CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201803Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 12, 2012
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # Supplement #	201803
Applicant Name	Pfizer Consumer Healthcare (PCH)
Date of Submission	December 16, 2011
PDUFA Goal Date	June 16, 2012
Proprietary Name / Established (USAN) Name	Advil/ sodium ibuprofen dihydrate
Dosage Forms / Strength	Tablet/ ibuprofen 200 mg
Proposed Indication(s)	1. minor aches and pains 2. fever reducer
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	P. Callahan-Lyons/ L. Furlong
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	J. Hill/ A. Al Hakim
Microbiology Review	
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	
OSE/DMEPA	
OSE/DDRE	
OSE/DRISK	
Other DNRD labeling	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The applicant, Pfizer Consumer Healthcare (PCH), has developed a tablet containing ibuprofen as a sodium salt. The tablet contains 200 mg of ibuprofen, provided as 256 mg sodium ibuprofen dihydrate (Na IBU). PCH supported the safety and efficacy of the Na IBU by showing bioequivalence to the reference product, Advil Liqui-Gels.

This review will cover the following: 1) a review of the 483 issue; 2) a brief review of the safety data submitted; 3) a discussion of the pediatric development program and PREA related issues. The reader is also referred to previous reviews for more details of the PK and safety data.

2. Background

During the first round of review, all information to assess the efficacy and safety of sodium ibuprofen were provided and found to be adequate (the reader is referred to the previous discipline reviews for details). However, the applicant received a 483 for manufacturing site deficiencies, and this precluded approval. A complete response letter was issued on April 29, 2011 listing this deficiency and on December 16, 2011 the applicant provided a complete response to these issues.

The applicant has now submitted information to address this deficiency as well as a safety update, which is the focus of this review. For additional details of the previous regulatory history of this product, the reader is referred to my previous review as well as the previous MO and CDTL reviews.

3. CMC/Device

A 483 form was issued to the applicant during the first review cycle. Several observations delineated in the 483 are pertinent to the manufacture of this product (although this product was not named specifically in the 483) as follows:

1) Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.
2) The responsibilities and procedures applicable to the quality control unit are not fully followed.

3) Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.
4) There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

The CMC reviewer now provides the following comments:

On 29-APR-2011 a Complete Response (CR) letter was issued for this NDA, citing serious deviations from cGMPs at the listed manufacturing facility. The CR letter also indicated that satisfactory resolution of these deficiencies was required before this application could be approved. On 16-DEC-2011 the Applicant submitted a resubmission for this Application, indicating that the manufacturing deficiencies noted at the facility in question had been resolved and that this facility was now in compliance with cGMPs.

*In support of this claim, the overall recommendation filed in EES (see attachment) was noted as **acceptable** on 06- DEC-2011, with an overall re-evaluation date of 04-JUN-2013. This update to the overall EES recommendation to **acceptable** resolves the outstanding cGMP violations cited in the CR letter dated 29-ARP-2011. No new CMC information has been provided in this resubmission, thus the overall CMC recommendation of **approve** remains. From a CMC perspective, there are no further approvability issues with respect to this Application, the current CMC recommendation is **approve**.*

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the information concerning the manufacture of the drug product and drug substance.

4. Nonclinical Pharmacology/Toxicology

No new information was submitted.

5. Clinical Pharmacology/Biopharmaceutics

No new information was submitted for this review. Pivotal PK study AH-09-08, which was previously reviewed, compared the to-be marketed formulation of Na IBU to Advil Liqui-Gels and Motrin IB (all in the fasted state), and compared Na IBU to Advil Liqui-Gels (both in the fed state). The study demonstrated that Na IBU is bioequivalent to Advil Liqui-Gels for the active moiety by Cmax and AUC. The mean Tmax for Na IBU (about 35 minutes) was shorter than the mean Tmax for Advil Liqui-Gels (about 50 minutes) and this was felt to not be a clinically important difference. The reader is referred to the previous clinical pharmacology review in which this study was evaluated.

Therefore, I concur with the previous conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No specific efficacy studies were submitted for this application. PCH demonstrated bioequivalence of Na IBU to Advil Liqui-Gels. