CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211733Orig1s000

Trade Name:	Advil Dual Action with Acetaminophen tablet
Generic or Proper Name:	Ibuprofen 125 mg / acetaminophen 250 mg
Sponsor:	Pfizer, Inc.
Approval Date:	February 28, 2020
Indication:	For temporary relief of minor aches and pains due to: headache, toothache, backache, menstrual cramps, muscular aches, and minor pain of arthritis, in adults and children 12 years of age and older.

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211733Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	X
Product Quality Review(s)	X
Non-Clinical Review(s)	X
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 211733

NDA APPROVAL

Pfizer Inc.
Attention: Wendy Ann McManus
Director, Regulatory
1 Giralda Farms
Madison, NJ 07940

Dear Ms. McManus:

Please refer to your new drug application (NDA) dated and received January 31, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Advil Dual Action with Acetaminophen (ibuprofen 125 mg/acetaminophen 250 mg) tablet.

We acknowledge receipt of your major amendment dated November 21, 2019, which extended the goal date by 3 months.

This new drug application provides for the use of Advil Dual Action with Acetaminophen (ibuprofen 125 mg/acetaminophen 250 mg) tablet for temporary relief of minor aches and pains due to: headache, toothache, backache, menstrual cramps, muscular aches, and minor pain of arthritis, in adults and children 12 years of age and older.

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 minor editorial revisions listed below.

Increase the size of the modifier “with Acetaminophen” within the proprietary name by an additional 5% on the principal display panel for the labeling items listed in the table immediately below.

SUBMITTED LABELING	DATE SUBMITTED
50 x 2-Count Pouch Dispenser	February 18, 2020
8-Count Packed Vial Large Backer Card	February 18, 2020
18-Count Outer Carton	February 18, 2020
144-Count Outer Carton	February 18, 2020
144-Count Immediate Container (Bottle)	February 18, 2020
144-Count Immediate Container (Stand-Alone Bottle)	February 18, 2020
18-Count IRC (Peel-Off PDP) $1.00 Off	February 18, 2020

Per 21 CFR 201.326, bullets are required for the liver damage warning and the stomach bleeding warning. Use bullets to separate statements under the “Acetaminophen liver damage warning” and “NSAID stomach bleeding warning” on all immediate container labeling items listed in the table immediately below.

SUBMITTED LABELING	DATE SUBMITTED
8-Count Packed Vial (“Old DWG” Style)	February 27, 2020
8-Count Packed Vial (“New DWG” Style)	February 27, 2020
18-Count Immediate Container (Bottle)	February 24, 2020
24-Count (18+6-Count) Immediate Container (Bottle)	February 24, 2020
36-Count Immediate Container (Bottle)	February 24, 2020
72-Count Immediate Container (Bottle)	February 24, 2020
90-Count (72+18-Count) Immediate Container (Bottle)	February 24, 2020
144-Count Immediate Container (Bottle)	February 18, 2020
162-Count (144+18-Count) Immediate Container (Bottle)	February 24, 2020
216-Count Immediate Container (Bottle)	February 27, 2020
240-Count Immediate Container (Bottle)	February 27, 2020

Per 21 CFR 201.66(d)(5), a visual graphic (e.g., an arrow) shall be used to signal the continuation of the Drug Facts labeling to the next adjacent panel. The “Lift Here” designation is not part of the drug facts label (DFL). Insert an arrow within the second panel of the DFL for the 8-count packed vial small backer card extended label submitted February 27, 2020, and the 90-count immediate container (bottle) extended label submitted February 24, 2020.

Indent the sub-bulleted statements under ***Uses*** on the peel back drug facts label (DFL) for the 4-count carton (2 x 2 pouches) submitted February 27, 2020. We refer you to Question 21 in *Guidance for Industry Labeling OTC Human Drug Products — Questions and Answers* (December 2008) at https://www.fda.gov/media/72441/download.

On the same 4-count carton (2 x 2 pouches) extended label, submitted February 27, 2020, revise the DFL so that the first bulleted warning under **Do not use** is not split between two panels.

Display the ***Directions*** in table format in the 8-Count Packed Vial (“New DWG” Style) immediate container label. Revise your labeling to include a table like the table provided below.

adults and children 12 years and over	▪ **take 2 caplets every 8 hours** while symptoms persist
children under 12 years	▪ ask a doctor

(b) (4)

LABELING

Submit final printed labeling (FPL) as soon as they are available, but no more than 30 days after they are printed. Except for the revisions listed above, the final printed labeling must be identical to the enclosed labeling as described in the table below and must be in the “Drug Facts” format (21 CFR 201.66), where applicable.

