CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78682Orig1s020

Name: Ibuprofen Capsules, 200 mg (OTC)

Sponsor: Bionpharma Inc

Approval Date: March 24, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78682Orig1s020

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Reviews / Information Included in this Review

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Labeling	**X**
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78682Orig1s020

APPROVAL LETTER

ANDA 078682/S-020

PRIOR APPROVAL SUPPLEMENT APPROVAL

Bionpharma Inc.
600 Alexander Road
Suite 2-4 B
Princeton, NJ 08540
Attention: Usha Sankaran
Associate Vice President, Regulatory Affairs

Dear Sir or Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on September 10, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Ibuprofen Capsules, 200 mg (OTC).

Reference is also made to the complete response letter issued by this office on March 8, 2019, and to any amendments thereafter.

The sANDA, submitted as “Prior Approval Supplement," provides for:

> Addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product.

We have completed the review of this sANDA, as amended, and it is approved.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Office of Generic Drugs should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Office of Generic Drugs in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the

strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions [1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, USPHS
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Catherine Poole

Digitally signed by Catherine Poole
Date: 11/12/2019 01:43:22PM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78682Orig1s020

LABELING

†Compare to the active ingredient in Advil® LIQUI-GELS®

NDC 69452-238-06

Ibuprofen Capsules, 200 mg

Pain Reliever/ Fever Reducer (NSAID)

mini capsule

Softgels**
**Liquid filled capsules

8 Capsules

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

DO NOT USE IF TAMPER-EVIDENT SEAL UNDER BOTTLE CAP IMPRINTED WITH "*SEALED for YOUR PROTECTION*" IS BROKEN OR MISSING.

Uses

- temporarily relieves minor aches and pains due to: headache, muscular aches, menstrual cramps, the common cold, backache, toothache, minor pain of arthritis.
- 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, 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: hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. 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.
- **Stomach bleeding warning:** This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause severe 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 prescription or nonprescription NSAIDs (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.

Manufactured for:
Biomphama Inc.
600 Alexander Road,
Princeton, NJ 08540

Rev # 11/18
Lot No.:
Exp. Date:

PEEL HERE

FOLD PROOF ALONG DOTTED LINE

to simulate an actual printed label layout

- **Heart attack and stroke warning:** NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher 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**
- 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**

Questions or comments?

call toll free **1-888-235-2466**

† All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Advil® LIQUI-GELS®.

(b) (4)

Label Size : 2" x 5.625"

Track : (b) (4)

(b) (4)

NOT OFFICIAL SIZE/DIELINE

(b) (4)

9.4375 x 8.59375 Flat
2.03125 x 2.03125 x 3.875

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- **do not take more than directed** - **the smallest effective dose should be used**
- 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. Keep carton. - store at 20° to 25°C (68° to 77°F)
- avoid excessive heat above 40°C (104°F). Protect from light.

Inactive ingredients FD&C Blue #1, gelatin, glycerin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan and sorbitol

Questions or comments? call toll free **1-888-235-2466**

NDC 69452-238-06

†Compare to the active ingredient in Advil® LIQUI-GELS®

NEW
Smaller Capsule
Same Strength

Ibuprofen Capsules, 200 mg

Pain Reiever/Fever Reducer (NSAID)

mini capsule

Softgels**
**Liquid filled capsules

8 Capsules

Ibuprofen
Capsules, 200 mg
Pain Reiever/Fever Reducer (NSAID)
mini capsule
Softgels**
**Liquid filled capsules
8 Capsules

DO NOT USE IF TAMPER-EVIDENT SEAL UNDER BOTTLE CAP IMPRINTED WITH "SEALED for YOUR PROTECTION" IS BROKEN OR MISSING.

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

(b) (4)

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: - headache - toothache - backache - menstrual cramps - the common cold - muscular aches - minor pain of arthritis
- temporarily reduces fever

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: - hives - facial swelling - asthma (wheezing) - shock - skin reddening - rash - blisters
If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs [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

Drug Facts (continued)

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer 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
- stomach bleeding warning applies to you - you have problems or serious side effects from taking pain relievers or fever reducers - you have a history of stomach problems, such as heartburn - you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke - you are taking a diuretic

Ask a doctor or pharmacist before use if you are - 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

Stop use and ask a doctor if - you experience any of the following signs of stomach bleeding:
- feel faint - vomit blood - have bloody or black stools - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
- chest pain - trouble breathing - weakness in one part or side of body - slurred speech - leg swelling
- pain gets worse or lasts more than 10 days - fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area - any new symptoms appear

Manufactured for: **Bionpharma Inc.**
600 Alexander Road, Princeton, NJ 08540

3 69452 23806 6

Rev # 11/18
Lot No.:
Exp. Date:

†All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Advil® LIQUI-GELS®.

Carton Size : 2.031" x 2.031" x 3.875"
Track : (b) (4)
(b) (4)

(b) (4)

(b) (4)

NOT OFFICIAL SIZE/DIELINE

†Compare to the active ingredient in Advil® LIQUI-GELS®

NDC 69452-238-83

NEW
Smaller Capsule
Same Strength

Ibuprofen Capsules, 200 mg

Pain Reliever/Fever Reducer (NSAID)

mini capsule

Softgels**
**Liquid filled capsules

300 Capsules

DO NOT USE IF TAMPER-EVIDENT SEAL UNDER BOTTLE CAP IMPRINTED WITH *"SEALED for YOUR PROTECTION"* IS BROKEN OR MISSING.

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:
  - headache
  - toothache
  - backache
  - menstrual cramps
  - the common cold
  - muscular aches
  - minor pain of arthritis
- temporarily reduces fever

Warnings

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

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

Stomach bleeding warning: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs (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

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer 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
- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are
- 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

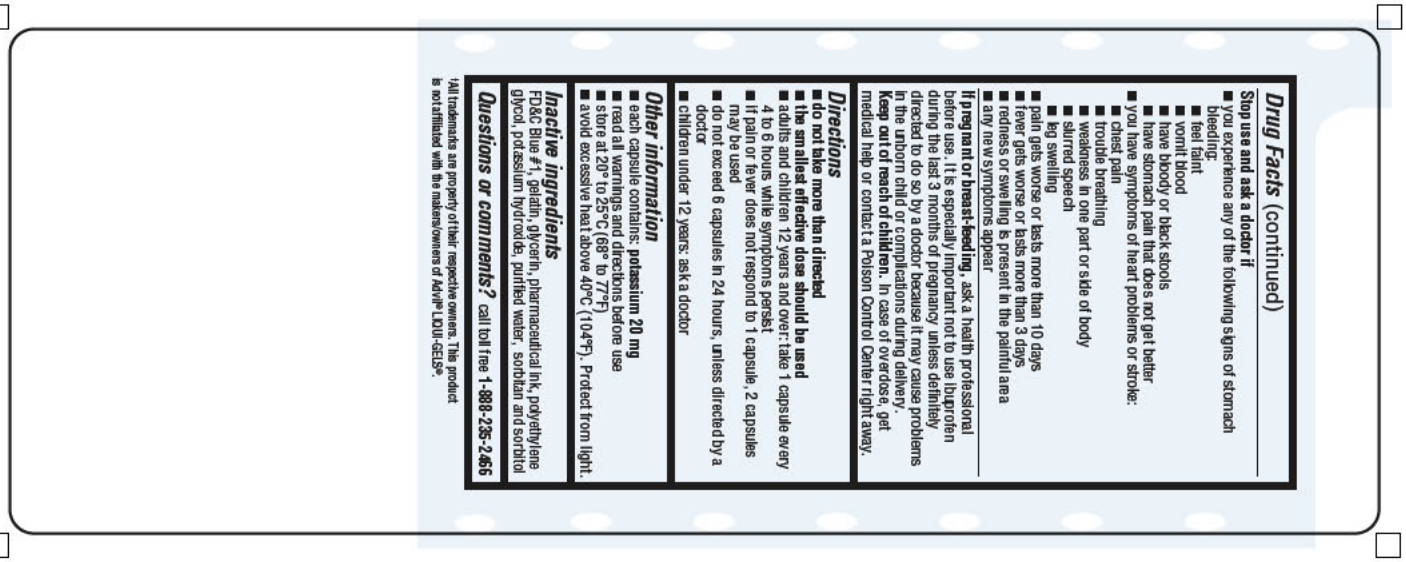
When using this product
- take with food or milk if stomach upset occurs

Manufactured for:
Bionpharma Inc.
600 Alexander Road,
Princeton, NJ 08540
Rev # 11/18

3 69452 23883 7

Lot No.:
Exp. Date:

PEEL HERE



Drug Facts (continued)

Stop use and ask a doctor if
- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
  - chest pain
  - trouble breathing
  - weakness in one part or side of body
  - slurred speech
  - leg swelling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

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

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

Directions
- **do not take more than directed**
- **the smallest effective dose should be used**
- 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). Protect from light.

Inactive ingredients
FD&C Blue #1, gelatin, glycerin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan and sorbitol

Questions or comments? call toll free **1-888-235-2466**

†All trademarks are property of their respective owners. This product is not affiliated with the makers/owners of Advil® LIQUI-GELS®.

(b) (4)

Label Size : 2.62" x 7.12"

Track : (b) (4)

(b) (4)

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78682Orig1s020

LABELING REVIEWS

***** This document contains proprietary information that cannot be released to the public***v.40**

SUPPLEMENT LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of this Review	2/1/2019
Review Cycle Number	2
ANDA(s) and Supplement Number(s)	078682/**S-020**, S-016 and S-021
Applicant Name	Bionpharma Inc.
Proprietary Name, Established Name, and Strength(s) [Add "(OTC)" after strength if applicable]	Ibuprofen Capsules, 200 mg (OTC)
Current Received Date	12/3/2018
Previous Received Date(s) of Proposed Supplement	S-020: 9/26/2018; 9/10/2018 S-016: 8/28/2017 S-021: 11/6/2018
Primary Labeling Reviewer	Oluwakemi O. Odesina
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE - No Comments.

☐ ACCEPTABLE - Include Post approval comments.

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

☐ **For labeling supplement(s):**

This Changes Being Effected supplemental abbreviated new drug CLICK HERE

We have completed the review of this supplemental application. Choose an item. effective on the date of this letter. Choose an item.

OR

We have completed the review of your applications and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address

1. CONTAINER LABEL
2. CARTON LABELING
3. PRESCRIBING INFORMATION
4. MEDICATION GUIDE
5. STRUCTURED PRODUCT LABELING (SPL)

☒ **For combined supplement(s):**

.

The Division of Labeling Review has no comments. Labeling is acceptable.

Contents

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in DLR's SharePoint Drug Facts? If Yes, please explain:	**NO**
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint? If Yes, please explain:	**NO**
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? **https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm**	NO

Reason for Submission:

- **12/3/2018 Ammendment:**

The below comments are from the C1 labeling review based on the submission dated 9/26/2018

To facilitate
container/carto
1, Section 1.1

Please refer t
changes.

The Applicant has made the requested revisions; we find it acceptable.

- **Original Submission:**

S-020 (PAS)

thi

S-021 (CBE)

As pe
Supp
consi
Migr

S-016 (CBE)

Bionpharma is hereby submitting a CBE-0 Labeling Supplement to revise the labeling for its Ibuprofen Capsules, 200 mg, to be in line with the revised labeling approved for the Reference Listed Drug, Advil® Liqui-Gels®, (NDA 020402, S-043) on August 8, 2017. The revised labeling is provided in m1 1.14.1.1. A side-by-side comparison of the revised labeling and the updated RLD labeling is provided in m1 1.14.1.2. The submission also includes the labeling history in m1 1.14.1.5 which summarizes the changes made to the labeling. As the labeling has been revised in line with the RLD, side-by-side comparison of the revised labeling with the previous approved labeling is not relevant and hence not included.

Is this supplement combined with another discipline?	**YES (S-020_**
Is this product an OTC product?	**YES**
Is this ANDA the RLD?	**NO**

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

2.1 MATERIALS REVIEWED

Tables 1 and 2 provide a summary of recommendations for each material analyzed in this review.

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	S-016 (Pain Reliever/Fever Reducer)	08/28/2017 11/06/2018	Satisfactory

		• Blue Colored Capsules 8's, 20's, 200's, 240's, 300's Bottle Label • Orange Colored Capsules 8's, 20's, 200's, 240's 300's Bottle Label • Clear Capsules 8's 20's, 200's, 240's, 300's Bottle Label --- **S-021 (Migraine)** 20's Bottle Label --- **S-020 (Minis)** 8's, 300's Bottle Label	**12/3/2018**	
Pouch	Draft	**S-016 (Pain Reliever/Fever Reducer)** • Blue Colored Capsules 2's Pouch Label • Orange Colored Capsules 2's Pouch Label • Clear Capsules 2's Pouch Label	**08/28/2017**	Satisfactory
Carton	Draft	**S-016 (Pain Reliever/Fever Reducer)**	**08/28/2017** **11/06/2018**	Satisfactory

		• Blue Colored Capsules 4's Pouch Carton 20's Bottle Carton • Orange Colored Capsules 4's Pouch Carton 20's Bottle Carton • Clear Capsules 4's Pouch Carton 20's Bottle Carton --- **S-021 (Migraine)** 20 Capsules per Carton --- **S-020 (Minis)** 8 capsules per carton	12/3/2018	
(Other – specify)	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

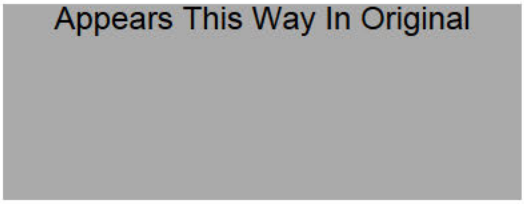
Table 2 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Medication Guide	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

2.2 MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

Table 3: Review Model Labeling for Prescribing Information, Patient Labeling, and Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)



☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 020402/S-042; 020402/S-043

Supplement Approval Date: 03/08/2017; 08/08/2018

Proprietary Name: Advil Liqui-Gels Minis; Advil Liqui-Gels

Established Name: Solubilized Ibuprofen Capsules

Description of Supplement:

S-042

This "Prior Approval" supplemental new drug application proposes a new line extension product for a smaller liquid-filled capsule (identified as minis) as compared to the currently approved Advil® Liqui-Gels®.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We remind you to remove the 'NEW' flag from the statement "NEW Smaller Capsule" on the principal display panel 6 months after introduction to the marketplace.

S-043

This "Prior Approval" supplemental new drug application provides for the following changes:

- the addition of heart attack and stroke warning information to all Advil® LIQUI-GELS® and Advil® Migraine labels
- the addition of medication overuse headache warning information to the Advil® Migraine labels
- updates to the graphics on the principal display panel
- updates to the net quantity statement on the 2-count immediate container (pouch) label
- minor revisions to immediate container and carton labels (e.g., inactive ingredients revisions, update copyright and patent information)
- new bonus labeling (e.g., 100-, 180- child resistant, 180- non-child resistant count sizes)
- the addition of two instantly redeemable coupons for the Advil® Migraine 20- and 80-count cartons
- the removal of the 4-count carton (hang card), 8-count carton, 120-count carton, and 240-count immediate container (standalone bottle) labels approved in Supplement 025

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the following revisions listed below:

(b) (4)

Table 3: Review Model Labeling for Prescribing Information, Patient Labeling, and Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
****We note that the Applicant's proposed S-021 is to be in accordance with the RLD's S-043 and proposed S-020 is to be in accordance with the RLD's S-042. We note that approved RLD labeling for S-046 and S-047 approved on 8/2/2018 and 8/31/2018 respectively provide for: S-046 This "Prior Approval" supplemental new drug application proposes a new $1.00 instantly redeemable coupon (IRC) to be placed on the approved 40-count carton. We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. S-047 This "Prior Approval" supplemental new drug application provides for an alternate 8-count immediate container label to accompany previously approved small and large backer cards. We note that these supplements do not provide for changes to the Drug Facts Labeling.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **NO**
If yes, then comment below regarding the current model labeling.

Comment:

2.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/1/2019.

Are there any remaining unexpired patents or marketing exclusivities for Model Labeling? **NO**

If YES go to the Table 4 and assessments below.

Table 4 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling (020402) and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 4: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
NA					

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling				
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
NA				

Reviewer Assessment:

Are there any recently expired patents or exclusivities? **NO**
If yes, did these patents or exclusivities have any labeling impact? **N/A**

Comment:

2.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 2/1/2019.

Table 6: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labels/labeling? **NA**

Comment:

2.5 HISTORY OF ANDA

We evaluated previously approved and pending supplements (Table 7) to determine if actions are needed for the current review.

Table 7: Labeling History of ANDA		
Original or Supplement	**Approval Date**	**What post approval changes were requested and were the changes addressed?**
S-012	07/31/2013	None
Are there any Pending Labeling Supplements for this ANDA that impact labeling? NO		
Pending Supplement	**Submission Date**	**Labeling Impact**

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1 CONTAINER AND CARTON LABELS

Reviewer Assessment:

Were container or carton labels submitted in this supplement? **YES**
If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Comment:

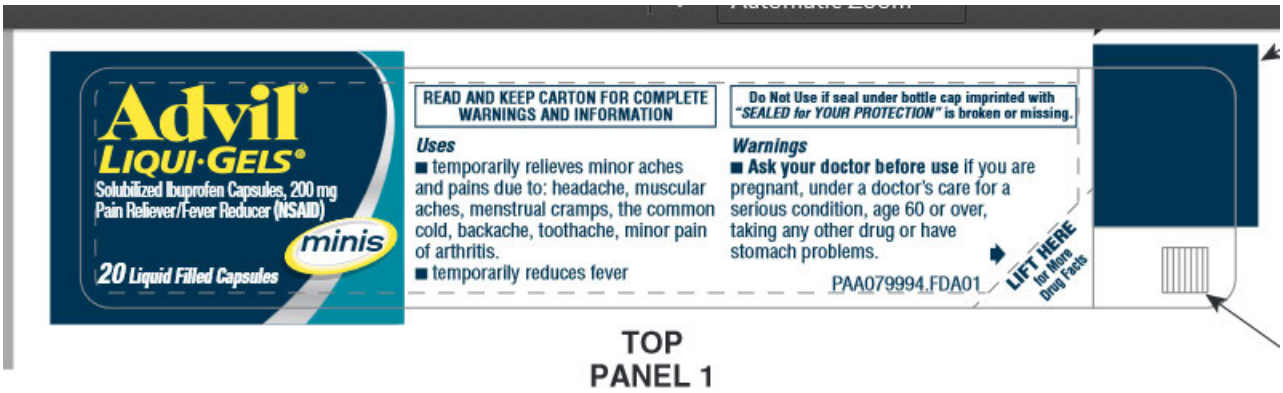
We note that this is an OTC drug product; the Applicant has submitted revised labeling in accordance with the RLD's approved S-042 and S-043; we find it acceptable.

3.1.1 MODEL CONTAINER LABELS

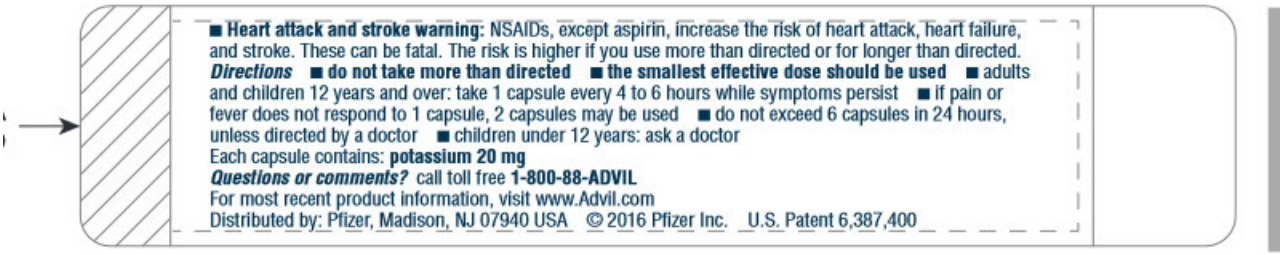
Please provide the reference listed drug labels if applicant submits container, blister, carton, etc.

Model container/carton/blister labels [Source: Drugs@FDA]

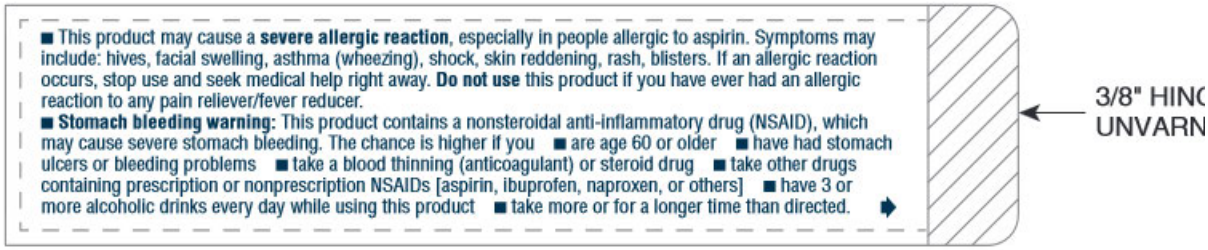
NDA 020402/S-042 approved on 03/08/2017

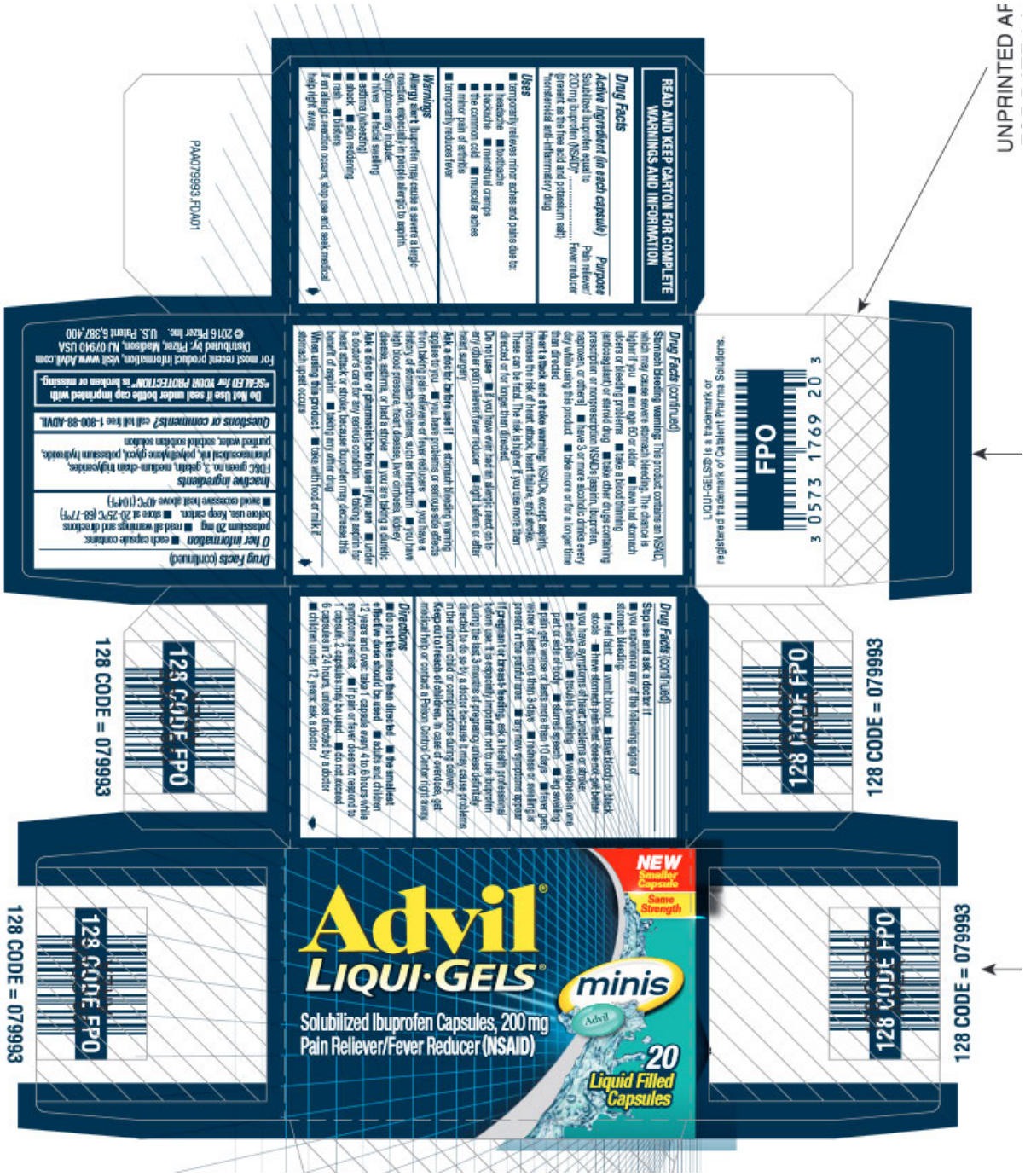


TOP
PANEL 1



BASE
PANEL 3

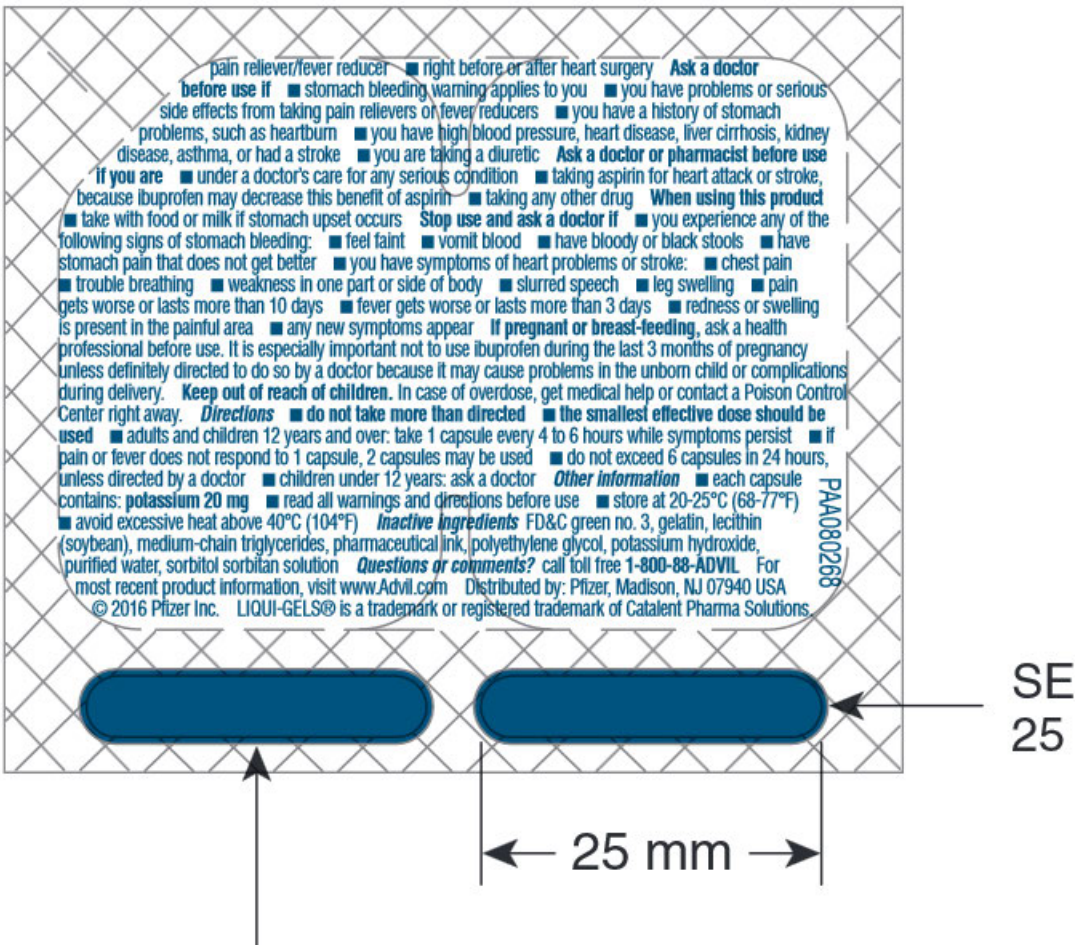




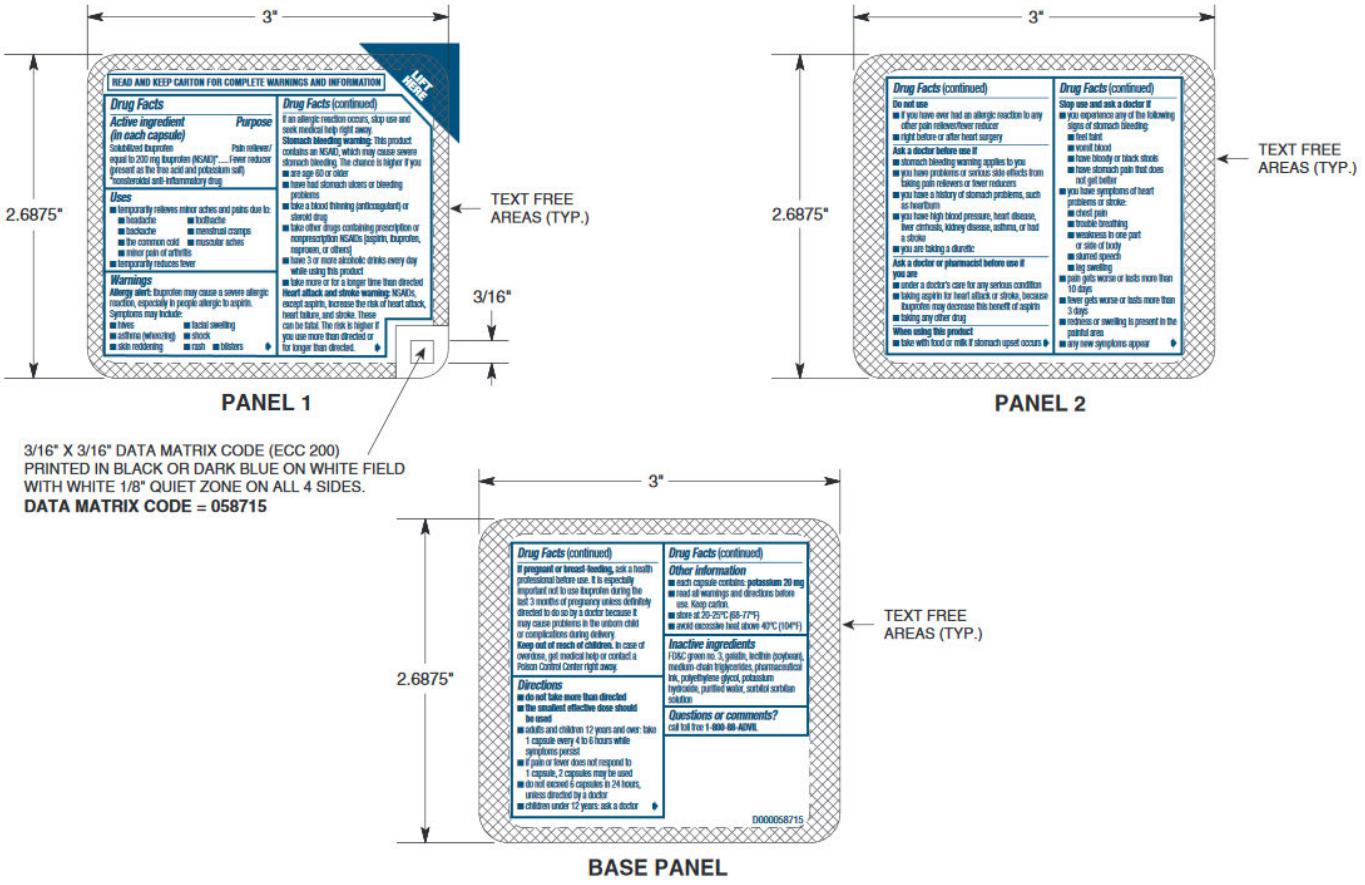
NDA 020402/S-043 approved on 08/08/2017

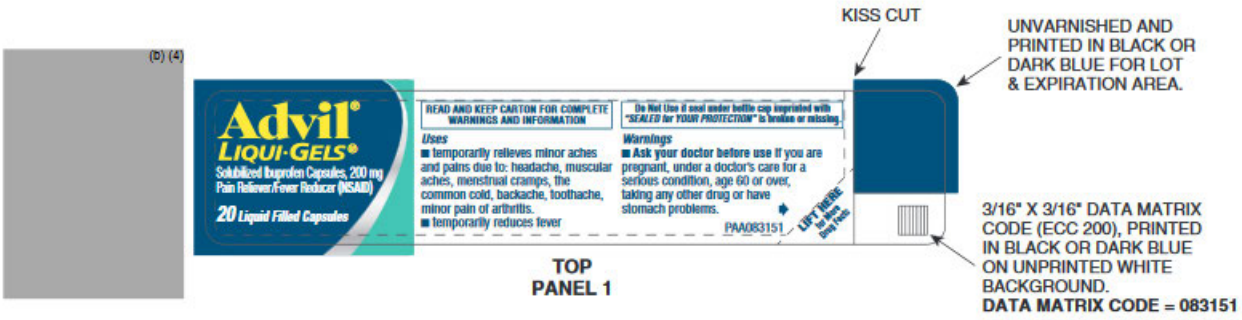

Advil®
LIQUI-GELS®
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
2 Liquid Filled Capsules
Active Ingredient (in each capsule)
Purpose
Solubilized ibuprofen equal to 200 mg (present as the free acid and potassium salt)
Pain reliever/ ibuprofen (NSAID)* .....Fever reducer
*nonsteroidal anti-inflammatory drug
Uses
■ temporarily relieves minor aches and pains due to: ■ headache ■ toothache ■ backache ■ menstrual cramps ■ the common cold ■ muscular aches ■ minor pain of arthritis
■ temporarily reduces fever
Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: ■ hives ■ facial swelling ■ asthma (wheezing) ■ shock ■ skin reddening ■ rash ■ blisters If an allergic reaction occurs, stop use and seek medical help right away. Stomach bleeding warning: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs [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 Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed. Do not use ■ if you have ever had an allergic reaction to any other
TO OPEN: FOLD BACK ON DOTTED LINE.
TEAR ON ARROW OR USE SCISSORS.
Do Not Use if pouch is broken or torn.
PAA080267

BACK

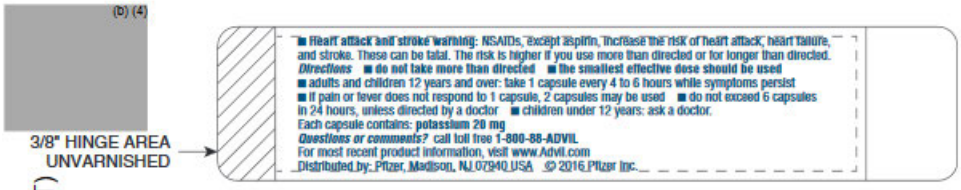

pain reliever/fever reducer ■ right before or after heart surgery **Ask a doctor before use if** ■ stomach bleeding warning applies to you ■ you have problems or serious side effects from taking pain relievers or fever reducers ■ you have a history of stomach problems, such as heartburn ■ you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke ■ you are taking a diuretic **Ask a doctor or pharmacist before use if you are** ■ 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 **Stop use and ask a doctor if** ■ you experience any of the following signs of stomach bleeding: ■ feel faint ■ vomit blood ■ have bloody or black stools ■ have stomach pain that does not get better ■ you have symptoms of heart problems or stroke: ■ chest pain ■ trouble breathing ■ weakness in one part or side of body ■ slurred speech ■ leg swelling ■ pain gets worse or lasts more than 10 days ■ fever gets worse or lasts more than 3 days ■ redness or swelling is present in the painful area ■ any new symptoms appear **If pregnant or breast-feeding,** ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away. ***Directions*** ■ **do not take more than directed** ■ **the smallest effective dose should be used** ■ 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 20-25°C (68-77°F) ■ avoid excessive heat above 40°C (104°F) ***Inactive ingredients*** FD&C green no. 3, gelatin, lecithin (soybean), medium-chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitol sorbitan solution ***Questions or comments?*** call toll free **1-800-88-ADVIL** For most recent product information, visit www.Advil.com Distributed by: Pfizer, Madison, NJ 07940 USA
© 2016 Pfizer Inc. LIQUI-GELS® is a trademark or registered trademark of Catalent Pharma Solutions.
PAA080268
SE
25
25 mm


(2) 2 ct PACKETS
Advil
LIQUI-GELS
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
4
Liquid Filled
Capsules
FPO
3 0573 1769 04 3
Do Not Use if the sealed child resistant
pouch is broken or torn.
For most recent product information, visit www.Advil.com
Pfizer, Madison, NJ 07940 USA © 2017 Pfizer Inc.
D000057830
128 CODE = 057830
FPO 128 CODE
AREA
AREA FOR LOT AND
EXPIRATION DATE
128 CODE = 057830
HIGH DENSITY CODE 128,

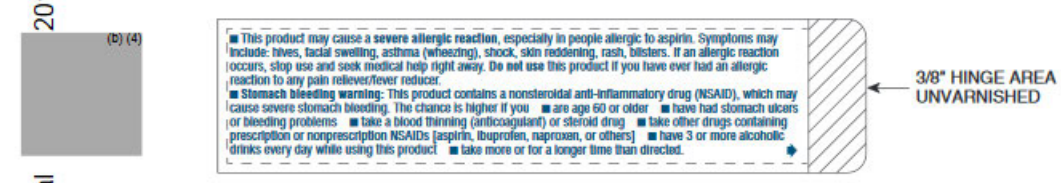

3"
2.6875"
READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION
LIFT HERE
Drug Facts
Active ingredient (in each capsule)
Purpose
Solubilized ibuprofen
Pain reliever/ equal to 200 mg ibuprofen (NSAID)* ..... Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug
Uses
■ temporarily relieves minor aches and pains due to:
■ headache ■ toothache
■ backache ■ menstrual cramps
■ the common cold ■ muscular aches
■ minor pain of arthritis
■ temporarily reduces fever
Warnings
Allergy alert: ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include:
■ hives ■ facial swelling
■ asthma (wheezing) ■ shock
■ skin reddening ■ rash ■ blisters
Drug Facts (continued)
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warnings: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs (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
Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.
TEXT FREE AREAS (TYP.)
3/16"
PANEL 1
3/16" X 3/16" DATA MATRIX CODE (ECC 200)
PRINTED IN BLACK OR DARK BLUE ON WHITE FIELD
WITH WHITE 1/8" QUIET ZONE ON ALL 4 SIDES.
DATA MATRIX CODE = 058715
3"
2.6875"
Drug Facts (continued)
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
■ stomach bleeding warning applies to you
■ you have problems or serious side effects from taking pain relievers or fever reducers
■ you have a history of stomach problems, such as heartburn
■ you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
■ you are taking a diuretic
Ask a doctor or pharmacist before use if you are
■ 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
Drug Facts (continued)
Stop use and ask a doctor if
■ you experience any of the following signs of stomach bleeding:
■ feel faint
■ vomit blood
■ have bloody or black stools
■ have stomach pain that does not get better
■ you have symptoms of heart problems or stroke:
■ chest pain
■ trouble breathing
■ weakness in one part or side of body
■ slurred speech
■ leg swelling
■ pain gets worse or lasts more than 10 days
■ fever gets worse or lasts more than 3 days
■ redness or swelling is present in the painful area
■ any new symptoms appear
TEXT FREE AREAS (TYP.)
PANEL 2
3"
2.6875"
Drug Facts (continued)
If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
■ do not take more than directed
■ the smallest effective dose should be used
■ adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
■ if pain or fever does not respond to 1 capsule, 2 capsules may be used
■ do not exceed 6 capsules in 24 hours, unless directed by a doctor
■ children under 12 years: ask a doctor
Drug Facts (continued)
Other information
■ each capsule contains: potassium 20 mg
■ read all warnings and directions before use. Keep carton
■ store at 20-25°C (68-77°F)
■ avoid excessive heat above 40°C (104°F)
Inactive ingredients
FD&C green no. 3, gelatin, lecithin (soybean), medium-chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitol sorbitan solution
Questions or comments?
call toll free 1-800-88-ADVIL
D000058715
TEXT FREE AREAS (TYP.)
BASE PANEL



TOP PANEL 1



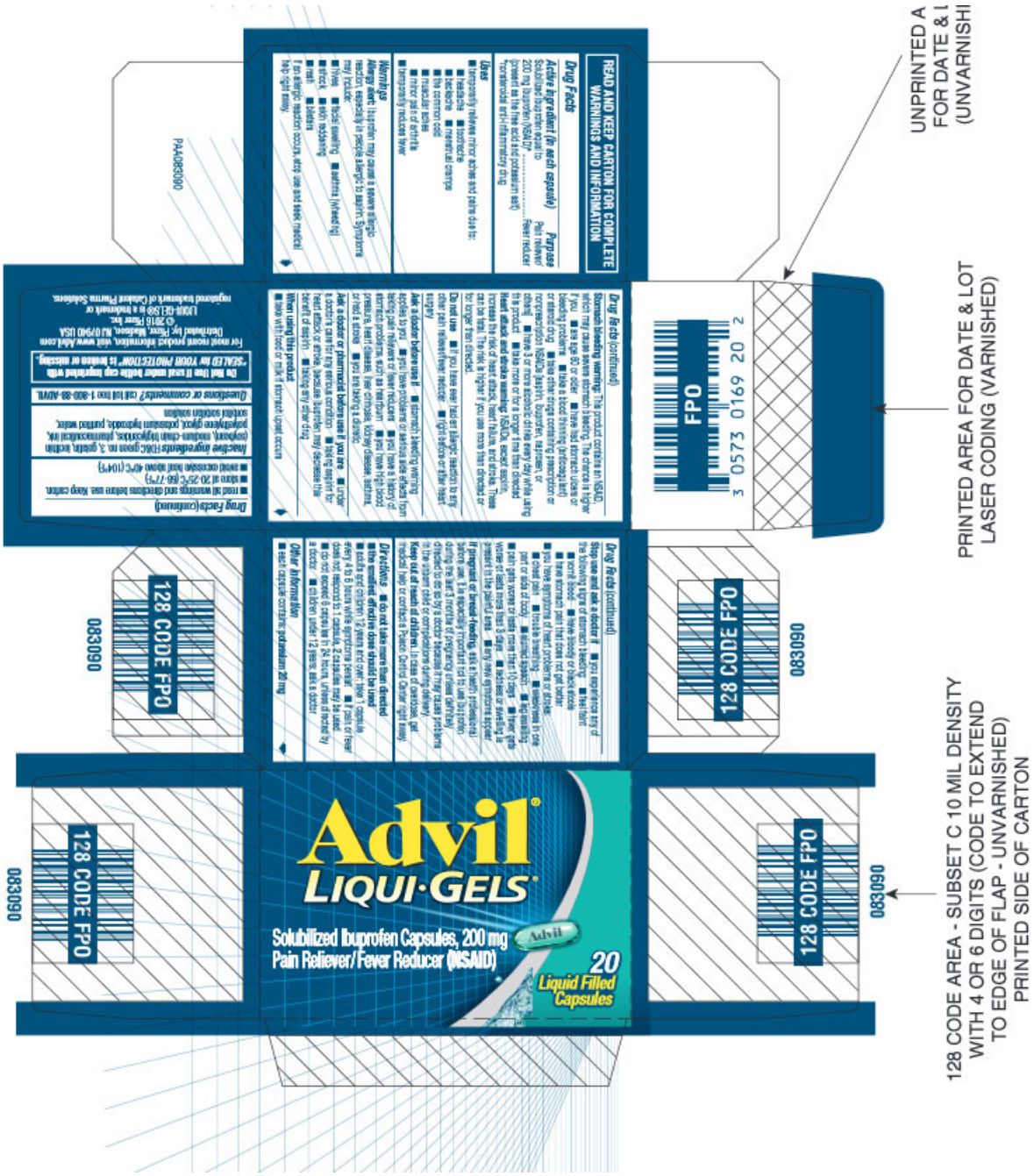
BASE PANEL 3

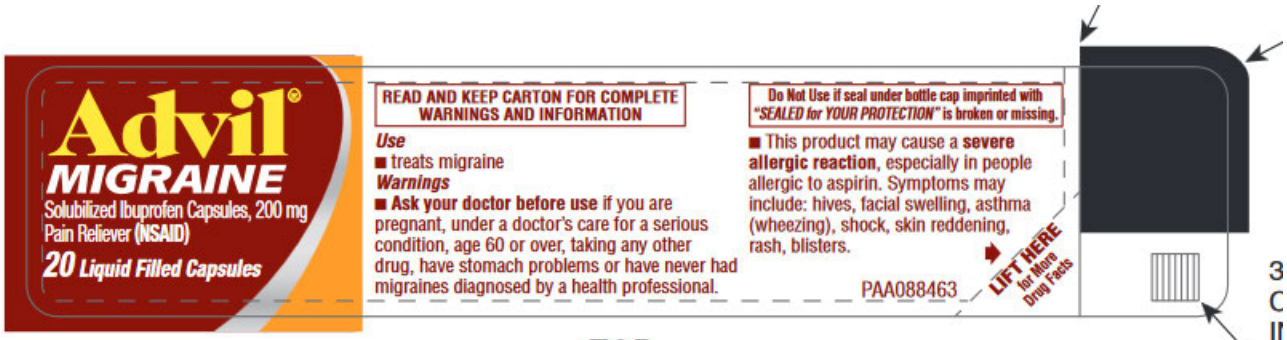


RELEASED BACK PANEL 2

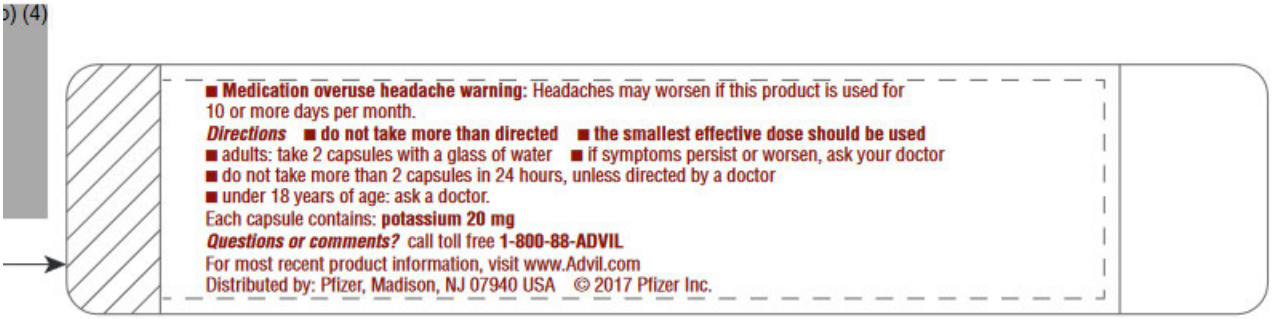
2017 16:06 (GMT)

al\Final

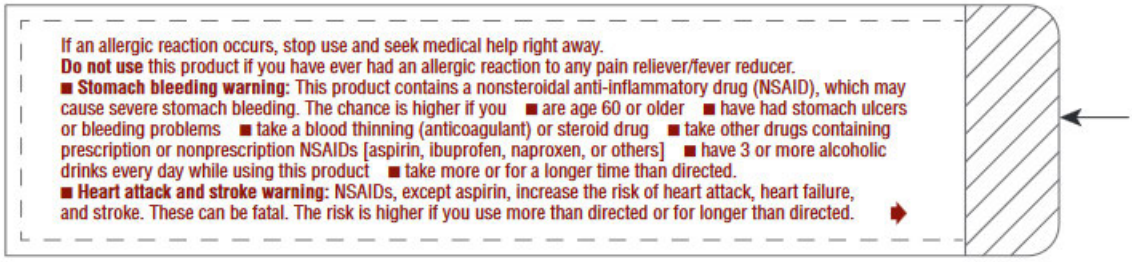

UNPRINTED A
FOR DATE & L
(UNVARNISH
PRINTED AREA FOR DATE & LOT
LASER CODING (VARNISHED)
128 CODE AREA - SUBSET C 10 MIL DENSITY
WITH 4 OR 6 DIGITS (CODE TO EXTEND
TO EDGE OF FLAP - UNVARNISHED)
PRINTED SIDE OF CARTON
Advil
LIQUI-GELS
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
20
Liquid Filled
Capsules
128 CODE FPO
083090
FPO
READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION
Drug Facts
Uses
Warnings
Drug Facts (continued)
Other information
PA4083090



TOP PANEL 1



BASE



RELEASED BACK PANEL 2

020402Orig1s043lbl.pdf

020402s042lbl.pdf

3.1.2 RX PRESCRIBING INFORMATION, PATIENT LABELING, & DRUG FACTS LABELING (OTC)

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**
Are the Prescribing Information or Drug Facts Labeling (OTC) contained in the submission the same as the review model labeling (not including allowable differences under 21 CFR 314.94(a)(8))? **YES**
Is the Prescribing Information shared by other ANDAs? **NO** (If yes please list ANDA numbers).
Are the specific requirements for format met under 21 CFR 201.57 (new), or 201.80 (old), or 201.66 (OTC)? **YES**

Comment:

Acceptable

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURED BY STATEMENT

[For OTC products, please include the inactives in Table 8; package sizes being marketed in Table 9; and drug product manufacturer/distributor statement in Table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED section or OTC package sizes? **YES**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	FD&C Blue #1, gelatin, glycerin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan and sorbitol	We note that the Applicant has different colors for their respective proposed drug products; we find it acceptable.

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Packaging sizes of 20s, 40s, 80s, 120s	S-016 (Pain Reliever/Fever Reducer) • Blue Colored Capsules 8's, 20's, 200's, 240's, 300's Bottle Label • Orange Colored Capsules 8's, 20's, 200's, 240's 300's Bottle Label • Clear Capsules 8's 20's, 200's, 240's, 300's Bottle Label --- S-021 (Migraine) 20's Bottle Label --- S-020 (Minis) 8's, 300's Bottle Label	We note that there are different additional packaging sizes for the Applicant's new proposed packaging, we find it acceptable.

Table 10: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Distributed by: McNeil Consumer Healthcare Division of McNEIL-PPC, Inc. Fort Washington, PA 19034 USA	Manufactured for: Bionpharma Inc. 600 Alexander Road, Princeton, NJ 08540	We note that application was transferred to Bionpharmac Inc per the 12/4/2015 Administrative Change/Applicant cover letter; we find it acceptable.

4. SPECIAL CONSIDERATIONS

Please include other information that may pertain to your drug product application.

Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 2/01/2019 02:04:41PM
GUID: 5423006c00721f6b43db6c5df1f43327

Theresa Liu

Digitally signed by Theresa Liu
Date: 2/04/2019 01:17:48PM
GUID: 508da70a00028d58911de18a598cda6f

***** This document contains proprietary information that cannot be released to the public***v.40**

SUPPLEMENT LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of this Review	11/13/2018
Review Cycle Number	1
ANDA(s) and Supplement Number(s)	078682/**S-020**, S-016 and S-021
Applicant Name	Bionpharma Inc.
Proprietary Name, Established Name, and Strength(s) [Add "(OTC)" after strength if applicable]	Ibuprofen Capsules, 200 mg (OTC)
Current Received Date	S-020: 9/26/2018 S-016: 8/28/2017 S-021: 11/6/2018
Previous Received Date(s) of Proposed Supplement	S-020: 9/10/2018
Primary Labeling Reviewer	Oluwakemi O. Odesina
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE - No Comments.

☐ ACCEPTABLE - Include Post approval comments.

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

☐ **For labeling supplement(s):**

This Changes Being Effected supplemental abbreviated new drug CLICK HERE

We have completed the review of this supplemental application. Choose an item. effective on the date of this letter. Choose an item.

OR

We have completed the review of your applications and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address

1. CONTAINER LABEL
2. CARTON LABELING
3. PRESCRIBING INFORMATION
4. MEDICATION GUIDE
5. STRUCTURED PRODUCT LABELING (SPL)

☒ **For combined supplement(s):**

.

Labeling deficiencies determined on 11/16/2018, based on your submissions received on 9/26/2018

1. CONTAINER LABEL

Revise the expression of the established name to remove the term “Mini” (e.g. Ibuprofen Capsules). Instead, the term “Mini” should be used as a modifier, in accordance with the reference listed drug (RLD).

2. CARTON LABELING

We recommend adding the statement “Smaller Capsule Same Strength” to the principal display panel (PDP), in accordance with the RLD.

Contents

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in DLR's SharePoint Drug Facts? If Yes, please explain:	**NO**
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint? If Yes, please explain:	**NO**
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? **https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm**	NO

Reason for Submission:

S-020 (PAS)

thi

S-021 (CBE)

As pe
Supp
consi
Migr

S-016 (CBE)

Bionpharma is hereby submitting a CBE-0 Labeling Supplement to revise the labeling for its Ibuprofen Capsules, 200 mg, to be in line with the revised labeling approved for the Reference Listed Drug, Advil® Liqui-Gels®, (NDA 020402, S-043) on August 8, 2017. The revised labeling is provided in m1 1.14.1.1. A side-by-side comparison of the revised labeling and the updated RLD labeling is provided in m1 1.14.1.2. The submission also includes the labeling history in m1 1.14.1.5 which summarizes the changes made to the labeling. As the labeling has been revised in line with the RLD, side-by-side comparison of the revised labeling with the previous approved labeling is not relevant and hence not included.

Is this supplement combined with another discipline?	**YES (S-020_**
Is this product an OTC product?	**YES**

Is this ANDA the RLD?	NO

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

2.1 MATERIALS REVIEWED

Tables 1 and 2 provide a summary of recommendations for each material analyzed in this review.

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	**S-016 (Pain Reliever/Fever Reducer)** • Blue Colored Capsules 8's, 20's, 200's, 240's, 300's Bottle Label • Orange Colored Capsules 8's, 20's, 200's, 240's 300's Bottle Label • Clear Capsules 8's 20's, 200's, 240's, 300's Bottle Label --- **S-021 (Migraine)** 20's Bottle Label --- **S-020 (Minis)** 8's, 300's Bottle Label	08/28/2017 11/06/2018 9/10/2018	Revise
Pouch	Draft	**S-016 (Pain Reliever/Fever Reducer)** • Blue Colored Capsules	08/28/2017 11/06/2018 9/10/2018	Satisfactory

		2's Pouch Label • Orange Colored Capsules 2's Pouch Label • Clear Capsules 2's Pouch Label		
Carton	Draft	**S-016 (Pain Reliever/Fever Reducer)** • Blue Colored Capsules 4's Pouch Carton 20's Bottle Carton • Orange Colored Capsules 4's Pouch Carton 20's Bottle Carton • Clear Capsules 4's Pouch Carton 20's Bottle Carton --- **S-021 (Migraine)** 20 Capsules per Carton --- **S-020 (Minis)** 8 capsules per carton	**08/28/2017** **11/06/2018** **9/10/2018**	Revise
(Other – specify)	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

Table 2 Review Summary of Prescribing Information and Patient Labeling

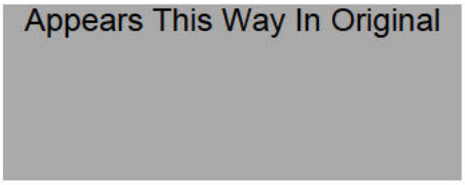
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation

Prescribing Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Medication Guide	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

2.2 MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

Table 3: Review Model Labeling for Prescribing Information, Patient Labeling, and Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)



☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 020402/S-042; 020402/S-043

Supplement Approval Date: 03/08/2017; 08/08/2018

Proprietary Name: Advil Liqui-Gels Minis; Advil Liqui-Gels

Established Name: Solubilized Ibuprofen Capsules

Description of Supplement:

S-042

This "Prior Approval" supplemental new drug application proposes a new line extension product for a smaller liquid-filled capsule (identified as minis) as compared to the currently approved Advil® Liqui-Gels®.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We remind you to remove the 'NEW' flag from the statement "NEW Smaller Capsule" on the principal display panel 6 months after introduction to the marketplace.

S-043

This "Prior Approval" supplemental new drug application provides for the following changes:

- the addition of heart attack and stroke warning information to all Advil® LIQUI-GELS® and Advil® Migraine labels
- the addition of medication overuse headache warning information to the Advil® Migraine labels
- updates to the graphics on the principal display panel
- updates to the net quantity statement on the 2-count immediate container (pouch) label
- minor revisions to immediate container and carton labels (e.g., inactive ingredients revisions, update copyright and patent information)
- new bonus labeling (e.g., 100-, 180- child resistant, 180- non-child resistant count sizes)
- the addition of two instantly redeemable coupons for the Advil® Migraine 20- and 80-count cartons
- the removal of the 4-count carton (hang card), 8-count carton, 120-count carton, and 240-count immediate container (standalone bottle) labels approved in Supplement 025

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the following revisions listed below:

(b) (4)

Table 3: Review Model Labeling for Prescribing Information, Patient Labeling, and Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
****We note that the Applicant's proposed S-021 is to be in accordance with the RLD's S-043 and proposed S-020 is to be in accordance with the RLD's S-042. We note that approved RLD labeling for S-046 and S-047 approved on 8/2/2018 and 8/31/2018 respectively provide for: S-046 This "Prior Approval" supplemental new drug application proposes a new $1.00 instantly redeemable coupon (IRC) to be placed on the approved 40-count carton. We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. S-047 This "Prior Approval" supplemental new drug application provides for an alternate 8-count immediate container label to accompany previously approved small and large backer cards. We note that these supplements do not provide for changes to the Drug Facts Labeling.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **NO** If yes, then comment below regarding the current model labeling.

Comment:

2.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 11/13/2018.

Are there any remaining unexpired patents or marketing exclusivities for Model Labeling? **NO**

If YES go to the Table 4 and assessments below.

Table 4 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling (020402) and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 4: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
NA					

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling				
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
NA				

Reviewer Assessment:

Are there any recently expired patents or exclusivities? **NO**
If yes, did these patents or exclusivities have any labeling impact? **N/A**

Comment:

2.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 11/13/2018.

Table 6: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labels/labeling? **NA**

Comment:

2.5 HISTORY OF ANDA

We evaluated previously approved and pending supplements (Table 7) to determine if actions are needed for the current review.

Table 7: Labeling History of ANDA		
Original or Supplement	**Approval Date**	**What post approval changes were requested and were the changes addressed?**
S-012	07/31/2013	None
Are there any Pending Labeling Supplements for this ANDA that impact labeling? NO		
Pending Supplement	**Submission Date**	**Labeling Impact**

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1 CONTAINER AND CARTON LABELS

Reviewer Assessment:

Were container or carton labels submitted in this supplement? **YES**
If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Comment:

We note that this is an OTC drug product; the Applicant has submitted revised labeling in accordance with the RLD's approved S-042 and S-043; we do not find the labeling to be acceptable. We will issue the following comments to the Applicant:

1. CONTAINER LABEL

Revise the expression of the established name to remove the term "Mini" (e.g. Ibuprofen Capsules). Instead, the term "Mini" should be used as a modifier, in accordance with the reference listed drug (RLD).

2. CARTON LABELING

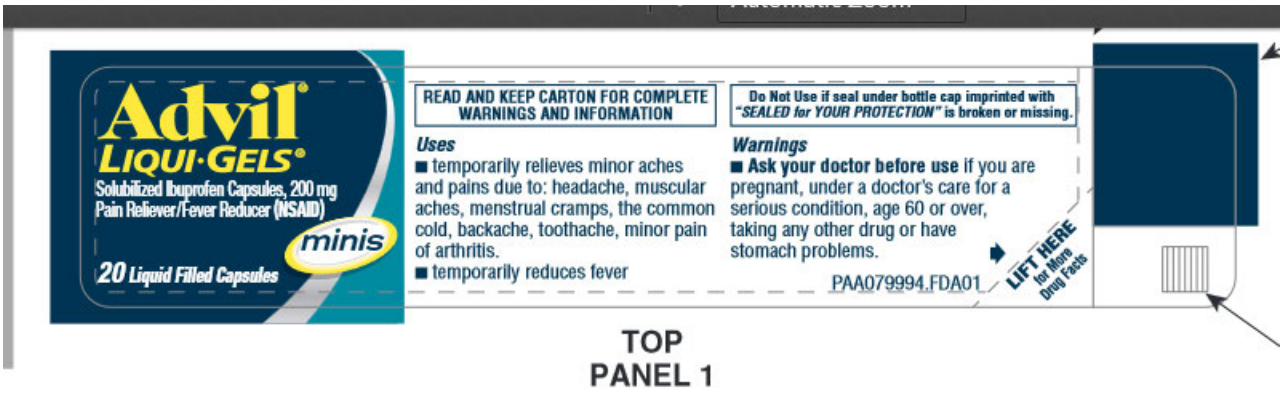
We recommend adding the statement "Smaller Capsule Same Strength" to the principal display panel (PDP), in accordance with the RLD.

3.1.1 MODEL CONTAINER LABELS

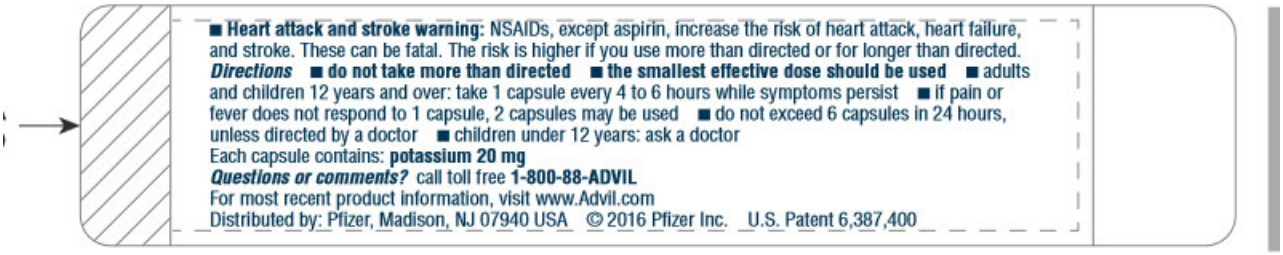
Please provide the reference listed drug labels if applicant submits container, blister, carton, etc.

Model container/carton/blister labels [Source: Drugs@FDA]

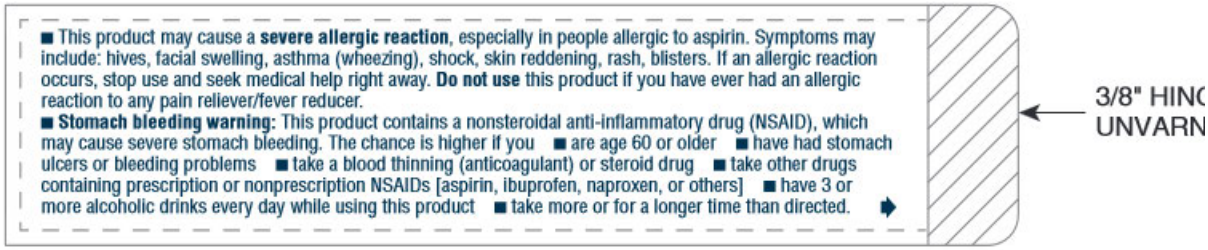
NDA 020402/S-042 approved on 03/08/2017

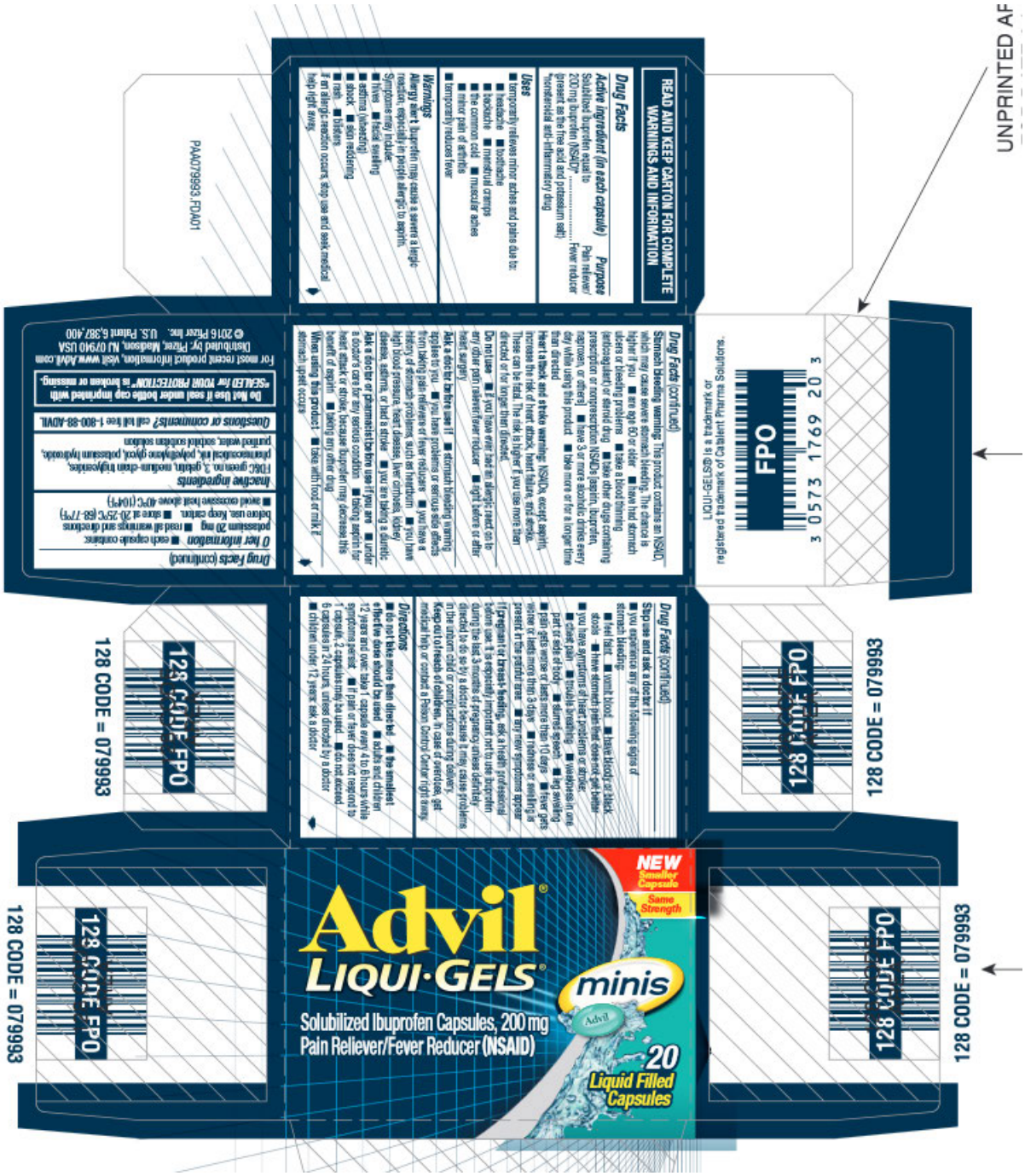


TOP
PANEL 1



BASE
PANEL 3

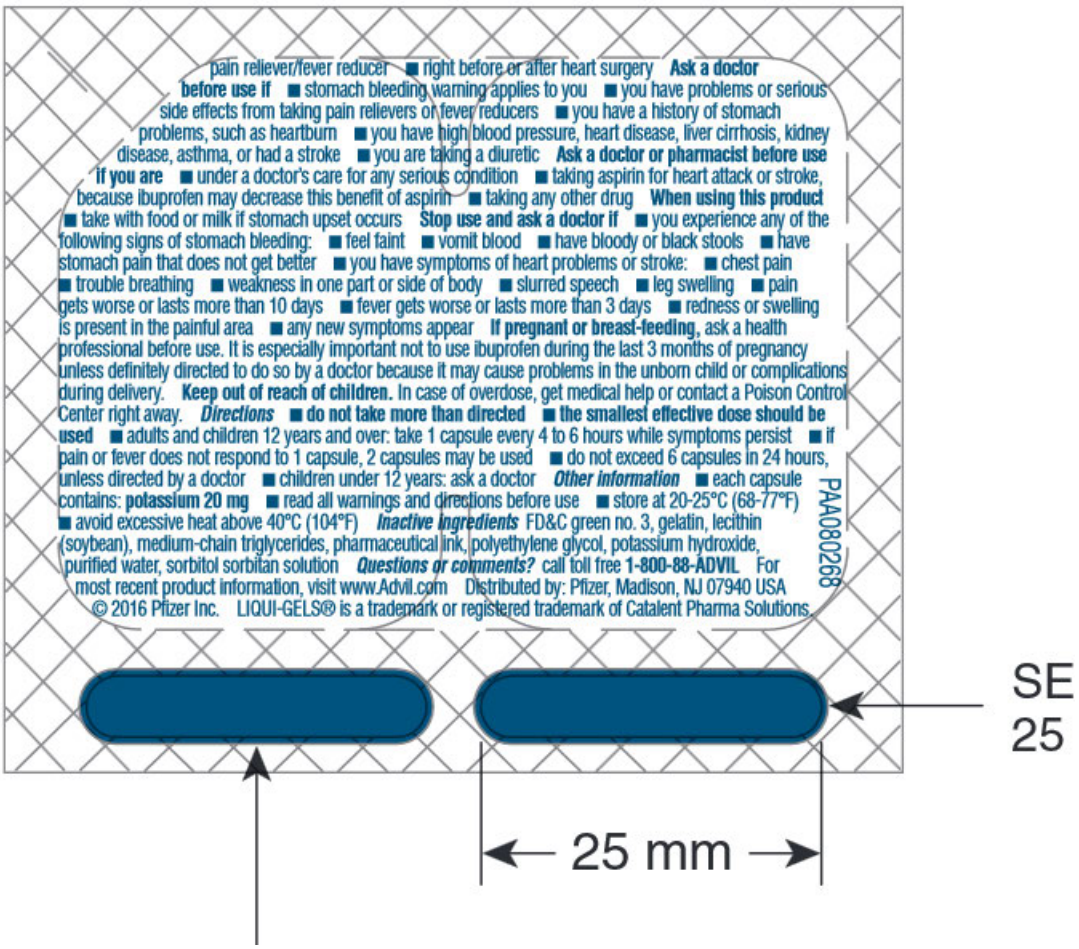




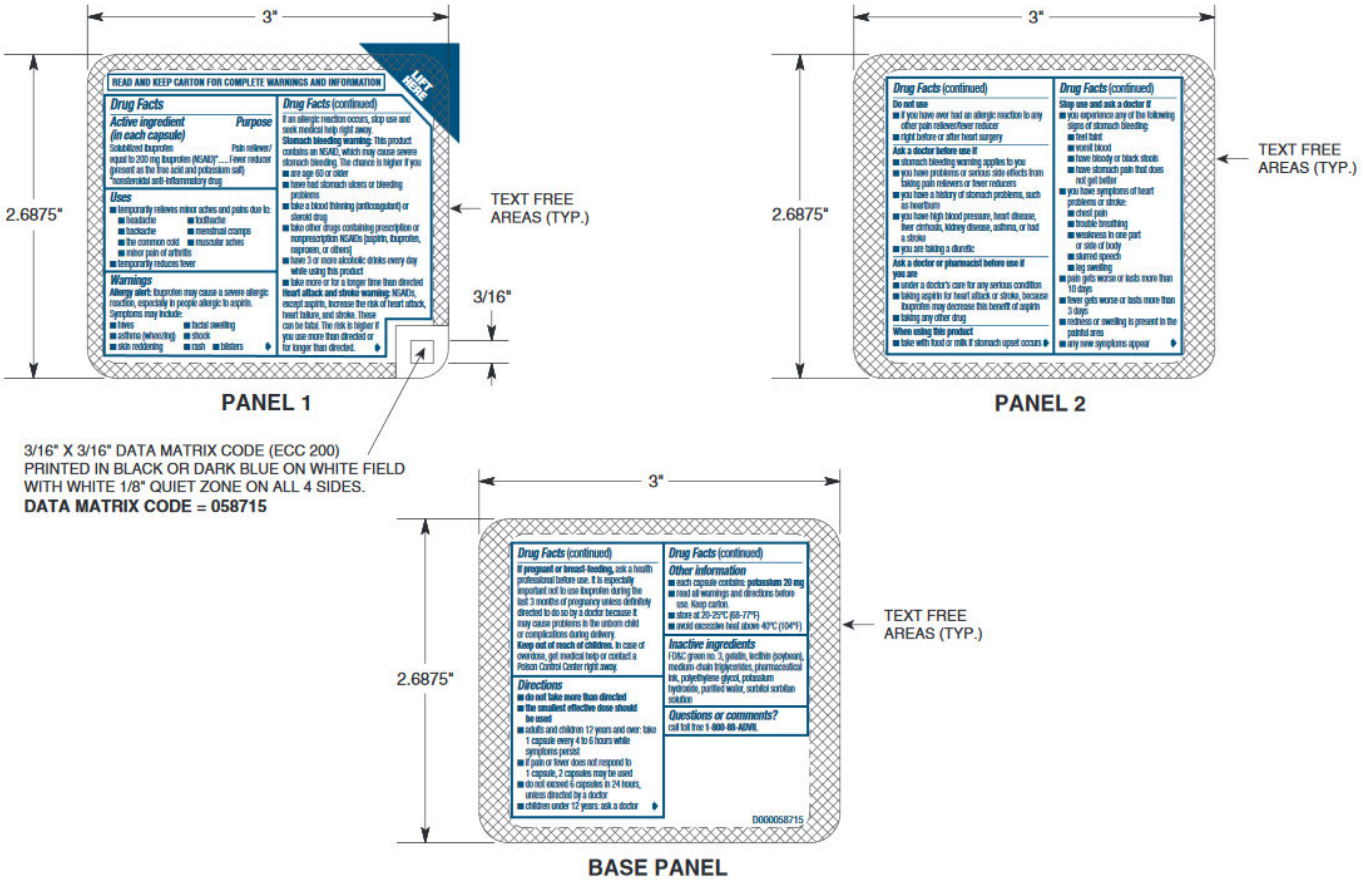
NDA 020402/S-043 approved on 08/08/2017

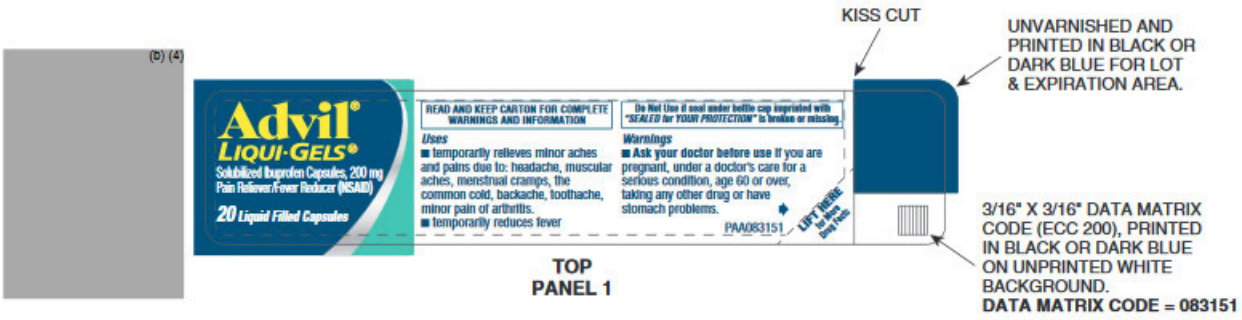

Advil®
LIQUI-GELS®
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
2 Liquid Filled Capsules
Active Ingredient (in each capsule)
Purpose
Solubilized ibuprofen equal to 200 mg (present as the free acid and potassium salt)
Pain reliever/ ibuprofen (NSAID)* .....Fever reducer
*nonsteroidal anti-inflammatory drug
Uses
■ temporarily relieves minor aches and pains due to: ■ headache ■ toothache ■ backache ■ menstrual cramps ■ the common cold ■ muscular aches ■ minor pain of arthritis
■ temporarily reduces fever
Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: ■ hives ■ facial swelling ■ asthma (wheezing) ■ shock ■ skin reddening ■ rash ■ blisters If an allergic reaction occurs, stop use and seek medical help right away. Stomach bleeding warning: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs [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 Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed. Do not use ■ if you have ever had an allergic reaction to any other
TO OPEN: FOLD BACK ON DOTTED LINE.
TEAR ON ARROW OR USE SCISSORS.
Do Not Use if pouch is broken or torn.
PAA080267

BACK

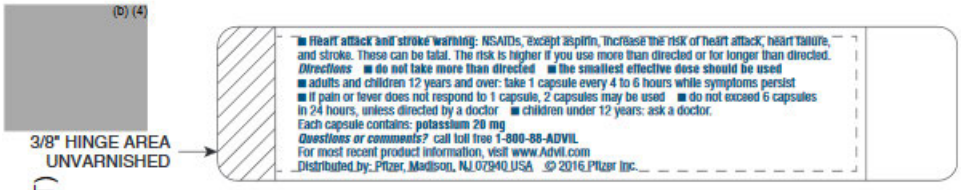

pain reliever/fever reducer ■ right before or after heart surgery **Ask a doctor before use if** ■ stomach bleeding warning applies to you ■ you have problems or serious side effects from taking pain relievers or fever reducers ■ you have a history of stomach problems, such as heartburn ■ you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke ■ you are taking a diuretic **Ask a doctor or pharmacist before use if you are** ■ 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 **Stop use and ask a doctor if** ■ you experience any of the following signs of stomach bleeding: ■ feel faint ■ vomit blood ■ have bloody or black stools ■ have stomach pain that does not get better ■ you have symptoms of heart problems or stroke: ■ chest pain ■ trouble breathing ■ weakness in one part or side of body ■ slurred speech ■ leg swelling ■ pain gets worse or lasts more than 10 days ■ fever gets worse or lasts more than 3 days ■ redness or swelling is present in the painful area ■ any new symptoms appear **If pregnant or breast-feeding,** ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away. ***Directions*** ■ **do not take more than directed** ■ **the smallest effective dose should be used** ■ 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 20-25°C (68-77°F) ■ avoid excessive heat above 40°C (104°F) ***Inactive ingredients*** FD&C green no. 3, gelatin, lecithin (soybean), medium-chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitol sorbitan solution ***Questions or comments?*** call toll free **1-800-88-ADVIL** For most recent product information, visit www.Advil.com Distributed by: Pfizer, Madison, NJ 07940 USA
© 2016 Pfizer Inc. LIQUI-GELS® is a trademark or registered trademark of Catalent Pharma Solutions.
PAA080268
SE
25
25 mm


(2) 2 ct PACKETS
Advil
LIQUI-GELS
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
4
Liquid Filled
Capsules
FPO
3 0573 1769 04 3
Do Not Use if the sealed child resistant
pouch is broken or torn.
For most recent product information, visit www.Advil.com
Pfizer, Madison, NJ 07940 USA © 2017 Pfizer Inc.
D000057830
128 CODE = 057830
FPO 128 CODE
AREA
AREA FOR LOT AND
EXPIRATION DATE
128 CODE = 057830
HIGH DENSITY CODE 128.

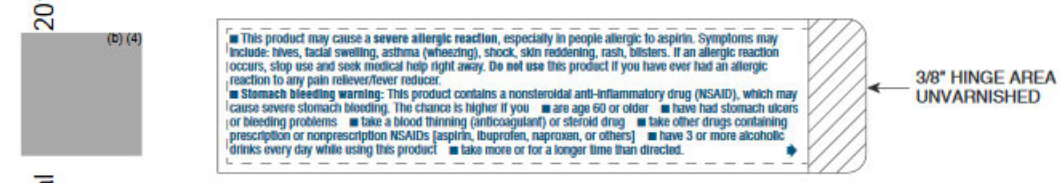

3"
2.6875"
READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION
LIFT HERE
Drug Facts
Active ingredient (in each capsule)
Purpose
Solubilized ibuprofen
Pain reliever/ equal to 200 mg ibuprofen (NSAID)* ..... Fever reducer
(present as the free acid and potassium salt)
*nonsteroidal anti-inflammatory drug
Uses
■ temporarily relieves minor aches and pains due to:
■ headache ■ toothache
■ backache ■ menstrual cramps
■ the common cold ■ muscular aches
■ minor pain of arthritis
■ temporarily reduces fever
Warnings
Allergy alert: ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.
Symptoms may include:
■ hives ■ facial swelling
■ asthma (wheezing) ■ shock
■ skin reddening ■ rash ■ blisters
Drug Facts (continued)
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warnings: This product contains an NSAID, which may cause severe 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 prescription or nonprescription NSAIDs (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
Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.
TEXT FREE AREAS (TYP.)
3/16"
PANEL 1
3/16" X 3/16" DATA MATRIX CODE (ECC 200)
PRINTED IN BLACK OR DARK BLUE ON WHITE FIELD
WITH WHITE 1/8" QUIET ZONE ON ALL 4 SIDES.
DATA MATRIX CODE = 058715
3"
2.6875"
Drug Facts (continued)
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
■ stomach bleeding warning applies to you
■ you have problems or serious side effects from taking pain relievers or fever reducers
■ you have a history of stomach problems, such as heartburn
■ you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
■ you are taking a diuretic
Ask a doctor or pharmacist before use if you are
■ 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
Drug Facts (continued)
Stop use and ask a doctor if
■ you experience any of the following signs of stomach bleeding:
■ feel faint
■ vomit blood
■ have bloody or black stools
■ have stomach pain that does not get better
■ you have symptoms of heart problems or stroke:
■ chest pain
■ trouble breathing
■ weakness in one part or side of body
■ slurred speech
■ leg swelling
■ pain gets worse or lasts more than 10 days
■ fever gets worse or lasts more than 3 days
■ redness or swelling is present in the painful area
■ any new symptoms appear
TEXT FREE AREAS (TYP.)
PANEL 2
3"
2.6875"
Drug Facts (continued)
If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
■ do not take more than directed
■ the smallest effective dose should be used
■ adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
■ if pain or fever does not respond to 1 capsule, 2 capsules may be used
■ do not exceed 6 capsules in 24 hours, unless directed by a doctor
■ children under 12 years: ask a doctor
Drug Facts (continued)
Other information
■ each capsule contains: potassium 20 mg
■ read all warnings and directions before use. Keep carton
■ store at 20-25°C (68-77°F)
■ avoid excessive heat above 40°C (104°F)
Inactive ingredients
FD&C green no. 3, gelatin, lecithin (soybean), medium-chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitol sorbitan solution
Questions or comments?
call toll free 1-800-88-ADVIL
D000058715
TEXT FREE AREAS (TYP.)
BASE PANEL



TOP
PANEL 1



BASE
PANEL 3



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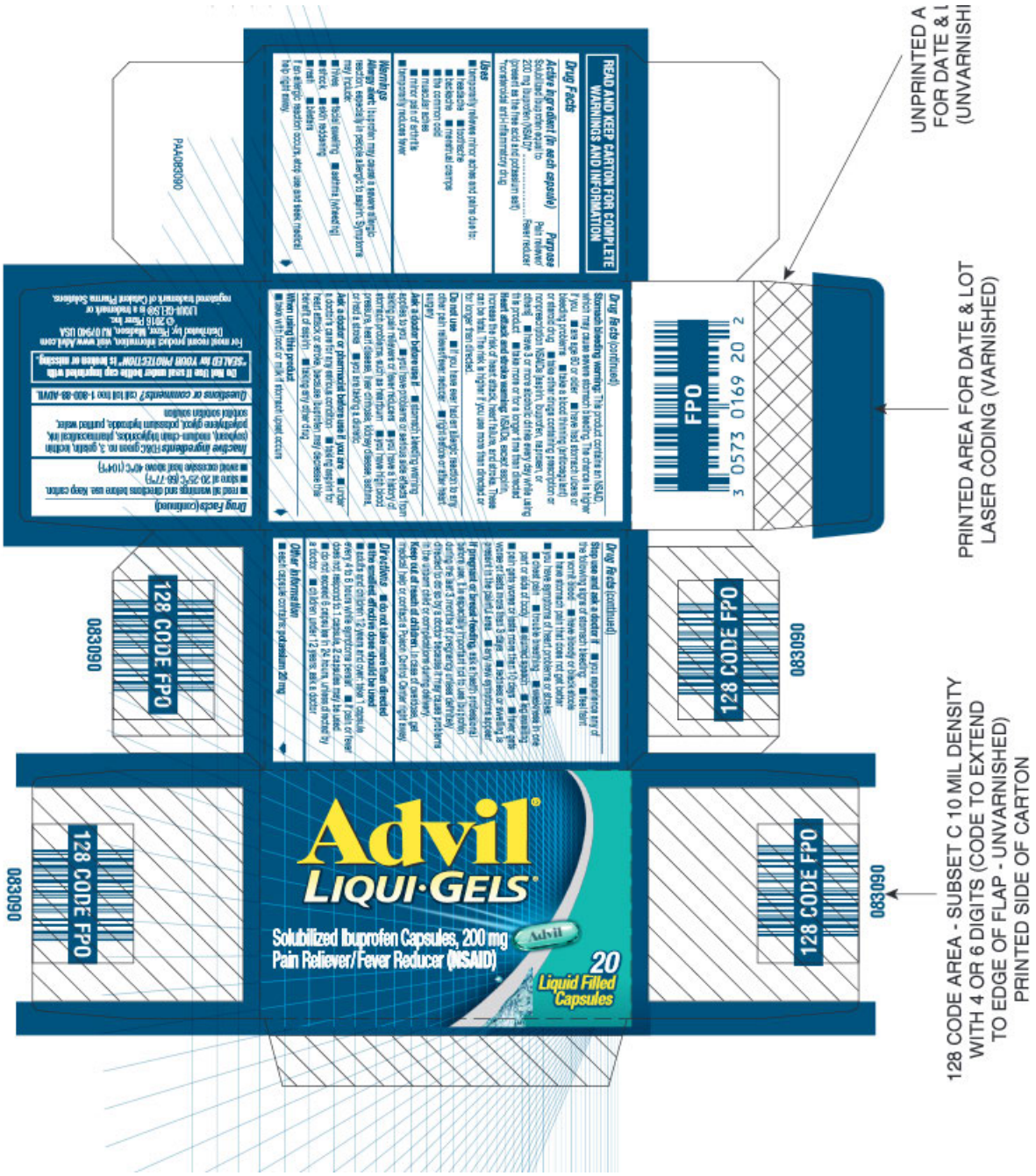
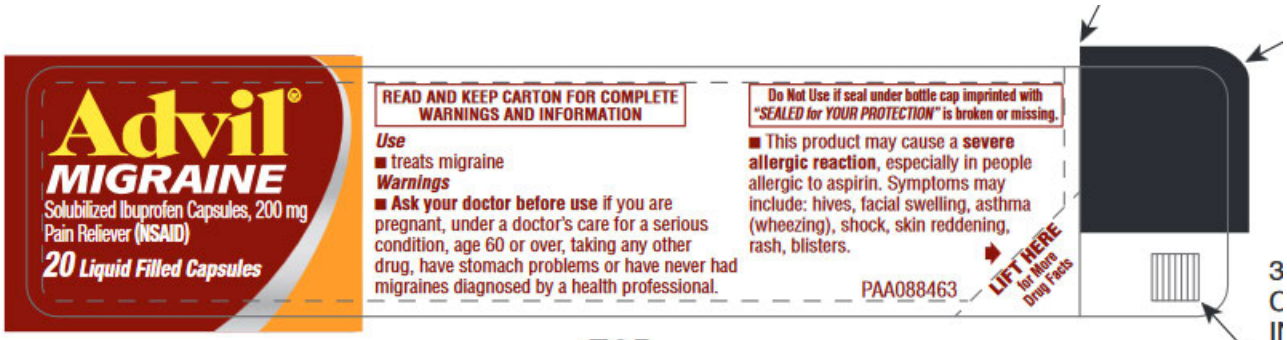
PANEL 2

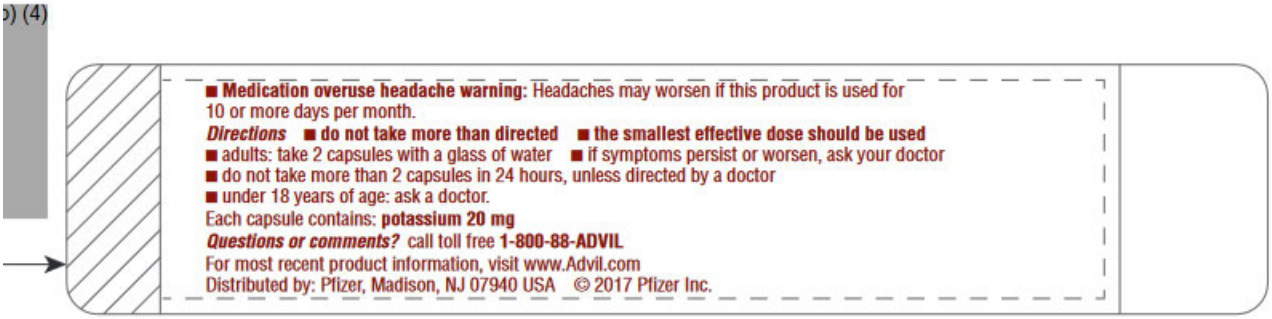
2017 16:06 (GMT)

al\Final

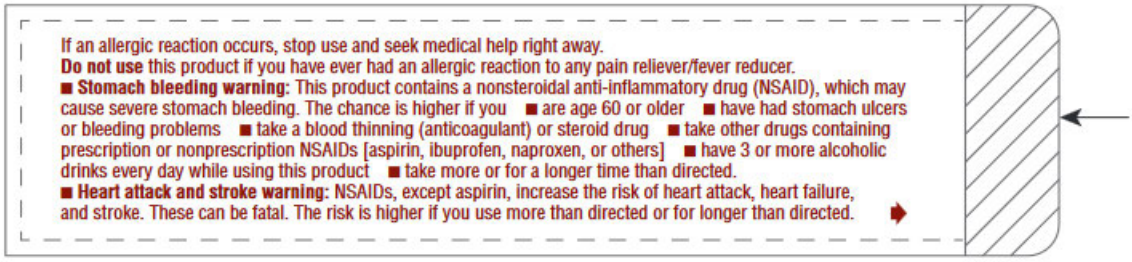

Advil
LIQUI-GELS
Solubilized Ibuprofen Capsules, 200 mg
Pain Reliever/Fever Reducer (NSAID)
20
Liquid Filled
Capsules
128 CODE FPO
083090
FPO
3 0573 0169 20 2
UNPRINTED A
FOR DATE & L
(UNVARNISH
PRINTED AREA FOR DATE & LOT
LASER CODING (VARNISHED)
128 CODE AREA - SUBSET C 10 MIL DENSITY
WITH 4 OR 6 DIGITS (CODE TO EXTEND
TO EDGE OF FLAP - UNVARNISHED)
PRINTED SIDE OF CARTON



TOP PANEL 1



BASE



RELEASED BACK PANEL 2

020402Orig1s043lbl.pdf

020402s042lbl.pdf

3.1.2 RX PRESCRIBING INFORMATION, PATIENT LABELING, & DRUG FACTS LABELING (OTC)

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**
Are the Prescribing Information or Drug Facts Labeling (OTC) contained in the submission the same as the review model labeling (not including allowable differences under 21 CFR 314.94(a)(8))? **YES**
Is the Prescribing Information shared by other ANDAs? **NO** (If yes please list ANDA numbers).
Are the specific requirements for format met under 21 CFR 201.57 (new), or 201.80 (old), or 201.66 (OTC)? **YES**

Comment:

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURED BY STATEMENT

[For OTC products, please include the inactives in Table 8; package sizes being marketed in Table 9; and drug product manufacturer/distributor statement in Table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED section or OTC package sizes? **YES**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	**FD&C Blue #1, gelatin, glycerin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan and sorbitol**	**We note that the Applicant has different colors for their respective proposed drug products; we find it acceptable.**

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Packaging sizes of 20s, 40s, 80s, 120s	S-016 (Pain Reliever/Fever Reducer) • Blue Colored Capsules 8's, 20's, 200's, 240's, 300's Bottle Label • Orange Colored Capsules 8's, 20's, 200's, 240's 300's Bottle Label • Clear Capsules 8's 20's, 200's, 240's, 300's Bottle Label ---------- S-021 (Migraine) 20's Bottle Label ---------- S-020 (Minis) 8's, 300's Bottle Label	We note that there are different additional packaging sizes for the Applicant's new proposed packaging, we find it acceptable.

Table 10: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Distributed by: McNeil Consumer Healthcare Division of McNEIL-PPC, Inc. Fort Washington, PA 19034 USA	Manufactured for: Bionpharma Inc. 600 Alexander Road, Princeton, NJ 08540	We note that application was transferred to Bionpharmac Inc per the 12/4/2015 Administrative Change/Applicant cover letter; we find it acceptable.

4. SPECIAL CONSIDERATIONS

Please include other information that may pertain to your drug product application.

Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 11/16/2018 10:30:33AM
GUID: 5423006c00721f6b43db6c5df1f43327

Theresa Liu

Digitally signed by Theresa Liu
Date: 11/16/2018 01:39:32PM
GUID: 508da70a00028d58911de18a598cda6f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA78682Orig1s020

CHEMISTRY REVIEWS

Disciplines Involved	Outcome		Disciplines Involved	Outcome
Chemistry	AC		Biopharmaceutics	AC
Microbiology	NA		Bioequivalence	AC
Facilities	AC		DMF (Chemistry)	NA
Labeling	AC		DMF (Microbiology)	NA
Submissions Assessed				
Received Date:	9/10/2018			
Amendment(s) Received Date:	9/26/2018 (Amendment to filling review comments) 5/15/2019 (CR response) 9/13/2019 (1st IR response) 9/30/2019 (2nd IR response) 10/18/2019 (3rd IR response)			

OFFICE OF PHARMACEUTICAL QUALITY
ASSESSMENT OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

Chemistry Assessment Number : 2

ANDA/Supplement Number : 078682/20

Drug Product Name, Strength : Ibuprofen Capsules, 200 mg
(No USP monograph)

Pharmacological Category/ Indication(s) : Temporarily relieves minor aches and pains

Applicant Name (or US Agent if Applicable) : Bionpharma Inc.
600 Alexander Road, Suite 2-4B, Princeton, NJ 08540

Supplement Provides For : Addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product

Filing Category with basis for decision/comments (based on guidance for industry/CFR quotes) : PAS

Relevant Supporting DMF(s) Cited (If Applicable)

DMF No.	DMF		Result of Assessment	Date Assessment Completed
	NA			
	Comment	(if any) on DMF Assessment, Assessor		

ASSESSMENT NOTES

In the original Supplement, Bionpharma proposes for addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product. This review covers the firm's CR response (received on 5/15/2019) to the Agency's CR letter dated 3/8/2019.

Facilities

Facilities status is "Approve" in Panorama.

