th>
<th>Study Objective</th>
<th>Treatments (Dose, Dosage Form, Route) [Product ID]</th>
<th>Subjects (No. (M/F) Type Age: mean (Range))</th>
<th>Mean Parameters +/-SD (% CV)</th>
<th>Study Report Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>US/07/024</td>
<td>Single-dose, open label, two period, two treatment, two sequence, randomized, crossover study</td>
<td>* The objective of this study is to demonstrate bioequivalence between Test Product and Reference Product</td>
<td>Test product: Ibuprofen Soft Gelatin Capsules 200 mg p.o [Batch # FH7006]</td>
<td>Subjects</td>
<td><strong>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</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26.90 ± 5.93 (19-36)</td>
<td>12.08 ± 3.26 (27.12)</td>
<td>2.50 ± 0.75-6.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.91 ± 3.72 (29.04)</td>
<td>3.00 ± 1.25-4.00</td>
</tr>
</tbody>
</table>
Table 2  Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I. Lower</th>
<th>90% C.I. Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (hr *µg/ml)</td>
<td>63.70</td>
<td>68.13</td>
<td>0.93</td>
<td>90.00</td>
<td>97.13</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>65.65</td>
<td>69.98</td>
<td>0.94</td>
<td>90.61</td>
<td>97.14</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>24.93</td>
<td>26.47</td>
<td>0.94</td>
<td>86.85</td>
<td>102.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I. Lower</th>
<th>90% C.I. Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (hr *µg/ml)</td>
<td>52.64</td>
<td>54.90</td>
<td>0.96</td>
<td>92.99</td>
<td>98.85</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>56.07</td>
<td>58.13</td>
<td>0.96</td>
<td>93.26</td>
<td>99.77</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>11.69</td>
<td>12.34</td>
<td>0.95</td>
<td>88.18</td>
<td>101.73</td>
</tr>
</tbody>
</table>
Table 3. Reanalysis of Study Samples

<table>
<thead>
<tr>
<th>Reason why assay was repeated</th>
<th>Number of samples reanalyzed</th>
<th>Number of recalculated values used after reanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual number</td>
<td>% of total assays</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Reason B (Sample Repeated For Inconsistent Internal Standard Response)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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 C_{max} 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

<table>
<thead>
<tr>
<th>Location in appendix</th>
<th>Section 4.2, Page 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a tablet, is the RLD scored?</td>
<td>N/A</td>
</tr>
<tr>
<td>If a tablet, is the test product biobatch scored</td>
<td>N/A</td>
</tr>
<tr>
<td>Is the formulation acceptable?</td>
<td>FORMULATION ACCEPTABLE</td>
</tr>
<tr>
<td>If not acceptable, why?</td>
<td></td>
</tr>
</tbody>
</table>

3.8 In Vitro Dissolution

<table>
<thead>
<tr>
<th>Location of DBE Dissolution Review</th>
<th>DFS N079205 N 000 30-Aug-2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of Method (USP, FDA or Firm)</td>
<td>FDA-recommended method</td>
</tr>
<tr>
<td>Medium</td>
<td>Phosphate buffer pH 7.2</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>900 mL</td>
</tr>
<tr>
<td>USP Apparatus type</td>
<td>USP 1 (Basket)</td>
</tr>
<tr>
<td>Rotation (rpm)</td>
<td>150</td>
</tr>
<tr>
<td>DBE-recommended specifications</td>
<td>Not less than (NLT $\geq Q$) in 20 minutes</td>
</tr>
<tr>
<td>If a modified-release tablet, was testing done on $\frac{1}{2}$ tablets?</td>
<td>N/A</td>
</tr>
<tr>
<td>F2 metric calculated?</td>
<td>No</td>
</tr>
<tr>
<td>If no, reason why F2 not calculated</td>
<td>Single strength and High %CV at 5 and 10 minutes</td>
</tr>
<tr>
<td>Is method acceptable?</td>
<td>COMPLETE (see comment below)</td>
</tr>
<tr>
<td>If not then why?</td>
<td></td>
</tr>
</tbody>
</table>

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 $\geq Q$ 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

<table>
<thead>
<tr>
<th>Medium:</th>
<th>Phosphate buffer, pH 7.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume:</td>
<td>900 mL</td>
</tr>
<tr>
<td>USP Apparatus:</td>
<td>1 (Basket)</td>
</tr>
<tr>
<td>Rotation Speed:</td>
<td>150 rpm</td>
</tr>
</tbody>
</table>

NLT 90% (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 in minutes for this drug product”.

3.12 Comments for Other OGD Disciplines

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>APPENDIX</td>
</tr>
<tr>
<td>4.1</td>
<td>Individual Study Reviews</td>
</tr>
<tr>
<td>4.1.1</td>
<td>Single-dose Fasted Bioequivalence Study</td>
</tr>
<tr>
<td>4.1.1.1</td>
<td>Study Design</td>
</tr>
</tbody>
</table>

Table 4 Study Information

<table>
<thead>
<tr>
<th>Study Number</th>
<th>US/07/023</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Title</td>
<td>A randomized, single dose, open label, bioequivalence study of Ibuprofen Soft Gelatin Capsules 200 mg in normal, healthy, adult, human subjects under fasted condition.</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>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</td>
</tr>
<tr>
<td>Clinical Investigator</td>
<td>Dr. Suhas Khandave M.D. (Pharmacology)</td>
</tr>
<tr>
<td>Analysis Date</td>
<td>Date of Initiation of Subject Analysis: 23rd July 2007 Date of Completion of Subject analysis: 27th July 2007</td>
</tr>
<tr>
<td>Analytical Director</td>
<td></td>
</tr>
<tr>
<td>Storage Period of Biostudy Samples No. of days from the first day of sample collection to the last day of sample analysis.</td>
<td>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.</td>
</tr>
</tbody>
</table>
### Table 5. Product Information

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

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

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

<table>
<thead>
<tr>
<th><strong>Number of Subjects</strong></th>
<th>24 healthy, adult human subjects (18 male and 6 female) enrolled; 23 completed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Sequences</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>No. of Periods</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>No. of Treatments</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>No. of Groups</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Washout Period</strong></td>
<td>7 days</td>
</tr>
<tr>
<td><strong>Randomization Scheme</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Blood Sampling Times</strong></td>
<td>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</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Fasted Bioequivalence Study, Study No.US/07/023 Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Product N = 23</td>
</tr>
<tr>
<td>Age (years) Mean ± SD Range</td>
</tr>
<tr>
<td>25.87 ± 5.50</td>
</tr>
<tr>
<td>18-37</td>
</tr>
<tr>
<td>Age Groups</td>
</tr>
<tr>
<td>&lt; 18 Nil</td>
</tr>
<tr>
<td>18 – 39 23 (100%)</td>
</tr>
<tr>
<td>40 – 64 Nil</td>
</tr>
<tr>
<td>65 – 75 Nil</td>
</tr>
<tr>
<td>&gt; 75 Nil</td>
</tr>
<tr>
<td>Sex Male 18 (78.26%) Female 5 (21.74%)</td>
</tr>
<tr>
<td>Race Asian 23 (100%) Black Nil</td>
</tr>
<tr>
<td>Caucasian Nil</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

Table 8. Dropout Information, Fasted Bioequivalence Study

<table>
<thead>
<tr>
<th>Subject No</th>
<th>Reason for dropout/withdrawn replacement</th>
<th>Period</th>
<th>Replaced?</th>
<th>Replaced with</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Dropped out in period I due to personal reasons; having sequence (BA)</td>
<td>I</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>
Table 9. Study Adverse Events, Fasted Bioequivalence Study

<table>
<thead>
<tr>
<th>Body system/Adverse Event</th>
<th>Reported Incidence by Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast Bioequivalence Study No.: US/07/023</td>
</tr>
<tr>
<td></td>
<td>Test n (%)</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
</tr>
<tr>
<td>Burning sensation (Epigastric region)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>1 (50.0%)</td>
</tr>
</tbody>
</table>

Table 10. Protocol Deviations, Fasted Bioequivalence Study

<table>
<thead>
<tr>
<th>Type</th>
<th>Subject #s (Test)</th>
<th>Subject #s (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation in scheduled time in blood sample collection</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Curve Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioequivalence Study No. : US/07/023</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen Capsules (Liquid Filled) 200 mg</td>
<td></td>
</tr>
<tr>
<td>Concentration (µg/mL)</td>
<td>0.251  0.502  2.009  10.044 30.133 60.265 80.353 99.940</td>
</tr>
<tr>
<td>Inter day Precision (%CV)</td>
<td>2.53   5.08   2.31   1.59   2.02   1.66   1.45   2.43</td>
</tr>
<tr>
<td>Inter day Accuracy (% Actual)</td>
<td>100.36 98.28  103.12  103.20  97.99  95.88  99.62  101.47</td>
</tr>
</tbody>
</table>
Table 12. SOP’s Dealing with Bioanalytical Repeats of Study Samples

<table>
<thead>
<tr>
<th>SOP No.</th>
<th>Effective Date of SOP</th>
<th>SOP Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARL/AL/SOP/069/02</td>
<td>27/01/07</td>
<td>STANDARD OPERATING PROCEDURE FOR REPEAT ANALYSIS</td>
</tr>
</tbody>
</table>
Table 13. Additional Comments on Repeat Assays

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were all SOPs followed?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did recalculation of PK parameters change the study outcome?</td>
<td>NA</td>
</tr>
<tr>
<td>Does the reviewer agree with the outcome of the repeat assays?</td>
<td>NA</td>
</tr>
<tr>
<td>If no, reason for disagreement</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>%CV</td>
<td>Min</td>
</tr>
<tr>
<td>AUC0-t (hr * µg/ml)</td>
<td>66.613</td>
<td>32.38</td>
<td>42.55</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>68.919</td>
<td>34.15</td>
<td>43.71</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>25.298</td>
<td>19.48</td>
<td>16.73</td>
</tr>
<tr>
<td>Tmax* (hr)</td>
<td>0.750</td>
<td>.</td>
<td>0.50</td>
</tr>
<tr>
<td>Kel (hr⁻¹)</td>
<td>0.379</td>
<td>22.80</td>
<td>0.20</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>1.937</td>
<td>27.29</td>
<td>1.23</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>%CV</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>AUC0-t (hr *µg/ml)</td>
<td>63.70</td>
<td>68.13</td>
<td>.95</td>
<td>90.00</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>65.66</td>
<td>69.98</td>
<td>.94</td>
<td>90.62</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>24.93</td>
<td>26.47</td>
<td>.94</td>
<td>86.85</td>
</tr>
</tbody>
</table>
### 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

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>AUC₀-t (hr *µg/ml)</td>
<td>63.70</td>
<td>68.13</td>
<td>0.93</td>
<td>90.00</td>
</tr>
<tr>
<td>AUC∞ (hr *µg/ml)</td>
<td>65.65</td>
<td>69.98</td>
<td>0.94</td>
<td>90.61</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>24.93</td>
<td>26.47</td>
<td>0.94</td>
<td>86.85</td>
</tr>
</tbody>
</table>
Table 17. Additional Study Information, Fasted Study No.US/07/023

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kel and AUC∞ determined for how many subjects?</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Do you agree or disagree with firm’s decision?</td>
<td>Agree</td>
<td>Agree</td>
</tr>
<tr>
<td>Indicate the number of subjects with the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>measurable drug concentrations at 0 hr</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>first measurable drug concentration as Cmax*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Were the subjects dosed as more than one group?</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>n</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of AUC0-t/AUC∞</td>
<td>Test</td>
<td>23</td>
<td>0.97</td>
<td>0.90</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>23</td>
<td>0.97</td>
<td>0.92</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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 lnCmax 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

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Test (n= 23)</th>
<th>Reference (n=23 )</th>
<th>T/R Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (µg/mL)</td>
<td>% CV</td>
<td>Mean (µg/mL)</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>.</td>
<td>0.00</td>
</tr>
<tr>
<td>0.25</td>
<td>5.40</td>
<td>130.76</td>
<td>6.77</td>
</tr>
<tr>
<td>0.50</td>
<td>22.96</td>
<td>41.07</td>
<td>21.76</td>
</tr>
<tr>
<td>0.75</td>
<td>23.76</td>
<td>19.27</td>
<td>23.04</td>
</tr>
<tr>
<td>1.00</td>
<td>21.68</td>
<td>21.05</td>
<td>21.05</td>
</tr>
<tr>
<td>1.25</td>
<td>18.69</td>
<td>19.87</td>
<td>18.08</td>
</tr>
<tr>
<td>1.50</td>
<td>16.78</td>
<td>24.29</td>
<td>16.38</td>
</tr>
<tr>
<td>1.75</td>
<td>14.90</td>
<td>26.77</td>
<td>14.64</td>
</tr>
<tr>
<td>2.00</td>
<td>13.61</td>
<td>31.19</td>
<td>13.28</td>
</tr>
<tr>
<td>2.25</td>
<td>12.15</td>
<td>33.47</td>
<td>11.78</td>
</tr>
<tr>
<td>2.50</td>
<td>11.08</td>
<td>36.89</td>
<td>10.72</td>
</tr>
<tr>
<td>3.00</td>
<td>9.04</td>
<td>38.27</td>
<td>8.69</td>
</tr>
<tr>
<td>4.00</td>
<td>6.72</td>
<td>47.46</td>
<td>6.80</td>
</tr>
<tr>
<td>6.00</td>
<td>2.98</td>
<td>61.87</td>
<td>2.96</td>
</tr>
<tr>
<td>8.00</td>
<td>1.69</td>
<td>83.59</td>
<td>1.52</td>
</tr>
<tr>
<td>12.00</td>
<td>0.47</td>
<td>140.65</td>
<td>0.40</td>
</tr>
<tr>
<td>24.00</td>
<td>0.01</td>
<td>479.58</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Figure 1. Mean Plasma Concentrations, Single-Dose Fasted Bioequivalence Study

PLASMA Ibuprofen LEVELS
Ibuprofen Liquid Gel Capsules, ANDA 79205
UNDER FAST CONDITIONS
DOSE = 1 X 200 MG

1 = TEST  2 = REF
4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

<table>
<thead>
<tr>
<th>Study Number</th>
<th>US/07/024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Title</td>
<td>A randomized, single dose, open label, bioequivalence study of Ibuprofen soft gelatin capsules 200 mg in normal, healthy, adult, human subjects under fed condition.</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>Accutest Research Laboratories (I) Pvt., 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</td>
</tr>
<tr>
<td>Clinical Investigator</td>
<td>Dr. Suhas Khandave M.D. (Pharmacology)</td>
</tr>
<tr>
<td>Dosing Dates</td>
<td>22nd June 2007 01st July 2007</td>
</tr>
<tr>
<td>Analysis Date</td>
<td>Date of Initiation of Subject Analysis: 24th July 2007 Date of Completion of Subject analysis: 28th July 2007</td>
</tr>
</tbody>
</table>

Table 20. Product Information

<table>
<thead>
<tr>
<th>Product</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Name</td>
<td>Ibuprofen Soft Gelatin Capsules 200 mg</td>
<td>Advil® LIQUI-GELS® Solubilized Ibuprofen Capsules 200 mg</td>
</tr>
<tr>
<td>Batch/Lot No.</td>
<td>FH7006</td>
<td>B98587</td>
</tr>
<tr>
<td>Manufacture Date</td>
<td>April 2007</td>
<td>August 2008</td>
</tr>
<tr>
<td>Expiration Date</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Strength</td>
<td>200 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Soft gelatin capsules</td>
<td>Soft gelatin capsules</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Bio-batch Size</td>
<td>(b) (d) <strong>Capsules</strong>*</td>
<td>----------------------</td>
</tr>
<tr>
<td>Production Batch Size</td>
<td>(b) (d) Capsules</td>
<td>----------------------</td>
</tr>
<tr>
<td>Potency</td>
<td>(b) (4)%</td>
<td>(b) (4)%</td>
</tr>
<tr>
<td></td>
<td>198.6 mg/Capsule</td>
<td>198.8 mg/Capsule</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>(b) (4)%</td>
<td>(b) (4)%</td>
</tr>
<tr>
<td></td>
<td>(98.0%-100.6%)</td>
<td>(94.2%-103.7%)</td>
</tr>
<tr>
<td>Dose Administered</td>
<td>A single oral dose of test formulation Ibuprofen capsules 200 mg in each period with 240 mL of water</td>
<td>A single oral dose of reference formulation Advil® LIQUI-GELS® 200 mg in each period with 240 mL of water</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
</tbody>
</table>

*As presented in the submission. This number may be a typographical error
Table 21. Study Design, Single-Dose Fed Bioequivalence Study

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>24 healthy, adult human subjects (18 male and 6 female) enrolled 21 completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Sequences</td>
<td>2</td>
</tr>
<tr>
<td>No. of Periods</td>
<td>2</td>
</tr>
<tr>
<td>No. of Treatments</td>
<td>2</td>
</tr>
<tr>
<td>No. of Groups</td>
<td>1</td>
</tr>
<tr>
<td>Washout Period</td>
<td>9 days</td>
</tr>
<tr>
<td>Randomization Scheme</td>
<td>AB:1,3,5,7,10,12,13,16,17,19,21,23</td>
</tr>
<tr>
<td></td>
<td>BA:2,4,6,8,9,11,14,15,18,20,22,24</td>
</tr>
<tr>
<td>Blood Sampling Times</td>
<td>Pre-dose samples were collected within 60 minutes before scheduled dosing</td>
</tr>
<tr>
<td></td>
<td>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,</td>
</tr>
<tr>
<td></td>
<td>6.00, 8.00, 12.00, 24.00 hours post dose</td>
</tr>
<tr>
<td>Blood Volume Collected/Sample</td>
<td>Samples were collected through an indwelling cannula placed in a forearm</td>
</tr>
<tr>
<td></td>
<td>vein or by direct vein puncture. A total of 17 blood samples (6 mL each)</td>
</tr>
<tr>
<td></td>
<td>were collected from 0 hour pre-dose to 24 hours post dose during each period.</td>
</tr>
<tr>
<td></td>
<td>Samples were collected in BD Vacutainer® containing K2 EDTA 10.8 mg</td>
</tr>
<tr>
<td>Blood Sample Processing/Storage</td>
<td>Post collection, study blood samples were centrifuged at 10º C and spun at</td>
</tr>
<tr>
<td></td>
<td>3500 rpm for 10 minutes. Plasma was dispensed in vials two in aliquots one</td>
</tr>
<tr>
<td></td>
<td>as analytical sample and the other as control sample. All plasma samples</td>
</tr>
<tr>
<td></td>
<td>were stored upright at -20ºC ± 5ºC.</td>
</tr>
<tr>
<td>IRB Approval</td>
<td>Yes, June 2, 2007</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>Yes, December 16, 2006</td>
</tr>
<tr>
<td>Length of Fast Before Meal</td>
<td>Overnight fast of at least 10 hours prior to the high fat breakfast given</td>
</tr>
<tr>
<td></td>
<td>half an hour before dosing.</td>
</tr>
<tr>
<td>Length of Confinement</td>
<td>Subjects were confined at 12 hours prior to dosing until after the 24 hour</td>
</tr>
<tr>
<td></td>
<td>post dose.</td>
</tr>
<tr>
<td>Safety Monitoring</td>
<td>Safety was evaluated by monitoring clinical adverse events during each</td>
</tr>
<tr>
<td></td>
<td>period. The investigator measured vital signs, including auxiliary</td>
</tr>
<tr>
<td></td>
<td>temperature, blood pressure, pulse and respiration rate.</td>
</tr>
<tr>
<td>Standard FDA Meal Used?</td>
<td>No</td>
</tr>
<tr>
<td>If No, then meal components and</td>
<td>Composition of Meal Used in Fed Bioequivalence Study US/07/024</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composition</th>
<th>Percent of total cal Test Meal</th>
<th>cal Test Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>55</td>
<td>531</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>27</td>
<td>260</td>
</tr>
<tr>
<td>Protein</td>
<td>18</td>
<td>168</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>959</td>
</tr>
</tbody>
</table>
## APPENDIX B
### MEALS FOR EACH STUDY PERIOD

<table>
<thead>
<tr>
<th>Food-item</th>
<th>Conventional Measure</th>
<th>Ingredients</th>
<th>CHO (g)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Energy (calories)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-FAT BREAKFAST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>2 cups</td>
<td>Whole milk</td>
<td>24</td>
<td>16</td>
<td>16</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Almond</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sugar</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Panner Paratha</td>
<td>1 (-100g)</td>
<td>Wheat flour</td>
<td>22</td>
<td>3</td>
<td>0</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panner</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Curds</td>
<td>1 cup</td>
<td>Butternut carrots</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coriander leaves + mint leaves + green chillies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cheese Singles</td>
<td>2 slices</td>
<td>Cheese</td>
<td>2</td>
<td>8</td>
<td>10</td>
<td>130</td>
</tr>
<tr>
<td>Cashew</td>
<td>10 pieces</td>
<td>Cashew</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cheese</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>65</td>
<td>42</td>
<td>59</td>
<td>960</td>
</tr>
<tr>
<td><strong>Total calories</strong></td>
<td></td>
<td></td>
<td>260</td>
<td>168</td>
<td>531</td>
<td></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td></td>
<td></td>
<td>27</td>
<td>18</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td><strong>LUNCH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puri/Dosa</td>
<td>2 nos (30g each)</td>
<td>Wheat flour (kneaded)</td>
<td>30</td>
<td>4</td>
<td>0</td>
<td>140</td>
</tr>
<tr>
<td>Rice</td>
<td>1 cup</td>
<td>Rice</td>
<td>30</td>
<td>4</td>
<td>0</td>
<td>140</td>
</tr>
<tr>
<td>Patti-Dal</td>
<td>1 cup</td>
<td>Dal</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onion</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Methi vegetable</td>
<td>1 cup cooked</td>
<td>Tomato</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methi leaves (chopped)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomato-cucumber salad</td>
<td>1 cup</td>
<td>Tomato + cucumber (chopped)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 tsp</td>
<td>Cooking oil</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>135</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>98</td>
<td>14</td>
<td>15</td>
<td>595</td>
</tr>
<tr>
<td><strong>SNACK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahi Vada</td>
<td>3 pieces</td>
<td>Maida vada</td>
<td>23</td>
<td>4</td>
<td>0</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curd (whole - milk)</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sugar</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Whole milk</td>
<td>½ cup</td>
<td>Whole milk</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>Fruit</td>
<td>1 no.</td>
<td>Banana</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oil</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>60</td>
<td>12</td>
<td>13</td>
<td>400</td>
</tr>
</tbody>
</table>
### Comments on Study Design:

The study design is acceptable

---

**DINNER**

<table>
<thead>
<tr>
<th>Item</th>
<th>Serving Size (g)</th>
<th>Calories</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Energy (calories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapati</td>
<td>2 nos.</td>
<td>140</td>
<td>4</td>
<td>0</td>
<td>685</td>
</tr>
<tr>
<td>Steamed Rice</td>
<td>1 cup</td>
<td>140</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dal</td>
<td>1 cup</td>
<td>70</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Onion</td>
<td>1 g</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Curd</td>
<td>1/2 cup</td>
<td>75</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cooked Vegetable</td>
<td>1 cup</td>
<td>70</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tomato-cucumber salad</td>
<td>1 cup</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td>1 no</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 tsp</td>
<td>1 banana</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cooking oil</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>685</td>
<td>20</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

**Nutritive Value of the Day's Menu:**

<table>
<thead>
<tr>
<th>Description</th>
<th>CHO (g)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Energy (calories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>65</td>
<td>42</td>
<td>59</td>
<td>560</td>
</tr>
<tr>
<td>Lunch</td>
<td>98</td>
<td>14</td>
<td>15</td>
<td>595</td>
</tr>
<tr>
<td>Evening Snack</td>
<td>60</td>
<td>12</td>
<td>13</td>
<td>400</td>
</tr>
<tr>
<td>Dinner</td>
<td>11</td>
<td>20</td>
<td>14</td>
<td>685</td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
<td>88</td>
<td>101</td>
<td>2640</td>
</tr>
<tr>
<td>Calories</td>
<td>1360</td>
<td>352</td>
<td>909</td>
<td></td>
</tr>
<tr>
<td>Percent Contributed</td>
<td>52</td>
<td>13</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>
4.1.2.2  Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

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

Table 23. Dropout Information, Fed Bioequivalence Study

<table>
<thead>
<tr>
<th>Study No.US/07/024</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject No</strong></td>
</tr>
<tr>
<td>04</td>
</tr>
<tr>
<td>05</td>
</tr>
<tr>
<td>19</td>
</tr>
</tbody>
</table>
### Table 24. Study Adverse Events, Fed Bioequivalence Study

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

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

### Table 25. Protocol Deviations, Fed Bioequivalence Study

<table>
<thead>
<tr>
<th>Type</th>
<th>Study No:US/07/024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation in scheduled time in blood sample collection</td>
<td>Subject (Test)</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Bioequivalence Study No.</th>
<th>US/07/024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen Capsules (Liquid Filled) 200 mg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Curve Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (µg/mL)</td>
<td>0.251 0.502 2.009 10.044 30.133 60.265 80.353 99.940</td>
</tr>
<tr>
<td>Inter day Precision (%CV)</td>
<td>2.53 5.08 2.31 1.59 2.02 1.66 1.45 2.43</td>
</tr>
<tr>
<td>Inter day Accuracy (% Actual)</td>
<td>100.36 98.28 103.12 103.20 97.99 95.88 99.62 101.47</td>
</tr>
<tr>
<td>Linearity (Range of Values)</td>
<td>(r &gt; 0.98) 0.9984-0.9997</td>
</tr>
<tr>
<td>Linearity Range (µg/mL)</td>
<td>0.251 to 99.940</td>
</tr>
<tr>
<td>Sensitivity/LOQ (µg/mL)</td>
<td>0.251</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>SOP No.</th>
<th>Effective Date of SOP</th>
<th>SOP Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARL/AL/SOP/069/02</td>
<td>27/01/07</td>
<td>STANDARD OPERATING PROCEDURE FOR REPEAT ANALYSIS</td>
</tr>
</tbody>
</table>

Table 28. Additional Comments on Repeat Assays

<table>
<thead>
<tr>
<th>Were all SOPs followed?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did recalculation of PK parameters change the study outcome?</td>
<td>No</td>
</tr>
<tr>
<td>Does the reviewer agree with the outcome of the repeat assays?</td>
<td>Yes</td>
</tr>
<tr>
<td>If no, reason for disagreement</td>
<td>NA</td>
</tr>
</tbody>
</table>

Summary/Conclusions, Study Assays:

1. The 90% CI for the least squares geometric means of lnAUCt, lnAUC\(_\infty\), and lnC\(_{\text{max}}\) 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

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Fed Bioequivalence Study, Study No. US/07/024</th>
<th>Reference</th>
<th>T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>%CV</td>
<td>Min</td>
</tr>
<tr>
<td>AUC0-t (hr*µg/m)</td>
<td>54.694</td>
<td>27.82</td>
<td>30.47</td>
</tr>
<tr>
<td>AUC(_\infty) (hr*µg/m)</td>
<td>58.342</td>
<td>28.56</td>
<td>30.97</td>
</tr>
<tr>
<td>C(_{\text{max}}) (µg/ml)</td>
<td>12.013</td>
<td>27.11</td>
<td>5.57</td>
</tr>
<tr>
<td>Tmax* (hr)</td>
<td>2.500</td>
<td>.</td>
<td>0.75</td>
</tr>
<tr>
<td>Kel (hr(^{-3}))</td>
<td>0.322</td>
<td>24.81</td>
<td>0.18</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>2.284</td>
<td>24.93</td>
<td>1.31</td>
</tr>
</tbody>
</table>

* Tmax values are presented as median, range
### Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>AUC0-t (hr * µg/ml)</td>
<td>52.71</td>
<td>54.85</td>
<td>0.96</td>
<td>92.90</td>
<td>99.41</td>
<td></td>
</tr>
<tr>
<td>AUCi (hr * µg/ml)</td>
<td>56.13</td>
<td>58.09</td>
<td>0.97</td>
<td>93.24</td>
<td>100.14</td>
<td></td>
</tr>
<tr>
<td>Cmax (hr * µg/ml)</td>
<td>11.67</td>
<td>12.36</td>
<td>0.94</td>
<td>87.98</td>
<td>101.26</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>AUC0-t (hr * µg/ml)</td>
<td>52.64</td>
<td>54.90</td>
<td>0.96</td>
<td>92.99</td>
<td>98.85</td>
<td></td>
</tr>
<tr>
<td>AUCi (hr * µg/ml)</td>
<td>56.07</td>
<td>58.13</td>
<td>0.96</td>
<td>93.26</td>
<td>99.77</td>
<td></td>
</tr>
<tr>
<td>Cmax (hr * µg/ml)</td>
<td>11.69</td>
<td>12.34</td>
<td>0.95</td>
<td>88.18</td>
<td>101.73</td>
<td></td>
</tr>
</tbody>
</table>
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 |

<table>
<thead>
<tr>
<th>Kel and AUC∞ determined for how many subjects?</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you agree or disagree with firm’s decision?</td>
<td>Agree</td>
<td>Agree</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indicate the number of subjects with the following:</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>measurable drug concentrations at 0 hr</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>first measurable drug concentration as Cmax</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Were the subjects dosed as more than one group?</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>21</td>
<td>0.94</td>
<td>0.80</td>
<td>0.98</td>
</tr>
<tr>
<td>Reference</td>
<td>21</td>
<td>0.94</td>
<td>0.88</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**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 lnCmax 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>
<thead>
<tr>
<th>Time (hr)</th>
<th>Test (n=21)</th>
<th>Reference (n=21)</th>
<th>Ratio (T/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (µg/mL)</td>
<td>CV%</td>
<td>Mean (µg/mL)</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>.</td>
<td>0.00</td>
</tr>
<tr>
<td>0.25</td>
<td>0.10</td>
<td>307.19</td>
<td>0.14</td>
</tr>
<tr>
<td>0.50</td>
<td>1.40</td>
<td>173.51</td>
<td>1.40</td>
</tr>
<tr>
<td>0.75</td>
<td>2.55</td>
<td>123.23</td>
<td>3.16</td>
</tr>
<tr>
<td>1.00</td>
<td>3.80</td>
<td>106.92</td>
<td>4.91</td>
</tr>
<tr>
<td>1.25</td>
<td>4.87</td>
<td>88.41</td>
<td>6.37</td>
</tr>
<tr>
<td>1.50</td>
<td>6.19</td>
<td>73.84</td>
<td>7.73</td>
</tr>
<tr>
<td>1.75</td>
<td>6.97</td>
<td>67.24</td>
<td>8.89</td>
</tr>
<tr>
<td>2.00</td>
<td>8.06</td>
<td>54.06</td>
<td>9.27</td>
</tr>
<tr>
<td>2.25</td>
<td>8.52</td>
<td>47.11</td>
<td>9.51</td>
</tr>
<tr>
<td>2.50</td>
<td>9.03</td>
<td>41.00</td>
<td>9.95</td>
</tr>
<tr>
<td>3.00</td>
<td>9.12</td>
<td>32.20</td>
<td>9.89</td>
</tr>
<tr>
<td>4.00</td>
<td>9.31</td>
<td>33.10</td>
<td>9.00</td>
</tr>
<tr>
<td>6.00</td>
<td>5.22</td>
<td>46.47</td>
<td>4.91</td>
</tr>
<tr>
<td>8.00</td>
<td>2.89</td>
<td>57.91</td>
<td>2.56</td>
</tr>
<tr>
<td>12.00</td>
<td>0.85</td>
<td>74.02</td>
<td>0.84</td>
</tr>
<tr>
<td>24.00</td>
<td>0.00</td>
<td>.</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study
4.2 Formulation Data

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Pharmacopoeia reference</th>
<th>mg / capsule</th>
<th>% per capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Ibuprofen</td>
<td>USP</td>
<td>200.00</td>
<td>(b)(4)</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there an overage of the active pharmaceutical ingredient (API)?</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the answer is yes, has the appropriate chemistry division been notified?</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Comments on the drug product formulation:

1. All of the excipients are within the IIG limits.
2. The color additive FD&C green No. 3 is per capsule, less than the 0.1% requirement, therefore its amount is insignificant.
3. 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 \( \frac{150}{\text{Q}} \% \) in 20 minutes in the Bioequivalence Amendment dated April 11, 2008. See Recommendation section 3.11

<table>
<thead>
<tr>
<th>Dissolution Conditions</th>
<th>Apparatus: USP Type I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of Rotation:</td>
<td>150 rpm</td>
</tr>
<tr>
<td>Medium:</td>
<td>Phosphate buffer pH 7.2</td>
</tr>
<tr>
<td>Volume:</td>
<td>900 mL</td>
</tr>
<tr>
<td>Temperature:</td>
<td>37°C ±0.5°C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Firm’s Proposed Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution Testing Site</td>
</tr>
<tr>
<td>(Name, Address)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Ref No.</th>
<th>Testing Date</th>
<th>Product ID \ Batch No.</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage Units</th>
<th>Collection Times (minutes)</th>
<th>Study Report Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Marksans Pharma Ltd.’s Ibuprofen Capsules, 200 mg (liquid filled) Lot # FH7006</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>Mean (%)</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range (%)</td>
<td>(1.2 to 5.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td>62.6</td>
</tr>
<tr>
<td>Study Ref No.</td>
<td>Testing Date</td>
<td>Wyeth Consumer Healthcare’s Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg) Lot # B98587</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>Mean (%)</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range (%)</td>
<td>(2.0 to 6.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td>37.3</td>
</tr>
</tbody>
</table>

4.4 Detailed Regulatory History (If Applicable)

4.5 Consult Reviews
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
Verifier: 
Date Completed: 
Date Verified: 
Division: Division of Bioequivalence
Description: Ibuprofen liqui-gel 200 mg

<table>
<thead>
<tr>
<th>ID</th>
<th>Letter Date</th>
<th>Productivity Category</th>
<th>Sub Category</th>
<th>Productivity</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>5829</td>
<td>8/30/2007</td>
<td>Bioequivalence Study</td>
<td>Fasted Study</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5829</td>
<td>8/30/2007</td>
<td>Bioequivalence Study</td>
<td>Fed Study</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5829</td>
<td>2/14/2008</td>
<td>Other</td>
<td>Dissolution Amendment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5829</td>
<td>4/11/2008</td>
<td>Dissolution Data</td>
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/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, Division 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

### Authorized U.S. Agent:
Mr. Nikanth J. Patel, Vice President
Pharmgen LLC, 1919 Middle Country Road, Suite #206
Centereach, NY 11720

### 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.

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<tr>
<th>Study Number (s)</th>
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<tbody>
<tr>
<td>Study Type (s)</td>
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<td>Strength(s)</td>
<td>200 mg</td>
<td>200 mg</td>
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<tr>
<td>Clinical Site</td>
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<td></td>
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<tr>
<td>Clinical Site Address</td>
<td>M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA</td>
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<td>Analytical Site</td>
<td>Accutest Research Laboratories (I) Pvt. Ltd., A-31</td>
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<td>Analytical Address</td>
<td>M.I.D.C., T.T.C., Industrial Area, Khairne, Navi Mumbai-400 709, INDIA</td>
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### 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 S1 level. The firm proposed specification of not less than (Q) in minutes differs from the FDA-recommended specification [NLT (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

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<td>Did the firm use the USP dissolution method</td>
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<td>Did the firm conduct dissolution testing with its own proposed method</td>
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<td>Is FDA method in the public dissolution database (on the web)</td>
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<td>Fed BE study</td>
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<td>PK parameters</td>
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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**

<table>
<thead>
<tr>
<th>Dissolution Conditions</th>
<th>Apparatus:</th>
<th>USP Type I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of Rotation:</td>
<td>150 rpm</td>
<td></td>
</tr>
<tr>
<td>Medium:</td>
<td>Phosphate buffer pH 7.2</td>
<td></td>
</tr>
<tr>
<td>Volume:</td>
<td>900 mL</td>
<td></td>
</tr>
<tr>
<td>Temperature:</td>
<td>37°C ±0.5°C</td>
<td></td>
</tr>
</tbody>
</table>

**Firm’s Proposed Specifications**
Not less than \( \text{ab} \)% of the labeled amount is dissolved in \( \text{ab} \) minutes

**Dissolution Testing Site**
(Marksans Pharma Ltd.)

<table>
<thead>
<tr>
<th>Study Ref No.</th>
<th>Testing Date</th>
<th>Product ID \ Batch No.</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage Units</th>
<th>Collection Times (minutes)</th>
<th>Study Report Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Report #: MV/AMV/DP/FH/017</td>
<td>Report date: 14\textsuperscript{th} August 2007</td>
<td>Marksans Pharma Ltd.’s Ibuprofen Capsules, 200 mg (liquid filled) Lot # FH7006</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>Mean (%)</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range (%)</td>
<td>(1.2 to 5.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td>62.6</td>
</tr>
<tr>
<td>Study Report #: MV/AMV/DP/FH/017</td>
<td>Report date: 14\textsuperscript{th} August 2007</td>
<td>Wyeth Consumer Healthcare’s Advil\textsuperscript{®} Liqui-Gels\textsuperscript{®} (solubilized Ibuprofen Capsules 200 mg) Lot # B98587</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>Mean (%)</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range (%)</td>
<td>(2.0 to 6.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td>37.3</td>
</tr>
</tbody>
</table>
B. Firm’s Proposed Dissolution Method

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

<table>
<thead>
<tr>
<th>Dissolution Conditions</th>
<th>Apparatus:</th>
<th>USP Type I</th>
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<tbody>
<tr>
<td>Speed of Rotation:</td>
<td>rpm</td>
<td></td>
</tr>
<tr>
<td>Medium:</td>
<td>Phosphate buffer pH 7.2 +</td>
<td></td>
</tr>
<tr>
<td>Volume:</td>
<td>900 mL</td>
<td></td>
</tr>
<tr>
<td>Temperature:</td>
<td>37°C ±0.5°C</td>
<td></td>
</tr>
</tbody>
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**Firm’s Proposed Specifications**

Not less than % of the labeled amount is dissolved in minutes

**Dissolution Testing Site**

Marksans Pharma Ltd.