Submitted Labeling	Dates Submitted
50 x 2-Count Pouch Dispenser	February 18, 2020
2-Count Pouch, Front Label	February 18, 2020
2-Count Pouch, Back Label	February 18, 2020
4-Count Carton (2 x 2-ct packets)	February 27, 2020
Peel-Back DFL for 4-Count Carton	February 27, 2020
8-Count Loose Vial (“Old DWG” Style)	February 27, 2020
8-Count Loose Vial Shelf Tray	February 27, 2020
8-Count Packed Vial (“Old DWG” Style)	February 27, 2020
8-Count Packed Vial (“New DWG” Style)	February 27, 2020
8-Count Packed Vial Large Backer Card	February 18, 2020
8-Count Packed Vial Small Backer Card	February 27, 2020
Peel-Back DFL for 8-Count Packed Vial Small Backer Card	February 27, 2020
18-Count Outer Carton	February 18, 2020
18-Count Immediate Container (Bottle)	February 24, 2020
24-Count (18+6-Count) Outer Carton	February 24, 2020
24-Count (18+6-Count) Immediate Container (Bottle)	February 24, 2020
36-Count Outer Carton	February 24, 2020
36-Count Immediate Container (Bottle)	February 24, 2020
Peel-back DFL for 18-Count, 24-Count (18+6-Count), and 36-Count Outer Carton	February 18, 2020
72-Count Outer Carton	February 24, 2020
72-Count Immediate Container (Bottle)	February 24, 2020
90-Count (72+18-Count) Outer Carton	February 24, 2020
90-Count (72+18-Count) Immediate Container (Bottle)	February 24, 2020
Peel-Back DFL for 72-Count and 90-Count (72+18-Count) Outer Carton	February 24, 2020
144-Count Outer Carton	February 18, 2020
144-Count Immediate Container (Bottle)	February 18, 2020
144-Count Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	February 18, 2020
162-Count (144+18-Count) Outer Carton	February 24, 2020
162-Count (144+18-Count) Immediate Container (Bottle)	February 24, 2020
162-Count (144+18-Count) Immediate Container (Stand-Alone Bottle) with “Easy Open” Cap	February 24, 2020
180-Count Immediate Container (Stand-Alone Bottle)	February 24, 2020
216-Count Outer Carton	February 27, 2020

216-Count Immediate Container (Bottle)	February 27, 2020
216-Count Immediate Container (Stand-Alone Bottle)	February 24, 2020
240-Count Outer Carton	February 27, 2020
240-Count Immediate Container (Bottle)	February 27, 2020
240-Count Immediate Container (Stand-Alone Bottle)	February 27, 2020
288-Count Immediate Container (Stand-Alone Bottle)	February 27, 2020
Instantly Redeemable Coupon (IRC) Sticker $1.00 Off Any "Advil Dual Action" 18-ct or Larger	January 31, 2019
IRC Sticker $2.00 Off Any "Advil Dual Action" 36-ct or Larger	January 31, 2019
IRC Sticker $2.00 Off Any "Advil Dual Action" 72-ct or Larger	January 31, 2019
IRC Sticker $3.00 Off Any "Advil Dual Action" 72-ct or Larger	January 31, 2019
IRC Sticker $2.00 Off Any "Advil Dual Action EZ Open" 144-ct or Larger	January 31, 2019
18-Count IRC (Peel-Off PDP) $1.00 Off	February 18, 2020
36-Count IRC (Peel-Off PDP) $1.00 Off	February 24, 2020
72-Count IRC (Peel-Off PDP) $1.00 Off	February 24, 2020
144-Count IRC (Peel-Off PDP) $1.00 Off	February 27, 2020

The final printed labeling should be submitted electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.[1] For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 211733**." Approval of this submission by FDA is not required before the labeling is used.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at FDA.gov.[2] Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As*. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 months because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. Infants less than 6 months of age with pain should be evaluated by a licensed healthcare professional.

We are deferring submission of your pediatric studies for ages 6 months to less than 12 years for this application because this product is ready for approval for use in adults and the pediatric studies in this age group have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

3808-1
Pediatric pharmacokinetic and tolerability study in children 2 years to < 12 years of age with acute pain suitable for treatment with a nonprescription analgesic

The objective of the study is to characterize the pharmacokinetic profile and tolerability of ibuprofen/acetaminophen fixed-dose combination in children 2 years to < 12 years with acute pain suitable for treatment with a nonprescription analgesic.

The timetable you submitted on February 25, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission	12/2020
Study Completion	10/2022
Final Report Submission	04/2023

3808-2
Pediatric pharmacokinetic, efficacy, and safety study in children 6 months to < 2 years of age with acute pain suitable for treatment with a nonprescription analgesic

The objective of the study is to evaluate analgesic efficacy, pharmacokinetics, and tolerability of ibuprofen/acetaminophen fixed-dose combination in children 6 months to <2 years of age with acute pain suitable for treatment with a nonprescription analgesic.

The timetable you submitted on February 25, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission	03/2021
Study Completion	06/2023
Final Report Submission	12/2023

3808-3
Pediatric targeted Label Comprehension Study for caregivers of children from birth to < 12 years of age

The objective of the study is to ensure that caregivers of children under the age of 12 adequately understand the labeling.

The timetable you submitted on February 25, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission	09/2023
Study Completion	09/2024
Final Report Submission	03/2025

3808-4
Pediatric Self-Selection Study
The design of this trial will be based on the results of the Label Comprehension Study (PMR 3808-3).

The timetable you submitted on February 25, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission	09/2025
Study Completion	09/2026
Final Report Submission	03/2027

3808-5
Pediatric Actual Use Study
The design of this trial will be based on the results of the Pediatric Label Comprehension Study (PMR 3808-3).

The timetable you submitted on February 25, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission	09/2025
Study Completion	09/2026
Final Report Submission	03/2027

FDA considers the word *final* in the phrase “final protocol submission” to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3] Of note, FDA must review and approve the protocols for the PREA-required studies prior to study initiation.

Submit the protocol(s) to your IND 112538, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

This product is appropriately labeled for use in ages 12 to 17 years for this indication; therefore, no additional studies are needed in this pediatric group. We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call LT Sally Doan, Regulatory Project Manager, at 301-796-8025.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Acting Deputy Director, Office of Nonprescription Drugs
Acting Deputy Director, Division of Nonprescription Drugs I
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN M MAHONEY
02/28/2020 02:05:43 PM