(b) (4)

CR comment #1(3/8/2019):

(b) (4)

CR response to comment #1 (5/15/2019):

(b) (4)

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Nini Guo

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Date: 10/21/2019 07:12:08PM
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George Miesegaes

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Disciplines Involved	Outcome		Disciplines Involved	Outcome
Chemistry	Inadequate-Major		Biopharmaceutics	Inadequate-Minor
Microbiology	NA		Bioequivalence	Inadequate-Major
Facilities	AC		DMF (Chemistry)	NA
Labeling	AC		DMF (Microbiology)	NA
Submissions Assessed				
Received Date:	9/10/2018			
Amendment(s) Received Date:	9/26/2018 (Amendment to filling review comments)			

OFFICE OF PHARMACEUTICAL QUALITY
ASSESSMENT OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

Chemistry Assessment Number : 1

ANDA/Supplement Number : 078682/20

Drug Product Name, Strength : Ibuprofen Capsules, 200 mg
(No USP monograph)

Pharmacological Category/ Indication(s) : Temporarily relieves minor aches and pains

Applicant Name (or US Agent if Applicable) : Bionpharma Inc.
600 Alexander Road, Suite 2-4B, Princeton, NJ 08540

Supplement Provides For : Addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product

Filing Category with basis for decision/comments (based on guidance for industry/CFR quotes) : PAS

Relevant Supporting DMF(s) Cited (If Applicable)

DMF No.	DMF		Result of Assessment	Date Assessment Completed
	NA			
	Comment	(if any) on DMF Assessment, Assessor		

ASSESSMENT NOTES

RLD (NDA 20402) has introduced a smaller liquid-filled capsule marketed as Advil® Liqui-Gels® (solubilized ibuprofen capsules, 200 mg) as a new line extension based on the approval of a Prior Approval Supplement (S-042). Through this Supplement, Bionpharma is proposing the following: Addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product

(b) (4)

The RLD NDA 20402/S042 providing for "a new line extension product for a smaller liquid-filled capsule (identified as minis) as compared to the currently approved Advil® Liqui-Gels®"was approved on 3/8/2017.

This PAS was found acceptable for filling on 9/27/208

Facilities

Facilities status is "Approve" in Panorama.

(b) (4)

Drug Substance

There are no changes to the drug substance in this supplement. The drug substance from the approved sources (b) (4) will be used for manufacturing Ibuprofen mini capsules.

Certificates of analysis for the drug substance lots used

(b) (4)

18 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

RECOMMENDATION

☐ Supplement is CMC Approvable

☒ Supplement is NOT CMC Approvable (with brief explanation:)

(Choose ☐ IR, ☐ CR-Minor, ☒ CR-Major); Deficiencies noted below:

Deficiencies to be communicated:

(b) (4)

[redacted]

Primary Assessor : Nini Guo **Date : 2/13/2019**

Nini Guo

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George Miesegaes

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78682Orig1s020

BIOEQUIVALENCE REVIEWS

BIOPHARMACEUTICS ASSESSMENT Office of New Drugs Products			
Application No.	ANDA-078682-S-20-AMEND-116	**Primary Reviewer:** Mathew John, Ph.D.	
Division	ONDP/Division of Biopharmaceutics		
Applicant	Bionpharma Inc	**Secondary Reviewer:** Min Li, Ph.D.	
Trade Name	--	**Branch Chief:** Kimberly Raines, Ph.D.	
Established Name	Ibuprofen Capsules 200 mg	**Division Director:** Paul Seo, Ph.D.	
Indication	NSAID, Analgesic		
Formulation/strength	IR Capsules / 200 mg	**Date Assigned**	------
Route of Administration	Oral	**Date of Review**	10/03/2019
Submission date(s)	05/05/2019		
Type of Submission	Prior Approval Supplement (PAS)	**GDUFA Goal date**	11/14/2019
Key Review Points	Evaluation of the dissolution method and acceptance criteria of the proposed Ibuprofen 200 mg smaller size (mini capsules)		
Recommendation	Adequate		

Background: Ibuprofen liquid filled Capsules 200 mg (ANDA 078682) was approved on 03/24/2009 for the treatment of pain. On 09/10/2018, the Applicant submitted a PAS for addition of an alternate formulation (smaller size or mini capsules) of their Ibuprofen liquid filled capsules 200 mg to be in line with the RLD. According to the bioequivalence (BE) review dated 02/13/2019, (b) (4) (b) (4) thus were considered as a Level-3 change per Section III of the SUPAC-IR guidance [FDA Guidance for Industry, Immediate Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation]. These changes are likely to have a significant impact on the quality and performance of the proposed formulation; therefore an in vivo fasting BE study was recommended to support such changes[1] and a complete Response Letter (CRL) was issued to the Applicant.[2]

Submission: In this amendment the Applicant has submitted the comparative dissolution studies of 3 exhibit batches of Ibuprofen Soft Gelatin Capsules (Minis), 200 mg (lots 147001042, 147001043 and 147001044) with Advil® Liqui-Gels® Minis lot R53091 (Expiry 10/2020) manufactured by

[1] Bioequivalence Discipline Review, dated 02/13/2019
[2] Final Decision, dated 03/08/2019

Pfizer Consumer Healthcare. The proposed dissolution method for the new formulation is the FDA dissolution database method which was also the previously approved method for the current formulation of Ibuprofen 200 mg regular sized capsules[3].

The Applicant has also submitted the results of a single-dose, two-way crossover fasting BE study comparing the proposed mini capsule to the corresponding RLD product, Pfizer Inc.'s Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg, Minis which was evaluated by the OGD division of bioequivalence and is deemed adequate[4].

Biopharmaceutics Assessment: The Applicant has adequately responded to the CR[5] comments by submitting an in vivo BE study of the proposed formulation Ibuprofen Capsules, 200 mg (Minis) to the Reference (R): Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis) under fasting condition. The in vivo BE study was evaluated and deemed adequate by the OGD division of bioequivalence.
For the dissolution specifications of the proposed new formulation, the Applicant used the same as those approved for the current formulation of Ibuprofen 200 mg regular sized capsules. The dissolution profiles of 3 exhibit batches of Ibuprofen Soft Gelatin Capsules (Minis), 200 mg (lots 147001042, 147001043 and 147001044) submitted by the Applicant supports the dissolution acceptance criterion as shown in Table 1 in Table 1:

Table 1: Dissolution method and acceptance criteria approved for the 200 mg mini capsules

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criterion
FDA Dissolution database	I (Basket)	150	Phosphate buffer pH 7.2/37.0°C ± 0.5 °C	900 mL	5,10,15,20, and 30 minutes	Not less than (b) (4)% ((b) (4)%) of the labeled amount of Ibuprofen is dissolved in (b) (4) minutes

Recommendation: This prior approval supplement is adequate from a biopharmaceutics perspective and is recommended for Approval.

[3] http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881fef067
[4]http://panorama fda.gov/document/preview?versionID=5d42ff6500488960c6d1562e74e21717&ID=5d42ff650048895fa7fd2a67bde01a2f
[5]Application 078682 - Sequence 0092 - Comments And Response Seq: 0092

APPENDIX I

Table 2: Summary of in-vitro dissolution studies submitted by the Applicant[6]

Dissolution Conditions	Apparatus:	USP Apparatus I (baskets)
	Speed of Rotation:	150 rpm
	Medium:	Phosphate Buffer pH 7.2
	Volume:	900 ml
	Temperature:	37.0 °C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% at (b) minutes	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 5 min	10 min	15 min	20 min	30 min	Study Report Location
NA	8/14/2018	Advil Liqui-Gels Minis Batch No.: R53091 Mfg. date: NA Exp. date: Oct 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	2	85	100	100	100	m2-2.7.1.2
					Range	(b) (4)					
					%CV	55.9	21.0	1.3	1.3	1.3	
NA	8/12/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001042 Mfg. date: March 19, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	9	93	100	101	101	m2-2.7.1.2
					Range	(b) (4)					
					%CV	68.1	3.8	1.5	1.4	1.5	
NA	8/12/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001043 Mfg. date: March 21, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	15	96	102	103	103	m2-2.7.1.2
					Range	(b) (4)					
					%CV	84.5	9.7	1.2	0.9	1.0	
NA	8/14/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001044 Mfg. date: March 22, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	10	98	102	103	103	m2-2.7.1.2
					Range	(b) (4)					
					%CV	142.7	4.1	1.5	1.1	1.1	

APPENDIX II:

Biopharmaceutics Information request in CRL dated 03/08/2019))

There is insufficient data to support the bridging of formulation. The evaluation of the dissolution specification for the new formulation will be pending the responses to Bioequivalence deficiencies regarding the biowaiver request.

Applicant's Response: We acknowledge the Agency's comment. As requested by the Agency, single dose fasting bioequivalence study has been performed comparing the proposed formulation to the RLD. The proposed formulation Ibuprofen Capsules, 200 mg (Minis) of Bionpharma Inc. is demonstrated to be bioequivalent to the Reference (R): Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis) under fasting condition.

[6] Application 078682 - Sequence 0092 - Summary Biopharm Seq: 0092

Min Li

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Mathew John

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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	078682/Supplement 20
Drug Product Name	Ibuprofen Capsules (mini)*, Over-the-counter (OTC) Note: The applicant used "mini" capsule to refer to the proposed smaller-size capsule in the previous submission (Sequence 0087). In the current submission (Sequence 0092), the applicant uses "Minis" to refer to its new formulation. To be consistent, the reviewer uses "mini" throughout this review.
Strength(s)	EQ 200 mg Free Acid and Potassium Salt [1]
Applicant Name	Bionpharma Inc.
Applicant Address	600 Alexander Road, Suite 2-4B, Princeton, NJ, 08540, USA
US Contact Name and US Mailing Address	Usha Sankaran, Associate Vice President, Regulatory Affairs usha@bionpharma.com 600 Alexander Road, Suite 2-4B Princeton, NJ, 08540, USA
US Contact Telephone Number	609-380-3321
US Contact Fax Number	609-380-3311
Original Submission Date(s)	Original submission 07/06/2007 (Full Approval 03/24/2009) **09/10/2018: Supplement 20-Amendment 111**, Sequence 0087, addition of new formulation (mini capsules) of the drug product
Submission Date(s) of Amendment(s) Under Review	**5/15/2019: Supplement 20-Amendment 116**, Sequence 0092, Resubmission Major Complete Response Amendment
Primary Reviewer	Yi Zhang, M.D., Ph.D.
Secondary Reviewer	Kuldeep R. Dhariwal, Ph.D.
Tertiary Reviewer	Not Applicable (N/A)
Study Number(s)	**035/19**
Study Type(s)	**Fasting**
Strength(s)	**200 mg (mini capsule)**
Clinical Site	Actimus Biosciences Private Limited
Clinical Site Address	D-2, D-Block, Beside Lakshmi Hyundai Service center, Autonagar, Visakhapatnam. -530012, Andhra Pradesh, India. Tel: +91-891-2750977 Fax: +91-891-6672111
Analytical Site	(b) (4)
Analytical Site Address	

[1] From here onwards in the review EQ 200 mg Free Acid and Potassium Salt will be referred as 200 mg.

	(b) (4)		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) [2]	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent) [2]	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	*Reminder: Check PSG in development spreadsheet on V: drive (if PSG is under development, wait for PSG to post to finalize the review)* ☒ Recommended/Latest Revision Date: March 2015 RLD Number: NDA 020402 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
116	**Fasting**	**200 mg**	☒ Adequate ☐ Inadequate

Reviewer's note: This review was updated on 10/29/2019. The purpose is to only change the OSIS inspection status. Revisions were made in OSIS section of the table, Executive Summary, and Section 3.5. All other information, including the retrieval dates for the reference information obtained from internal/external websites and internal databases, remains the same as the previous version (up to 08/02/2019).

[2] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1 EXECUTIVE SUMMARY

This is review of an amendment dated 5/15/2019.

Bionpharma Inc. (Bionpharma) holds the approved ANDA 078682, regular-sized Ibuprofen Capsule, 200 mg, Over-the-counter (OTC).[3] On 9/10/2018, the applicant submitted a Prior Approval Supplement (PAS) to include a new line extension product of smaller-sized Ibuprofen Capsule, 200 mg (mini capsule) in line with the reference listed drug (RLD). Per the previous bioequivalence (BE) review dated 02/13/2019, (b) (4) (b) (4) thus were considered as a Level-3 change per Section III of the SUPAC-IR guidance [FDA Guidance for Industry, Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation]. These changes are likely to have a significant impact on the quality and performance of the proposed formulation; therefore an in vivo fasting BE study was recommended to support such changes.[4] A Complete Response Letter (CRL) was issued on 3/8/2019.[5]

In the current amendment dated 5/15/2019, as response to the CRL, the applicant submitted the results of a fasting BE study comparing the proposed mini capsule to the corresponding RLD product, Pfizer Inc.'s Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg, Minis. The BE study was designed as a single-dose, two-way crossover study in healthy male subjects. The fasting study is acceptable. The results as calculated by the reviewer are summarized in the table below.

Ibuprofen Capsules, 200 mg (Mini), Dose (1 x 200 mg) Fasting Bioequivalence Study (Study No.: 035/19), N=26 (Male=26, Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr·µg/ml)	54.78	51.69	1.06	102.29	109.80
AUC∞ (hr·µg/ml)	57.57	54.63	1.05	101.99	108.91
Cmax (µg/ml)	21.49	19.90	1.08	95.89	121.66

Dissolution data were previously reviewed by the Division of Biopharmaceutics and the review outcome was inadequate. (See section 5.3 Dissolution Testing)

Per GDRP, OSIS uploaded a Decline to Inspect Memo on 8/13/2019 and recommended accepting data without an on-site inspection for the study site at (b) (4) (b) (4) (See Section 3.5). In addition, the fasting study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is Complete.

The supplement is adequate.

[3] Orange Book, last accessed 7/22/2019, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=078682

[4] ANDA-078682-SUPPL-20»Bioequivalence Discipline Review, dated 02/13/2019

[5] ANDA-078682-SUPPL-20»Final Decision, dated 03/08/2019

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Ibuprofen Capsules (mini), 200 mg, OTC
Reference Standard (RS) and Strength(s) [6]	Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg, OTC
RS Holder; NDA/ANDA Number; Approval Date	Pfizer Inc.; NDA 020402, Approval Date: April 20, 1995
Reference Listed Drug (RLD) and Strength(s)	Same as RS
RLD Holder; NDA/ANDA Number; Approval Date	Same as RS

Reviewer's note on the RS/RLD:

[6] Orange Book, last accessed 7/22/2019, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020402

NDA 020402 also lists Advil Migraine Liqui-Gels® (ibuprofen) Capsules, 200 mg (OTC), approved March 16, 2000, as RLD and RS. The reference product of the current submission (Advil® Liqui-Gels® Minis, 200 mg), which was approved on 3/8/2017 as a line extension product under NDA 20402/S-042 is not listed in the Orange Book.

3.2 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance[7]	 UCM436830-mar 2015.pdf	
Summary of OGD or DB History	Pending Citizen Petitions and other legal and regulatory issues:[8] If yes, please comment.	☐ Yes ☒ No

Reviewer's note: for more details on OGD history please see original BE review.

3.3 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	(b) (4)
Analyte	Ibuprofen
Internal standard (IS)	Ibuprofen -D3
Method description	(b) (4)
Limit of quantitation	0.510 µg/mL
Average recovery of drug (%) (CV%)	83.0 (5.4%) HQC: 77.8% (6.7%) MQC: 84.9% (3.9%) LQC: 86.2% (7.1%)
Average recovery of IS (%) (CV%)	88.8 (3.2%)

[7] Draft PSG on Ibuprofen (NDA 020402), Recommended Mar 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436830.pdf

[8] As per DLRS policy updates as of 7/22/2019 in the link http://sharepoint fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

Standard curve concentrations (µg/mL)	0.510, 1.020, 2.549, 5.098, 10.195, 20.391, 30.895, 40.753, 50.942					
QC concentrations (µg/mL)	**HQC**	**DQC**	**AQC**	**MQC**	**LQC**	**LLOQ QC**
	38.306	152.825	25.665	15.399	1.380	0.538
QC Intraday precision range (%)	Intraday batch (PA02&PA03) precision ranged from 0.8% to 13.1%.					
QC Intraday accuracy range (%)	Intraday batch (PA02&PA03) accuracy ranged from 89.1% to 98.4%.					
QC Interday precision range (%)	Interday batch (PA03&PA04) precision ranged from 0.8% to 13.1%.					
QC Interday accuracy range (%)	Interday batch (PA03&PA04) accuracy ranged from 87.5% to 98.4%.					
Bench-top stability(hrs.)	20hours 51minutes @ Bench top temperature.					
Stock stability(days)	04days 17 hours @ refrigerator (2°C-8°C).					
Processed stability(hrs.)	Auto Injector Stability for 50hours 58minutes @ 10°C.					
Freeze-thaw stability (cycles)	05 cycles					
Long-term storage stability(days)	19.2 days @ -25°C ± 5°C, -70°C ± 15°C					
Dilution integrity	Concentration diluted to 4-folds.					
Selectivity	No significant interference observed at the retention time of analyte and internal standard in the blank whole blood.					

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No Bioanalytical Method Validation (b) (4) (b) (4)
Is the same anticoagulant used in the pre-study method validation and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_2EDTA
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: **Adequate**

(b) (4)

3.4 In Vivo Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age (Years): mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (µg/mL)	#T_{max} (hr)	AUC_{0-t} (hr·µg/mL)	AUC_{∞} (hr·µg/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
035/19	To compare the oral bioavailability of Ibuprofen Capsules, 200 mg (Minis) Manufactured by Bionpharma Inc. with Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis). Distributed by P-fizer, Madison, NJ 07940 USA in healthy, adult, human subjects under **fasting** conditions. To evaluate the subject safety and tolerability of the investigational products.	An open-label, randomized, balanced, single oral dose, two-treatment, two-period, two-sequence, two-way, crossover BE study.	**Test Product (T)**: Ibuprofen Capsules 200 mg (Minis) Per oral [Lot No.: 147001042A]	28 healthy, adult, Male human subjects mean age: 33.32 (range: 19–44)	22.3929 ±6.3076 8 (28.2)	0.660 (0.330 – 3.000)	56.8092± 16.59502 (29.2)	59.5571± 16.65609 (28.0)	1.9549± 0.29122 (14.9)	0.3620± 0.05281 (14.6)	Fasting report body: 5.3.1.2 Sections, 1.0 to 15.0, page numbers 09 to 93
			Reference Product (R): Advil® Liqui-Gels® Capsules, 200 mg (Minis). Per oral [Lot No.: R50632]		20.9481 ±6.6683 0 (31.8)	0.830 (0.267– 3.500)	53.0884± 12.63978 (23.8)	56.0494± 13.10332 (23.4)	1.9212± 0.24609 (12.8)	0.3663± 0.04559 (12.4)	

For Tmax: median (min – max)

Reviewer's note: In applicant-submitted table, the units for Cmax and AUC are ng/mL and hr*ng/mL, respectively, which the reviewer considers typos.

3.5 OSIS Status

OSIS uploaded a Decline to Inspect Memo dated 8/13/2019 under ANDA (b) (4) and recommended accepting data without an on-site inspection for the study site at (b) (4) (b) (4). The rationale is provided below.[9]

(b) (4)

In addition, the fasting study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is Complete.

[9] GDRP, ANDA-213473-ORIG-1»Bioanalytical Sites, last accessed 10/29/2019, http://panorama.fda.gov/task/view?ID=5caf5840001702ebe07b19f402e48d44

4 REVIEW OF CURRENT AMENDMENT

4.1 Deficiency Comment

You propose an addition of a new line extension product, smaller liquid-filled Ibuprofen capsules, 200 mg (mini capsules). Your proposed formulation changes from regular to "mini" sized capsules are considered as Level-3 change as per Section III of the SUPAC guidance for IR products [FDA Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post Approval (SUPAC) Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation: November 1995]. In vivo bioequivalence (BE) study is recommended to support such changes. Please conduct a single dose fasting BE study comparing your proposed formulation (mini capsules) to the reference listed drug product, Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg (Minis).