<table>
<thead>
<tr>
<th>Study Ref No.</th>
<th>Testing Date</th>
<th>Product ID \ Batch No.</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage Units</th>
<th>Collection Times (minutes)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Marksans Pharma Ltd.’s Ibuprofen Capsules, 200 mg</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Study Report #: MV/AMV/DP/FH/011</td>
<td>Report date: 3rd May 2007</td>
<td>Lot # FH7006</td>
<td></td>
<td></td>
<td>1.69</td>
<td>41.35</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.9-2.2)</td>
<td>(8.9-87.6)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>21.5</td>
<td>55.3</td>
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<th>Product ID \ Batch No.</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage Units</th>
<th>Collection Times (minutes)</th>
<th>%CV</th>
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</thead>
<tbody>
<tr>
<td>Study Report #: MV/AMV/DP/FH/011</td>
<td>Report date: 3rd May 2007</td>
<td>Wyeth Consumer Healthcare’s Advil® Liqui-Gels® (solubilized Ibuprofen Capsules 200 mg)</td>
<td>200 mg Capsule</td>
<td>12</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot # B98587</td>
<td></td>
<td></td>
<td>2.43</td>
<td>45.55</td>
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<td>(1.4-5.9)</td>
<td>(5.7-87.6)</td>
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<td>50.4</td>
<td>66.4</td>
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</table>
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)

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

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

<table>
<thead>
<tr>
<th>Firm’s dissolution method</th>
<th>FDA-recommended method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Phosphate buffer, pH 7.2 Phosphate buffer, pH 7.2</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>900 900</td>
</tr>
<tr>
<td>USP Apparatus type</td>
<td>I (Basket) I (Basket)</td>
</tr>
<tr>
<td>Rotation (rpm)</td>
<td>150 150</td>
</tr>
<tr>
<td>Specification</td>
<td>Not less than (NLT) % (Q) in minutes Not less than (NLT) % (Q) in 20 minutes</td>
</tr>
</tbody>
</table>

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.
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 $\% (Q)$ in minutes differs from the FDA-recommended specification of NLT $\% (Q)$ 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.

<table>
<thead>
<tr>
<th>Medium:</th>
<th>Phosphate buffer, pH 7.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume:</td>
<td>900 mL</td>
</tr>
<tr>
<td>Temperature:</td>
<td>37°C ± 0.5°C</td>
</tr>
<tr>
<td>USP Apparatus:</td>
<td>1 (Basket)</td>
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<tr>
<td>Rotational Speed:</td>
<td>150 rpm</td>
</tr>
<tr>
<td>Sampling times:</td>
<td>5, 10, 15, 20, 30, and 45 minutes</td>
</tr>
<tr>
<td>Specification:</td>
<td>NLT $% (Q)$ in 20 minutes</td>
</tr>
</tbody>
</table>
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) % Q in 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 % (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

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

**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

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<td>☒</td>
<td>☒</td>
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<tr>
<td>Did the firm use the USP dissolution method</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>Did the firm use 12 units of both test and reference in dissolution testing</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>Did the firm conduct dissolution testing with its own proposed method</td>
<td>☒</td>
<td>☒</td>
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<td>Is FDA method in the public dissolution database (on the web)</td>
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<tr>
<td>Fed BE study</td>
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<tr>
<td>Other study</td>
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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.

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<tr>
<th>Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?</th>
<th>YES</th>
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If the LTSS is NOT sufficient please request the firm to provide the necessary data.
Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

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<td>Speed of Rotation:</td>
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<td>Medium:</td>
<td>Phosphate buffer pH 7.2</td>
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<td>Volume:</td>
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<tr>
<td>Temperature:</td>
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**Firm’s Proposed Specifications**

Not less than (b) % of the labeled amount is dissolved (b) (4) minutes

**Dissolution Testing Site**

Marksans Pharma Ltd.

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<tr>
<th>Study Ref No.</th>
<th>Testing Date</th>
<th>Product ID \ Batch No.</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage Units</th>
<th>Collection Times (minutes)</th>
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<th>Study Report Location</th>
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<tr>
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<td>5</td>
<td>10</td>
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<td>Ibuprofen Capsules, 200 mg</td>
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<td>Report date: 3rd May 2007</td>
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Study Report #: MV/AMV/DP/FH/011

Study Report Location

Module 5.3.1.3
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)

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<td>Division of System Files v 2.0. ANDA 078082 Review bioequivalence Biopharmaceutics N 078082 N 000 22-Dec-2005.</td>
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<td>Dissolution specification</td>
<td>Not less than (NLT) ( \geq 84% ) (Q) in 20 minutes</td>
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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.
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

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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

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

REVIEWER:

1. **Martin Shimer**
Chief, Reg. Support Branch
Contains GDEA certification: Yes ☐ No ☐
(required if sub after 6/1/92)
Determin. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD =Advil Liqui- NDA#20-402
Patent/Exclusivity Certification: Yes ☐ No ☐
If Para. IV Certification- did applicant Nothing Submitted
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days:Yes ☐ No ☐
Was case been settled: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Is applicant eligible for 180 day
Date settled:
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.

2. **Project Manager, Dat Doan**
Review Support Branch
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 _____

DRAFT Package

DATE27 May 2009 Initials MHS

FINAL Package

DATE 6/26/09 Initials rlw

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
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 ☐

Date5/27/09 Initials dd
Date Date
Initials _____

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 ☐
3. **Labeling Endorsement**

   Reviewer: Lee, Koung U  
   Date 6/26/09  
   Name/Initials:...

   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

---

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.**  
   Date 6/2/09
Chemistry Div. I II OR III InitialsRMP
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


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**
   Director, OGD
   Comments:
   - First Generic Approval ☐
   - PD or Clinical for BE ☐
   - Special Scientific or Reg.Issue ☐
   - Press Release Acceptable ☐

10. **Project Manager, Team Dat Doan**
   Review Support Branch
   Date 6/26/09
   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.

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**EER DATA:**

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*** Compliance Recommendations ***

MARKSANS PHARMA LIMITED

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**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:** MARKSAN 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

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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.

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
  Orange Book Data Updated Through May, 2009
  Patent and Generic Drug Product Data Last Updated: June 25, 2009
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN
INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content
of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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 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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------

Albert Mueller
9/5/2008 01:27:47 PM
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 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.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Dale Conner
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.

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, or protected from disclosure under applicable law.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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) \( \text{Q in } (b)^{(d)} \text{ minutes is not acceptable. Please provide your acknowledgment and acceptance of the following FDA-recommended dissolution method and specification:} \)

- **Medium:** Phosphate buffer, pH 7.2
- **Volume:** 900 mL
- **Temperature:** \( 37^\circ C \pm 0.5^\circ C \)
- **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:

- \( \text{NLT } (b)^{(d)} \% \text{ (Q) of the labeled amount of ibuprofen in the dosage form should be dissolved in 20 minutes.} \)

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

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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]" 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 to NMT % 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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------
Albert Mueller
2/14/2008 02:03:59 PM
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.
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BIOEQUIVALENCE DEFICIENCIES

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 D. 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 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

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

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

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

<table>
<thead>
<tr>
<th>Letter Date: AUGUST 30, 2007</th>
<th>Received Date: SEPTEMBER 4, 2007</th>
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<tr>
<td>Comments: EC - 1 YES</td>
<td>On Cards: YES</td>
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<tr>
<td>Therapeutic Code: 5030300 ACUTE PAIN, NON-OPIOID</td>
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</tr>
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</table>

Archival copy: PAPER (CTD FORMAT) Sections 1
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

<table>
<thead>
<tr>
<th>Reviewing CSO/CST</th>
<th>Rebekah Granger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>11/14/2007</td>
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</tbody>
</table>

Recommendation:
- ☐ FILE
- ☐ REFUSE to RECEIVE

ADDITIONAL COMMENTS REGARDING THE ANDA:
## MODULE 1
### ADMINISTRATIVE

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Status</th>
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<tbody>
<tr>
<td>1.1.2</td>
<td>Signed and Completed Application Form (356h) (original signature) (Check Rx/OTC Status) OTC</td>
<td>YES</td>
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<td>1.2</td>
<td>Cover Letter Dated: AUGUST 30, 2007</td>
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<td>1.3.2</td>
<td>Field Copy Certification (original signature) (N/A for E-Submissions)</td>
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<tr>
<td>1.3.3</td>
<td>Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Debarment Certification (original signature)</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>2. List of Convictions statement (original signature)</td>
<td></td>
</tr>
<tr>
<td>1.3.4</td>
<td>Financial Certifications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bioavailability/BIOeqivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455)</td>
<td>YES</td>
</tr>
<tr>
<td>1.3.5</td>
<td>Patent Information</td>
<td></td>
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<tr>
<td></td>
<td>Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations</td>
<td></td>
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<tr>
<td>1.3.5.1</td>
<td>Patent Certification</td>
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<tr>
<td></td>
<td>1. Patent number(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Paragraph: (Check all certifications that apply)</td>
<td></td>
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<tr>
<td></td>
<td>MOU □ PI □ PII □ PIII □ PIV □ (Statement of Notification)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Expiration of Patent(s): N/A</td>
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<tr>
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<td>a. Pediatric exclusivity submitted?</td>
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<tr>
<td></td>
<td>b. Expiration of Pediatric Exclusivity?</td>
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<tr>
<td></td>
<td>4. Exclusivity Statement: YES</td>
<td></td>
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</table>