Applicant's Response

As per Agency's request, an open-label, randomized, balanced, single oral dose, two-treatment, two-period, two-sequence, two-way, crossover bioequivalence study of Ibuprofen Capsules, 200 mg (Minis) manufactured for Bionpharma Inc. with Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis). Distributed by Pfizer, Madison, NJ 07940 USA in healthy, adult, human subjects under fasting conditions as per the Agency's BE recommendation. Based on the results, it is concluded that the Test (T): Ibuprofen Capsules, 200 mg (Minis) of Bionpharma Inc. is bioequivalent to the Reference (R): Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis) under fasting condition. The Bioequivalence summary tables are provided in m 2.2.7. The clinical study data is provided in module 5.

Reviewer's comment:

The fasting BE study (#035/19) is acceptable (see Section 5, Appendix for review details). The inspection status for the clinical and analytical site of the BE study is pending.

5 APPENDIX

5.1 Individual Study Reviews

5.1.1 Single-dose Fasting Bioequivalence Study

5.1.1.1 Study Design

5.1.1.1.1 Study Information

Study Number	035/19
Study Title	An open-label, randomized, balanced, single oral dose, two-treatment, two-period, two-sequence, two-way, cross-over oral bioequivalence study of Ibuprofen Capsules, 200 mg (Minis) Manufactured by Bionpharma Inc. with Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis). Distributed by Pfizer, Madison, NJ 07940 USA in healthy, adult, human subjects under fasting conditions.
Clinical Site (Name, Address, Phone #, Fax#)	Actimus Biosciences Private Limited, D-2, D-Block, Beside Lakshmi Hyundai Service center, Autonagar, Visakhapatnam. -530012, Andhra Pradesh, India. Tel: +91-891-2750977 Fax: +91-891-6672111.
Principal Clinical Investigator (Name, Email)	Dr. C. Gayatri Devi gayatri@actimusbio.com
Analytical Site (Name, Address, Phone #, Fax#)	(b) (4)
Principal Analytical Investigator (Name, Email)	
Dosing Dates	Period-1: 4/14/2019 Period-2: 4/21/2019
Analysis Dates	(b) (4)
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	18 days (14 Apr 2019 to 01 May 2019) -70°C ± 15°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte: Ibuprofen 19.2 days @ -25°C ± 5°C, -70°C ± 15°C
LTSS Data Location	Module :5.0 Location :5.3.1.4, Section: (b) (4) 17.0, Sub section: 17.7.3, Page 150-165 ((b) (4)

5.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Ibuprofen Capsules, 200 mg (Minis)	Advil® Liqui-Gels® (Ibuprofen) Capsules, 200 mg (Minis).
Manufacturer/ Distributor	**Manufactured by:** Bionpharma Inc.	**Distributed by:** Pfizer, Madison, NJ 07940 USA.
Lot No.	147001042A	R50632
Manufacture Date	19 Mar 2018	NA
Expiration Date	Feb 2020	09/20
Strength	200 mg	200 mg
Dosage Form	Soft Gelatin Capsules	Soft Gelatin Capsules
Bio-batch Size	(b) (4)	
Production Batch Size		
Potency		
Content Uniformity (mean, %CV)		
Dose Administered	1 x 200 mg	1 x 200 mg
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? **If Yes, please comment.**	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment.**	☒ Yes ☐ No Batch #147001042A was the (b) (4) Bottle packaged from Batch #147001042.[10] Batch #147001042 was used in both the fasting BE study and the dissolution testing.
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment.**	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment.**	☒ Yes ☐ No

[10] Packaging Batch Record- Lot # 147001042A-300 count (page 8 of 29)

5.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 28 (28+01 additional subject) checked in; 34 enrolled Dosed: 28 in period I, 26 in period II Completed: 26 Samples Analyzed: 28 (including 2 drop-outs) Statistically Analyzed: 26
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	07 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Pre-dose (0.00 hour) and at 0.167, 0.25, 0.33, 0.50, 0.66, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00 and 24.00 hours post dose in each period.
IRB Approval	☒ Yes Date: 05 April 2019 ☐ No
Informed Consent	☒ Yes Date: 05 April 2019 ☐ No
Length of Fasting	At least 10 hours prior to dosing until at least 4.00 hours post-dose in each period.
Length of Confinement	Subjects were housed in the facility from at least 11 hours prior to dosing until 24.00 hours post dose.
Was the drug product administered per labeling for specialized dosage forms (e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

5.1.1.2 Clinical Results

5.1.1.2.1 Demographic Profile of Subjects

Fasting Study No.035/19			
		Treatment Group	
		Test Product N =26	**Reference Product N =26**
Age (years)	Mean ± SD	34.23±6.68	34.23±6.68
	Range	19 - 44	19 - 44
Age Groups	< 18	00 (0.00%)	00 (0.00%)
	18 – 40	22 (84.62 %)	22 (84.62 %)

	41 – 64	04 (15.38 %)	04 (15.38 %)
	65 – 75	00 (0.00%)	00 (0.00%)
	> 75	00 (0.00%)	00 (0.00%)
Sex	Male	26 (100%)	26 (100%)
	Female	00 (0.00%)	00 (0.00%)
Race	Asian	26 (100%)	26 (100%)
	Black	00 (0.00%)	00 (0.00%)
	Caucasian	00 (0.00%)	00 (0.00%)
	Hispanic	00 (0.00%)	00 (0.00%)
	Other	00 (0.00%)	00 (0.00%)
BMI	Mean ± SD	23.00± 1.76	23.00 ± 1.76
	Range	19.60 – 24.74	19.60 – 24.74
Other Factors		Nil	Nil

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

5.1.1.2.2 Dropout Information

Study No.035/19				
Subject No.	**Reason for Dropout/Withdrawn/Replacement**	**Period**	**Replaced?**	**Replaced With**
(b) (6)	Subjects did not return for period-II admission.	II	No	NA
	Subjects did not return for period-II admission.	II	No	NA

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

5.1.1.2.3 Study Adverse Events

Body System/Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasting Bioequivalence Study No. 035/19	
	Test Product (T) (N=27)	**Reference Product (R) (N=27)**
NONE		
Total	--	
Post Study Abnormalities (N=28)		
Total	--	

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
N/A					

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No No AEs were reported during the study.
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

5.1.1.2.4 Protocol Deviations

Study No. 035/19		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
NONE		

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

5.1.1.3 Bioanalytical Results

5.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat analysis

All necessary SOPs submitted?	☒ Yes ☐ No

5.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 035/19 (Ibuprofen)									
Parameter	**Standard Curve Samples**								
Concentration (µg/mL)	STD-01	STD-02	STD-03	STD-04	STD-05	STD-06	STD-07	STD-08	STD-09
	0.510	1.020	2.549	5.098	10.196	20.392	30.897	40.745	50.931
Inter day Precision (%CV)	1.2	2.6	5.7	0.8	1.3	1.7	2.0	0.8	1.0
Inter day Accuracy (%Actual)	98.9	101.4	100.6	100.3	102.1	99.5	96.8	99.2	100.0
Linearity	0.9976 to 0.9998								
Linearity Range (µg/mL)	0.510 µg/mL to 50.931 µg/mL								
Sensitivity/LOQ (µg/mL)	0.510 µg/mL								

Parameter	**Quality Control Samples**			
	HQC	**MQC**	**AQC**	**LQC**
Concentration (µg/mL)	38.306	25.665	15.399	1.380
Inter day Precision (%CV)	1.9	2.1	1.5	2.3
Inter day Accuracy (%Actual)	100.7	101.1	99.8	100.4

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

5.1.1.3.3 Reanalysis of Study Samples

Bioequivalence Fasting Study No. 035/19 (Analyte: Ibuprofen) **Additional information in Volume(s), Page(s)** Module :5.0 Location: 5.3.1.4, Sub Folder: 035-19, Bioanalytical Study Report, Page 31 of 44								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0

Reason ISV (Internal Standard Variation)	0	2	0.0	0.2	0	2	0.0	0.2
Total	**0**	**2**	**0.0**	**0.2**	**0**	**2**	**0.0**	**0.2**

Note: Total Number of Samples Analyzed 1232

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

5.1.1.4 Pharmacokinetic Results

5.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters (Reviewer-calculated)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	µg.hr/mL	56.817	29.21	31.05	112.01	53.090	23.81	33.80	80.43	1.07
AUCI	µg.hr/mL	59.565	27.96	33.03	113.93	56.050	23.38	36.72	85.44	1.06
CMAX	µg/mL	22.393	28.17	11.89	32.59	20.948	31.83	9.62	31.92	1.07
TMAX*	hr	0.660	.	0.33	3.00	0.830	.	0.25	3.50	0.80
KE	hr-1	0.362	14.60	0.26	0.50	0.366	12.42	0.27	0.49	0.99
THALF	hr	1.955	14.90	1.38	2.65	1.921	12.78	1.41	2.55	1.02

* Tmax is expressed as Median and Range

5.1.1.4.2 Geometric Means and 90% Confidence Intervals (Applicant-calculated)

Ibuprofen Capsules, 200 mg (Minis) (No of subjects completed=26) Dose (01Capsulex 200 mg) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No.: 035/19) for Ibuprofen						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90%C.I.**
AUC_{0-t}	54.7727	26	51.6898	26	105.96	102.27 - 109.79
AUC_{∞}	57.5645	26	54.6277	26	105.38	101.97 - 108.90
C_{max}	21.4899	26	19.8961	26	108.01	95.89 - 121.66

5.1.1.4.3 Geometric Means and 90% Confidence Intervals (Reviewer-calculated)

Ibuprofen Capsules, 200 mg (Minis), Dose = 1× 200 mg (No of subjects completed= 26)

Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. 035/19)					
Parameter	**Test**	**Reference**	**Ratio (T/R)**	**90%CI**	
AUC_{0-t} (µg.hr/mL)	54.78	51.69	1.06	102.29	109.80
AUC_{∞} (µg hr/mL)	57.57	54.63	1.05	101.99	108.91
C_{max} (µg/mL)	21.49	19.90	1.08	95.89	121.66

5.1.1.4.4 Additional Information for the Study

Root Mean Square Error	**Parameter** / **RMSE**: LAUCT 0.0747; LAUCI 0.0692; LCMAX 0.2507
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No The observed median Tmax values are 0.660 (0.330-3.000) hrs. and 0.830 (0.267-3.500) hrs. for the test and reference product, respectively, with a T/R ratio 0.795. The Tmax range of test product is within that of the reference product.
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentrations as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time-point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC_{0-t}/AUC_{∞}				
Treatment	**N**	**Mean**	**Minimum**	**Maximum**
Test	26	0.95	0.90	0.98
Reference	26	0.95	0.90	0.98
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Comments on PK results: Adequate

The PK parameters and 90% CIs as calculated by the reviewer are in agreement with the applicant's calculations. The 90% confidence intervals of geometric mean test to reference ratios for AUC and Cmax met the acceptance BE criteria of 80-125%.

The fasting BE study is acceptable.

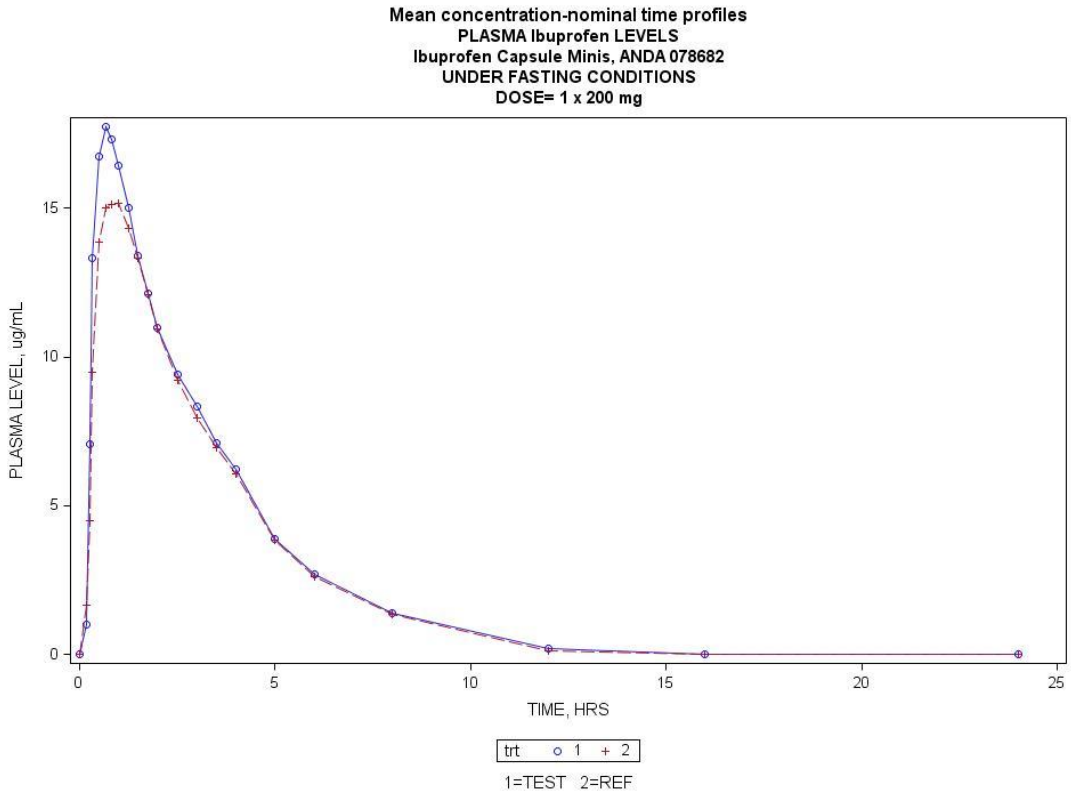
5.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n = 26)		Reference (n = 26)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	1.00	228.28	1.66	295.34	0.60
0.25	7.07	123.56	4.48	190.83	1.58
0.33	13.32	87.53	9.48	108.31	1.41
0.50	16.74	50.16	13.87	72.35	1.21
0.66	17.75	38.23	15.00	52.95	1.18
0.83	17.32	31.45	15.13	38.14	1.14
1.00	16.42	27.16	15.15	30.35	1.08
1.25	15.01	23.13	14.32	22.52	1.05
1.50	13.42	21.80	13.32	24.38	1.01
1.75	12.14	20.95	12.09	22.24	1.00
2.00	10.99	22.01	10.93	20.00	1.00
2.50	9.42	26.02	9.21	23.64	1.02
3.00	8.33	31.85	7.95	28.13	1.05
3.50	7.09	35.60	6.95	37.87	1.02
4.00	6.22	37.64	6.09	38.37	1.02
5.00	3.87	42.18	3.86	40.83	1.00
6.00	2.70	47.82	2.62	44.18	1.03
8.00	1.40	61.52	1.34	53.56	1.04
12.00	0.19	204.87	0.12	263.40	1.56
16.00	0.02	509.90	0.00	.	.
24.00	0.00	.	0.00	.	.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



5.2 Formulation Data

The formulation data were reviewed in the previous BE review.[4] The review conclusion remains same: (b) (4) (b) (4) (b) (4) therefore are considered as a Level-3 change per SUPAC-IR.

5.3 Dissolution Testing

The dissolution testing using the approved dissolution method for the approved Ibuprofen capsules (regular sized) was performed for the proposed Ibuprofen mini capsules (Batches #147001042, 147001043 & 147001044) against the RLD Minis product (Batch #R53091, expiry date Oct 2020). These data were present in the previous BE review.[4] Per the previous dissolution review conducted by the Division of Biopharmaceutics, the PAS was *inadequate due to insufficient data to support the bridging of formulation. The evaluation of the dissolution specification for the new formulation will be pending the responses to Bioequivalence deficiencies regarding the biowaiver request.*[11]

In the current submission, the applicant did not submit new dissolution data along with the fasting BE study (#035/19). The fasting BE study (#035/19) was conducted on the exhibit Batch #147001042 (manufacturing date 03/19/2018) and the RLD batch #R50632 (expiry date September 2020).

The dissolution data are to be reviewed by the Office of Pharmaceutical Quality.

5.4 Attachments

5.4.1 Additional Studies (If applicable)

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☐ Yes ☒ No

5.4.2 SAS Output

Study Type	Data	Stat Output	Result Table
Fasting	078682_FASTING_Datasets_Ibuprofen.doc	078682_FASTING_stat_Ibuprofen.doc	078682_FASTING_table_Ibuprofen.doc

[11] ANDA-078682-SUPPL-20»Biopharmaceutics Quality Review dated 2/14/2019, http://panorama.fda.gov/document/preview?versionID=5c65a7cd00e90bf13f7aabf007ba1ff3&ID=5c5b4cfa005dc9040fa0ded29cfcb683

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	078682/Supplement 20
APPLICANT:	Bionpharma Inc.
DRUG PRODUCT:	Ibuprofen Capsules (mini), EQ 200 mg Free Acid and Potassium Salt (OTC)

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

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns 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,

Hongling Zhang, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.5 Outcome Page

Completed Assignment for 078682 ID:39478

Reviewer: Zhang, Yi **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Ibuprofen Capsules Mini, 200 mg (OTC) (PAS)

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
39478	5/15/2019	BIO	Supplement [1]	1	1
39478	5/15/2019	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
39478	5/15/2019	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	2.75

http://cdsogd1/bioprod

BIOPHARMACEUTICS ASSESSMENT Office of New Drugs Products			
Application No.	ANDA 078682 S-20	**Primary Reviewer:** Mathew John, Ph.D.	
Division	ONDP/Division of Biopharmaceutics		
Applicant	Bionpharma Inc	**Secondary Reviewer:** Min Li, Ph.D.	
Trade Name	NA	**Branch Chief:** Kimberly Raines, Ph.D.	
Established Name	Ibuprofen mini capsules	**Division Director:** Paul Seo, Ph.D.	
Indication	NSAID, Analgesic		
Dosage Form / Strength	Capsules / 200 mg	**Date Assigned**	10/02/2018
Route of Administration	Oral	**Date of Review**	02/11/2018
Submission date(s)	9/10/2018		
Type of Submission	Prior Approval Supplement (PAS)	**GDUFA Goal date**	03/09/2019
Key Review Points	Evaluation of the dissolution method and acceptance criteria of the proposed Ibuprofen 200 mg smaller size (mini capsules)		
Recommendation	Inadequate		

Submission: The Applicant has submitted a PAS for addition of an alternate formulation (smaller size or mini capsules) of their Ibuprofen liquid filled capsules 200 mg (ANDA # 078682) which was approved on 3/24/2009. The comparative Qualitative / Quantitative (Q1/ Q2) composition of the currently approved Ibuprofen capsules and the proposed Ibuprofen mini capsules are tabulated in Table below. (b) (4)

(b) (4)

(b) (4). As per SUPAC IR this level 3 change requires an in vivo bioequivalence study or an in vitro in vivo correlation study. The Applicant has submitted a biowaiver which has been evaluated by the division of bioequivalence and the biowaiver was not granted.[1]

[1] Panorama; Bioequivalence Review 02/07/2019.