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

<table>
<thead>
<tr>
<th>1.12.12</th>
<th>Comparison between Generic Drug and RLD-505(j)(2)(A)</th>
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</thead>
<tbody>
<tr>
<td>1. Conditions of use</td>
<td>SAME</td>
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<tr>
<td>2. Active ingredients</td>
<td>SAME</td>
</tr>
<tr>
<td>3. Inactive ingredients</td>
<td>JUSTIFIED</td>
</tr>
<tr>
<td>4. Route of administration</td>
<td>SAME</td>
</tr>
<tr>
<td>5. Dosage Form</td>
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<tr>
<td>6. Strength</td>
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</table>

| 1.12.14 | Environmental Impact Analysis Statement **YES** |

<table>
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<tr>
<th>1.12.15</th>
<th>Request for Waiver</th>
</tr>
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<tbody>
<tr>
<td>Request for Waiver of In-Vivo BA/BE Study(ies): Paper, NA</td>
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<table>
<thead>
<tr>
<th>1.14.1</th>
<th>Draft Labeling (Mult Copies N/A for E-Submissions)</th>
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<tbody>
<tr>
<td>1.14.1.1</td>
<td>4 copies of draft (each strength and container) <strong>YES</strong></td>
</tr>
<tr>
<td>1.14.1.2</td>
<td>1 side by side labeling comparison of containers and carton with all differences annotated and explained <strong>YES</strong></td>
</tr>
<tr>
<td>1.14.1.3</td>
<td>1 package insert (content of labeling) submitted electronically <strong>YES</strong></td>
</tr>
<tr>
<td><em><strong>Was a proprietary name request submitted? NO</strong></em></td>
<td></td>
</tr>
<tr>
<td>(If yes, send email to Labeling Reviewer indicating such)</td>
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</table>

**HOW SUPPLIED:**

- Bottles of 32 Capsules
- Bottles of 600 Capsules

<table>
<thead>
<tr>
<th>1.14.3</th>
<th>Listed Drug Labeling</th>
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<tbody>
<tr>
<td>1.14.3.1</td>
<td>1 side by side labeling (package and patient insert) comparison with all differences annotated and explained <strong>YES</strong></td>
</tr>
<tr>
<td>1.14.3.3</td>
<td>1 RLD label and 1 RLD container label <strong>YES</strong></td>
</tr>
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</table>
### Module 2 Summaries

#### 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/](http://www.fda.gov/cder/ogd/)

**Question based Review (QbR)**  **YES**

#### 2.3.5 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**

#### 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**
### 3.2.S DRUG SUBSTANCE

#### 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
4. CFN or FEI numbers

#### 3.2.S.3 Characterization
Refer to DMF

#### 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 mfr(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

#### 3.2.S.7 Stability
Refer to DMF

---

(b) (4)
<table>
<thead>
<tr>
<th>3.2.P.1</th>
<th>Description and Composition of the Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Unit composition: YES</td>
<td></td>
</tr>
<tr>
<td>2) Inactive ingredients are appropriate per IIG: YES</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.2.P.2</th>
<th>Pharmaceutical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Development Report: YES</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>3.2.P.3</th>
<th>Manufacture</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)</td>
<td></td>
</tr>
<tr>
<td>1. Name and Full Address(es) of the Facility(ies): YES</td>
<td></td>
</tr>
<tr>
<td>2. CGMP Certification: YES</td>
<td></td>
</tr>
<tr>
<td>3. Function or Responsibility: YES</td>
<td></td>
</tr>
<tr>
<td>4. CFN or FEI numbers:</td>
<td></td>
</tr>
<tr>
<td>3.2.P.3.2 Batch Formula: YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.3.3 Description of Manufacturing Process and Process Controls</td>
<td></td>
</tr>
<tr>
<td>1. Description of the Manufacturing Process: YES</td>
<td></td>
</tr>
<tr>
<td>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified: YES</td>
<td></td>
</tr>
<tr>
<td>3. If sterile product: Aseptic fill / Terminal sterilization</td>
<td></td>
</tr>
<tr>
<td>4. Reprocessing Statement: YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.3.4 Controls of Critical Steps and Intermediates: YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.3.5 Process Validation and/or Evaluation: YES</td>
<td></td>
</tr>
<tr>
<td>1. Microbiological sterilization validation</td>
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</tr>
<tr>
<td>2. Filter validation (if aseptic fill)</td>
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<table>
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<tr>
<th>3.2.P.4</th>
<th>Controls of Excipients (Inactive Ingredients)</th>
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</thead>
<tbody>
<tr>
<td>Source of inactive ingredients identified: YES</td>
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<tr>
<td>3.2.P.4.1 Specifications</td>
<td></td>
</tr>
<tr>
<td>1. Testing specifications (including identification and characterization): YES</td>
<td></td>
</tr>
<tr>
<td>2. Suppliers' COA (specifications and test results): YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.4.2 Analytical Procedures: YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.4.3 Validation of Analytical Procedures: YES</td>
<td></td>
</tr>
<tr>
<td>3.2.P.4.4 Justification of Specifications:</td>
<td></td>
</tr>
<tr>
<td>Applicant COA: YES</td>
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</tbody>
</table>
### 3.2.P DRUG PRODUCT

<table>
<thead>
<tr>
<th>3.2.P.5 Controls of Drug Product</th>
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<tbody>
<tr>
<td>3.2.P.5.1 Specification(s)</td>
<td>YES</td>
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<td>3.2.P.5.2 Analytical Procedures</td>
<td>YES</td>
</tr>
<tr>
<td>3.2.P.5.3 Validation of Analytical Procedures</td>
<td></td>
</tr>
<tr>
<td>Samples - Statement of Availability and Identification of:</td>
<td></td>
</tr>
<tr>
<td>1. Finished Dosage Form</td>
<td>YES</td>
</tr>
<tr>
<td>2. Same lot numbers</td>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.2.P.5.4 Batch Analysis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Certificate of Analysis for Finished Dosage Form</td>
<td>YES</td>
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</table>

| 3.2.P.5.5 Characterization of Impurities | YES |
| 3.2.P.5.6 Justification of Specifications | YES |

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<thead>
<tr>
<th>3.2.P.7 Container Closure System</th>
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<tbody>
<tr>
<td>1. Summary of Container/Closure System (if new resin, provide data)</td>
<td>YES</td>
</tr>
<tr>
<td>2. Components Specification and Test Data</td>
<td>YES</td>
</tr>
<tr>
<td>3. Packaging Configuration and Sizes</td>
<td>YES</td>
</tr>
<tr>
<td>4. Container/Closure Testing</td>
<td>YES</td>
</tr>
<tr>
<td>5. Source of supply and suppliers address</td>
<td>YES</td>
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<table>
<thead>
<tr>
<th>3.2.P.8 Stability (Finished Dosage Form)</th>
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<tbody>
<tr>
<td>1. Stability Protocol submitted</td>
<td>YES</td>
</tr>
<tr>
<td>2. Expiration Dating Period</td>
<td>YES – 24 MONTHS</td>
</tr>
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<table>
<thead>
<tr>
<th>3.2.P.8.2 Post-approval Stability and Conclusion</th>
<th></th>
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<tbody>
<tr>
<td>Post Approval Stability Protocol and Commitments</td>
<td>YES</td>
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</table>

<table>
<thead>
<tr>
<th>3.2.P.8.3 Stability Data</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. 3 month accelerated stability data</td>
<td>YES</td>
</tr>
<tr>
<td>2. Batch numbers on stability records the same as the test batch</td>
<td>YES – Lot #FH7006</td>
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### 3.2.R Regional Information

<table>
<thead>
<tr>
<th>3.2.R (Drug Substance)</th>
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</thead>
<tbody>
<tr>
<td>3.2.R.1.S Executed Batch Records for drug substance (if available)</td>
<td>Refer to DMF</td>
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<tr>
<td>3.2.R.2.S Comparability Protocols</td>
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<tr>
<td>3.2.R.3.S Methods Validation Package</td>
<td>YES</td>
</tr>
<tr>
<td>Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)</td>
<td></td>
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<tr>
<td>(Required for Non-USP drugs)</td>
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</table>

MODULE 3

3.2.R Regional Information

ACCEPTABLE
### MODULE 3
#### 3.2.R Regional Information

<table>
<thead>
<tr>
<th>3.2.R (Drug Product)</th>
<th>3.2.R.1.P.1</th>
<th>Executed Batch Records</th>
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<tbody>
<tr>
<td></td>
<td>Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation</td>
<td>YES – See Attached</td>
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<table>
<thead>
<tr>
<th>3.2.R.1.P.2</th>
<th>Information on Components</th>
<th>YES</th>
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<tr>
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<th>Comparability Protocols</th>
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<th>3.2.R.3.P</th>
<th>Methods Validation Package</th>
<th>YES</th>
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<tr>
<td></td>
<td>Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)</td>
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### MODULE 5
#### CLINICAL STUDY REPORTS

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<thead>
<tr>
<th>5.2</th>
<th>Tabular Listing of Clinical Studies</th>
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<td>E-Submission: PDF YES</td>
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<td></td>
<td>Word Processed e.g., MS Word YES</td>
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<table>
<thead>
<tr>
<th>5.3.1</th>
<th>Bioavailability/Bioequivalence</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1. Formulation data same?</td>
</tr>
<tr>
<td></td>
<td>a. Comparison of all Strengths (check proportionality of multiple strengths)</td>
</tr>
<tr>
<td></td>
<td>b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v)</td>
</tr>
<tr>
<td></td>
<td>2. Lot Numbers of Products used in BE Study(ies): RLD: B98587 ANDA: FH7006</td>
</tr>
<tr>
<td></td>
<td>3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)</td>
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<th>5.3.1.2</th>
<th>Comparative BA/BE Study Reports</th>
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<td></td>
<td>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES</td>
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<td>2. Summary Bioequivalence tables:</td>
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<td></td>
<td>Table 10. Study Information YES</td>
</tr>
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<td></td>
<td>Table 12. Dropout Information YES</td>
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<td>Table 13. Protocol Deviations YES</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5.3.1.3</th>
<th>In Vitro-In-Vivo Correlation Study Reports</th>
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<tr>
<td></td>
<td>1. Summary Bioequivalence tables:</td>
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<tr>
<td></td>
<td>Table 11. Product Information YES</td>
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<td>Table 16. Composition of Meal Used in Fed Bioequivalence Study YES</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5.3.1.4</th>
<th>Reports of Bioanalytical and Analytical Methods for Human Studies</th>
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<tbody>
<tr>
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<td>1. Summary Bioequivalence table:</td>
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<tr>
<td></td>
<td>Table 9. Reanalysis of Study Samples YES</td>
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<tr>
<td></td>
<td>Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES</td>
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<tr>
<td></td>
<td>Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES</td>
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<tr>
<th>5.3.7</th>
<th>Case Report Forms and Individual Patient Listing</th>
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</table>

<table>
<thead>
<tr>
<th>5.4</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Type</td>
<td>IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 200 MG</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)</td>
<td>YES</td>
</tr>
<tr>
<td>2. EDR Email: Data Files Submitted:</td>
<td>YES SENT TO EDR</td>
</tr>
<tr>
<td>3. In-Vitro Dissolution:</td>
<td>YES</td>
</tr>
</tbody>
</table>

Updated 10/10/2006 C. Bina
<table>
<thead>
<tr>
<th>Number</th>
<th>Approved?</th>
<th>Active Ingredient</th>
<th>Formulation</th>
<th>Brand Name</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>020402</td>
<td>Yes</td>
<td>IUPROFEN</td>
<td>Capsule; Oral</td>
<td>ADVIL LIQUI-GELS</td>
<td>WYETH CON</td>
</tr>
<tr>
<td>020690</td>
<td>Yes</td>
<td>IUPROFEN</td>
<td>Suspension/Drops; 40mg/ml Oral</td>
<td>CHILDREN'S MOTRIN MCNEIL CON</td>
<td></td>
</tr>
<tr>
<td>075217</td>
<td>No</td>
<td>IUPROFEN</td>
<td>Suspension/Drops; 40mg/ml Oral</td>
<td>IUPROFEN</td>
<td>PERRIGO</td>
</tr>
<tr>
<td>020812</td>
<td>Yes</td>
<td>IUPROFEN</td>
<td>Suspension/Drops; 100mg/2.5ml Oral</td>
<td>PEDIATRIC ADVIL</td>
<td>WYETH CON</td>
</tr>
<tr>
<td>074916</td>
<td>No</td>
<td>IUPROFEN</td>
<td>Suspension; Oral 100mg/5ml</td>
<td>IUPROFEN</td>
<td>ACTAVIS MID ATLANTIC</td>
</tr>
<tr>
<td>021604</td>
<td>No</td>
<td>IUPROFEN</td>
<td>Suspension; Oral 100mg/5ml</td>
<td>CHILDREN'S ELIXSURE</td>
<td>ALTERNATIV-CHP LLC</td>
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<tr>
<td>020510</td>
<td>Yes</td>
<td>IUPROFEN</td>
<td>Suspension; Oral 100mg/5ml</td>
<td>CHILDREN'S MOTRIN MCNEIL</td>
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<tr>
<td>074937</td>
<td>No</td>
<td>IUPROFEN</td>
<td>Suspension; Oral 100mg/5ml</td>
<td>CHILDREN'S IUPROFEN</td>
<td>PERRIGO</td>
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<tr>
<td>020589</td>
<td>No</td>
<td>IUPROFEN</td>
<td>Suspension; Oral 100mg/5ml</td>
<td>CHILDREN'S ADVIL</td>
<td>WYETH CON</td>
</tr>
</tbody>
</table>
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 18, 2000
Reference Listed Drug: 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.

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

Print
### Table 3: 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{tot}</td>
<td>63.70</td>
<td>68.13</td>
<td>93.30</td>
<td>90.00-97.12</td>
</tr>
<tr>
<td>AUC_{m}</td>
<td>65.66</td>
<td>69.98</td>
<td>93.82</td>
<td>90.62-97.14</td>
</tr>
<tr>
<td>C_{max}</td>
<td>24.93</td>
<td>26.47</td>
<td>94.19</td>
<td>86.85-102.15</td>
</tr>
</tbody>
</table>

#### Ibuprofen Soft Gelatin Capsules 200 mg
**Dose (1x 200mg Capsule)**
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{tot}</td>
<td>52.71</td>
<td>54.85</td>
<td>96.10</td>
<td>92.90-99.41%</td>
</tr>
<tr>
<td>AUC_{m}</td>
<td>56.13</td>
<td>58.09</td>
<td>96.62</td>
<td>93.24-100.14%</td>
</tr>
<tr>
<td>C_{max}</td>
<td>11.67</td>
<td>12.36</td>
<td>94.59</td>
<td>87.98-101.28%</td>
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Table 6 Formulation Data:

Ibuprofen Soft Gelatin Capsules, 200 mg:

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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Pharmacopoeial reference</th>
<th>mg / capsule</th>
<th>% per capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Ibuprofen</td>
<td>USP</td>
<td>500.00</td>
<td>(b) (4)</td>
<td>Active ingredient</td>
</tr>
</tbody>
</table>
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Martin Shimer
11/16/2007 09:22:12 AM
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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