Table 1: Qualitative and quantitative composition of fill material of currently approved (Ibuprofen capsules 200 mg) and proposed (Ibuprofen mini capsules 200 mg) submitted by the Applicant

Component	Quality Standard	Function	Current Approved (Ibuprofen Capsules)	Proposed Composition (Ibuprofen Mini Capsules)
			mg/capsule	mg/capsule
Ibuprofen	USP	Drug substance	200.00	200.00
Potassium hydroxide (b) (4)	NF	(b) (4)		
Polyethylene glycol (b) (4)	NF			
Water	USP			
Theoretical Total Fill Weight				

Biopharmaceutics Assessment: The Applicant has submitted the comparative dissolution studies of 3 exhibit batches of Ibuprofen Soft Gelatin Capsules (Minis), 200 mg (lots 147001042, 147001043 and 147001044) with Advil® Liqui-Gels® Minis lot R53091 (Expiry 10/2020) manufactured by Pfizer Consumer Healthcare. The dissolution method used is the FDA dissolution database method which was also the previously approved method for the current formulation of Ibuprofen 200 mg capsules of the Applicant. The Applicant also has submitted the dissolution profiles of the currently approved product (which has (b) (4) % dissolution in (b) (4).[2] [3] As the biowaiver was not granted the bridging of the formulation is deemed inadequate. The evaluation of the dissolution specification for the proposed formulation is pending complete response from the Applicant to the bioequivalence deficiencies.

Table 2: Dissolution method and acceptance criteria proposed by the Applicant

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criterion/criteria
FDA Dissolution database	Type I Baskets	150	Phosphate buffer pH 7.2 37.0°C ± 0.5 °C	900 mL	5,10,15,20, and 30 minutes	Not less than (b) (4)% (Q) of the labeled amount of Ibuprofen is

[2] Application 078682 - Sequence 0087 - Supplement Summary Seq: 0087

[3] Application 078682 - Sequence 0088 - Summary Biopharm Seq: 0088

						dissolved in 20 minutes.

Table 3: Comparative in-vitro dissolution data of exhibit batches of Ibuprofen Soft Gelatin Capsules (Minis), 200 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus I (baskets)
	Speed of Rotation:	150 rpm
	Medium:	Phosphate Buffer pH 7.2
	Volume:	900 ml
	Temperature:	37.0 °C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4) minutes	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 5 min	10 min	15 min	20 min	30 min	Study Report Location
NA	8/14/2018	Advil Liqui-Gels Minis Batch No.: R53091 Mfg. date: NA Exp. date: Oct 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	2	85	100	100	100	m2-2.7.1.2
					Range	(b) (4)					
					%CV	55.9	21.0	1.3	1.3	1.3	
NA	8/12/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001042 Mfg. date: March 19, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	9	93	100	101	101	m2-2.7.1.2
					Range	(b) (4)					
					%CV	68.1	3.8	1.5	1.4	1.5	
NA	8/12/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001043 Mfg. date: March 21, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	15	96	102	103	103	m2-2.7.1.2
					Range	(b) (4)					
					%CV	84.5	9.7	1.2	0.9	1.0	
NA	8/14/2018	Ibuprofen Soft Gelatin Capsules (Minis), 200 mg Batch No.: 147001044 Mfg. date: March 22, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	10	98	102	103	103	m2-2.7.1.2
					Range	(b) (4)					
					%CV	142.7	4.1	1.5	1.1	1.1	

Recommendation: This PAS is inadequate due to insufficient data to support the bridging of formulation. The evaluation of the dissolution specification for the new formulation will be pending the responses to Bioequivalence deficiencies regarding the biowaiver request.

Signature	**Signature**
Mathew John, Ph. D	Min Li, Ph.D.
Division of Biopharmaceutics/Branch III	Division of Biopharmaceutics/Branch III
Office of New Drug Products	Office of New Drug Products

Mathew John

Digitally signed by Mathew John
Date: 2/12/2019 03:28:22PM
GUID: 5474a078001750e6b83c138c4ba05385

Min Li

Digitally signed by Min Li
Date: 2/12/2019 09:17:27AM
GUID: 5390b860000014ac1413f0693cdb1440

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	078682/Supplement 20
Drug Product Name	Ibuprofen Capsules (mini), Over-the-counter (OTC)
Strength(s)	EQ 200 mg Free Acid and Potassium Salt [1]
Applicant Name	Bionpharma Inc. (Bionpharma)
Applicant Address	600 Alexander Road, Suite 2-4B, Princeton, NJ, 08540, USA
US Contact Name and US Mailing Address	Usha Sankaran, Associate Vice President, Regulatory Affairs usha@bionpharma.com 600 Alexander Road, Suite 2-4B Princeton, NJ, 08540, USA
US Contact Telephone Number	609-380-3321
US Contact Fax Number	609-380-3311
Original Submission Date(s)	Original submission 07/27/2009 Full Approval 03/24/2009
Submission Date(s) of Amendment(s) Under Review	09/10/2018, Supplement 20, Sequence 0087 (111) Prior Approval Supplement - Addition of an alternate formulation (smaller size capsules or mini capsules) of the drug product
Primary Reviewer	Yi Zhang, M.D., Ph.D.
Secondary Reviewer	Kuldeep R. Dhariwal, Ph.D.
Tertiary Reviewer	Not Applicable (N/A)
Study Number(s)	N/A
Study Type(s)	Waiver request
Strength(s)	200 mg
Clinical Site	N/A
Clinical Site Address	N/A
Analytical Site	N/A
Analytical Site Address	N/A

Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)** [2]	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete** ☒ **N/A (Waiver/Deem Bioequivalent)** [2]

[1] From here onwards in the review EQ 200 mg Free Acid and Potassium Salt will be referred as 200 mg.
[2] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
QC Dissolution	☒ **Pending** ☐ **Adequate** ☐ **Inadequate**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☒ **Major** ☐ **Minor/IR** ☐ **N/A (Review is Adequate)**		
Major Deficiency Theme	New/Missing BE studies		
Justification for Major Designation	The bioequivalence deficiency has been classified as MAJOR because the deficiency pertains to inadequate in vivo or in vitro bioequivalence studies (i.e., a fasting bioequivalence study is requested) as noted in Appendix A, Section B.1.a of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	***Reminder: Check PSG in development spreadsheet on V: drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ **Recommended/Latest Revision Date: March 2015** **RLD Number: NDA 020402** ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
111, 112	**Waiver**	**200 mg (mini)**	☐ **Adequate** ☒ **Inadequate**

1 EXECUTIVE SUMMARY

This is review of a Prior Approval Supplement (PAS).

Bionpharma's Ibuprofen Capsule, 200 mg, regular-sized, was originally approved under ANDA 078682 on March 24, 2009.[3] On 9/10/2018, Bionpharma submitted this PAS to include a new line extension product of smaller-sized capsules (mini) of the drug product.

[3] Orange Book, last accessed 1/7/2019, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=078682

[redacted] (b) (4)

[redacted] (b) (4) therefore are considered as a Level-3 change per Section III of the SUPAC-IR guidance [FDA Guidance for Industry, Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation]. These changes are likely to have a significant impact on the quality and performance of the proposed formulation, and an in vivo bioequivalence (BE) study is recommended to support such changes. The applicant will be asked to conduct a single dose fasting BE study comparing its proposed formulation (mini capsule) to the reference listed drug (RLD) product Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg, Minis.

Comparative dissolution data are under review by the Office of Pharmaceutical Quality.

The supplement is inadequate.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Ibuprofen Capsules (mini), 200 mg OTC

Reference Standard (RS) and Strength(s) [4]	Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg OTC
RS Holder; NDA/ANDA Number; Approval Date	Pfizer Inc.; NDA 020402, Approval Date: April 20, 1995
Reference Listed Drug (RLD) and Strength(s)	Same as RS
RLD Holder; NDA/ANDA Number; Approval Date	Same as RS

Reviewer's note on the RS/RLD:

NDA 020402 also lists Advil Migraine Liqui-Gels® (ibuprofen) Capsules, 200 mg (OTC), approved March 16, 2000. Mini capsules are not listed in the Orange Book.

3.2 PK/PD Information

Most recent RLD label (provide embedded document)[5,6]	DailyMed 20180228.pdf
Indication[5]	• Temporarily relieves minor aches and pains due to: ✓ headache ✓ toothache ✓ backache ✓ menstrual cramps ✓ the common cold ✓ muscular aches ✓ minor pain of arthritis • Temporarily reduces fever
Boxed warning[5]	None
Bioavailability[7]	The bioavailability of ibuprofen is similar among the different oral dosage forms at approximately 80%.
Food Effect[7]	Administration of oral products immediately following a meal has a minimal effect on overall bioavailability; however, it decreases the Cmax and delays Tmax.
Tmax[7]	The time to reach peak concentrations differs among different oral dosage forms and is roughly 120, 62, and 47 minutes after administration of tablets, chewable tablets, or suspension, respectively.

[4] Orange Book, last accessed 2/7/2019, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020402

[5] Label form DailyMed, https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=ba5a9a04-993e-4fd6-bb40-6edfdfb69b34&type=pdf&name=ba5a9a04-993e-4fd6-bb40-6edfdfb69b34, last accessed 2/7/2019

[6] Carton Label from Drugs@FDA, action date 08/31/2018, last accessed 2/7/2019, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020402Orig1s047lbl.pdf

[7] Clinical Pharmacology, searching term 'Advil 200mg Liqui-Gel', http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=303&sec=monphar&t=0, last accessed 1/16/2019

Metabolism[7]	Ibuprofen is a racemate, and, on average, 60% of R-ibuprofen is converted to S-ibuprofen. S-ibuprofen is metabolized via hepatic oxidation by cytochrome P450 (CYP) 2C9 to inactive metabolites. CYP2C9 is polymorphic; CYP2C9(1) is the wild-type, and CYP2C9(2) and CYP2C9(3) are the most common variants. The variant CYP2C9(3) allele decreases enzyme activity to a greater extent than does CYP2C9(2), but clearance of racemic ibuprofen was reduced among all variant genotypes as compared with the wild-type (1/1). Higher S-ibuprofen concentrations led to greater inhibition of COX-1 (reduced thromboxane B2 concentrations) and greater inhibition of COX-2 (reduced prostaglandin E2 concentrations). Importantly, both thromboxane B2 and prostaglandin E2 concentrations were reduced the most among patients with the CYP2C9 genotypes (3/3), (1/3), (2/3), and (2/2). The elimination half-life of ibuprofen is significantly prolonged in patients with moderate to severe cirrhosis.
Excretion[7]	Ibuprofen is excreted in the urine: 50 to 60% as metabolites and approximately 10% as unchanged drug. Some biliary excretion may occur. Excretion is usually complete within 24 hours of administration.
Half-life[7]	Plasma half-life of both oral and parenteral forms is between 2 and 4 hours
General Administration Information[7]	Administer orally with milk or food to minimize GI irritation.
Maximum Daily Dose (MDD) [7]	1200 mg

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance[8]	UCM436830-mar 2015.pdf	
Summary of OGD or DB History	Approved ANDAs:	Yes. (See OGD History for details)
	Pending ANDAs:	None per DARRTS as of 12/11/2018. The current ANDA was listed as 'Approved' in DARRTS.

[8] Draft PSG on Ibuprofen (NDA 020402), Recommended Mar 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436830.pdf

	Controls:	Yes. Multiple legacy controls, none were from the current applicant. GDRP: Guidance finalization control (Ref #3067177)
	Protocols:	None
	Pending Citizen Petitions and other legal and regulatory issues:[9] If yes, please comment.	☐ Yes ☒ No

3.4 OGD History

RLD History

Advil® Liqui-Gels® (ibuprofen) Capsules 200 mg was originally approved on 4/20/1995 under NDA 020402 as regular liquid-filled capsules. A reduced-fill 200 mg capsule, identified as Advil® Liqui-Gels® Minis, was approved on 3/8/2017 as a line extension product under NDA 20402/S-042.[10] Per Chemistry review[11], the excipients used in *minis* formulation are qualitatively the same but at reduced amount when compared to the regular sized Advil® Liqui-Gels® capsules. (b) (4) (b) (4) (b) (4). Per Biopharmaceutics review[12], the proposed changes were considered a SUPAC-IR Level 3 change, which required a BE study. To support the PAS, in addition to CMC information and labeling, the applicant submitted results of a single dose fasting BE study (study #PV-08-26) and comparative dissolution data comparing reduced-fill 200 mg capsules to regular sized 200 mg capsules.

OGD History

As of 1/16/2019, the OGD has approved the following generic Ibuprofen Capsules (200 mg) per Orange Book.

ANDA No.	Strength	Applicant Holder	Approval Date	Mkt Status
A202300	200 mg	AMNEAL PHARMACEUTICALS	12/23/2011	OTC
A206999	200 mg	ASCENT PHARMACEUTICALS INC	12/21/2017	OTC
A207753	200 mg	AUROBINDO PHARMA LTD	6/29/2018	OTC
A078682	200 mg	BIONPHARMA INC	3/24/2009	OTC

[9] As per DLRS policy updates as of 01/14/2019 in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

[10] GDRP, NDA-020402-SUPPL-42, http://panorama.fda.gov/project/view?ID=5824691200011ede1b68e29a2942a3a6

[11] NDA-020402-SUPPL-42»Drug Product Quality Review- Drug Product Review, http://panorama.fda.gov/task/view?ID=582469190001209bc08e8c44db5f1f43, dated 3/2/2017

[12] NDA-020402-SUPPL-42»Biopharmaceutics Quality Review, dated 2/7/2017, http://panorama.fda.gov/task/view?ID=5824691900012113e85079b3d91b3270

A206568	200 mg	HUMANWELL PURACAP PHARMACEUTICAL WUHAN CO LTD	6/21/2016	OTC
A079205	200 mg	MARKSANS PHARMA LTD	6/26/2009	OTC
A077338	200 mg	P AND L DEVELOPMENT LLC DBA PLD DEVELOPMENTS LLC	7/10/2009	OTC
A203599	200 mg	SOFGEN PHARMACEUTICALS LLC	9/7/2016	OTC
A204469	200 mg	STRIDES PHARMA GLOBAL PTE LTD	3/28/2018	OTC
A074782	200 mg	CONTRACT PHARMACAL CORP	7/6/1998	DISCN
A070626	200 mg	BAYER HEALTHCARE LLC	9/2/1987	DISCN
A071002	200 mg	BAYER HEALTHCARE LLC	9/2/1987	DISCN

In addition to the current ANDA, two ANDAs (204469 and 206568) submitted PAS and proposed similar type of change for product line extension in line with RLD Minis.

1. ANDA 204469-Supp-003[13]

Ibuprofen is a BCS Class II compound. The (b) (4) excipients were (b) (4) from approved ANDA to achieve the desired smaller size capsule "minis". (b) (4) (b) (4) (b) (4) (b) (4) Postapproval Changes-Immediate Release Solid Oral Dosage Forms (SUPAC-IR) guidance (November 1995) for a level-3 composition change.[14]

2. ANDA-206568-Suppl-012[15]

(b) (4) (b) (4). Therefore, the proposed changes in formulation were considered SUPAC-IR Section III Level 2 changes. The dissolution test was performed against approved 200 mg generic product using pH 7.2 phosphate buffer. The PAS was found acceptable. In vivo BE data were not requested, the supplement was not reviewed by DB.

[13] GDRP, http://panorama.fda.gov/project/view?ID=5b46d96e01d1366f63a09d916a324586, ANDA-204469-SUPPL-3, CR dated 01/04/2019

[14] GDRP, ANDA-204469-GI-1-MEETING-29, meeting request submitted 1/17/2019, http://panorama.fda.gov/task/view?ID=5c47343300e380dfed89d96f3464eaa7

[15] GDRP, http://panorama.fda.gov/project/view?ID=5b21f1e400b20a9b7adf6be86fc5f8fd, ANDA-206568-SUPPL-12 approved 11/20/2018

3.5 Pre-Study Bioanalytical Method Validation

N/A

3.6 In Vivo Studies

N/A

3.7 OSIS Status

N/A

Reviewer's comment:

(b) (4)

4.1.4 Inactive Ingredients (IIG Table)

All excipients used in the proposed Mini capsule formulation are qualitatively the same (b) (4) compared to the approved regular-sized formulation (blue-colored), therefore are acceptable.

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

(b) (4) therefore are considered as a Level-3 change per SUPAC-IR.

4.2 Dissolution Testing

4.2.1 Dissolution Data

Dissolution Conditions	**Apparatus:**	USP Apparatus I (Basket)
	Speed of Rotation:	150 rpm
	Medium:	Phosphate Buffer pH 7.2
	Volume:	900 mL
	Temperature:	37.0 ± 0.5°C
Firm's Proposed Specifications	NLT (b)%	(b) (4) minutes
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						5 min	10 min	15 min	20 min	30 min	
NA	8/14/2018	Advil Liqui-Gels Minis (**Ref**) Batch No.: R53091 Exp. date: Oct 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	2	85	100	100	100	Module 2.7.1.2
					Range	(b) (4)					
					%CV	55.9	21.0	1.3	1.3	1.3	
NA	8/12/2018	Ibuprofen Capsules (Mini), 200 mg Batch No.: 147001042 Mfg. date: March 19, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	9	93	100	101	101	
					Range	(b) (4)					
					%CV	68.1	3.8	1.5	1.4	1.5	
NA	8/12/2018	Ibuprofen Capsules (Mini), 200 mg Batch No.: 147001043 Mfg. date: March 21, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	15	96	102	103	103	
					Range	(b) (4)					
					%CV	84.5	9.7	1.2	0.9	1.0	
NA	8/14/2018	Ibuprofen Capsules (Mini), 200 mg Batch No.: 147001044 Mfg. date: March 22, 2018 Exp. date: Feb 2020	200 mg Soft Gelatin Capsule	12	Mean (%)	10	98	102	103	103	
					Range	(b) (4)					
					%CV	142.7	4.1	1.5	1.1	1.1	

Reviewer's comment:

Comparative dissolution testing using the approved dissolution method for the currently approved Ibuprofen capsules (regular size) was performed for the proposed mini capsule product (Batches #147001042, 147001043 & 147001044) against the RLD Minis product (Batch # R53091). The dissolution data are under review by the Office of Pharmaceutical Quality.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:	078682/Supplement 20
APPLICANT:	Bionpharma Inc.
DRUG PRODUCT:	Ibuprofen Capsules (mini), EQ 200 mg Free Acid and Potassium Salt (OTC)

The Division of Bioequivalence (DB) II has completed its review and has identified the following deficiency:

You propose an addition of a new line extension product, smaller liquid-filled Ibuprofen capsules, 200 mg (mini capsules). Your proposed formulation changes from regular to "mini" sized capsules are considered as Level-3 change as per Section III of the SUPAC guidance for IR products [FDA Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post Approval (SUPAC) Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation: November 1995]. In vivo bioequivalence (BE) study is recommended to support such changes. Please conduct a single dose fasting BE study comparing your proposed formulation (mini capsules) to the reference listed drug product, Advil® Liqui-Gels® (ibuprofen) Capsules, 200 mg (Minis).

Sincerely yours,

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.3 Outcome Page

Completed Assignment for 078682 ID:

Reviewer: Zhang, Yi **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Ibuprofen Capsules mini, 200 mg (OTC) (PAS)

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
	09/10/2018	BIO	Supplement [1]	1	1
	09/10/2018	Parallel	Study Amendment [1]	1	1
	09/10/2018	Parallel	Pre-Screening [0.25]	0.25	0.25
	09/10/2018	Parallel	Anything Else Not Listed (Discuss with Management) [1]	1	1
				Total:	

http://cdsogd1/bioprod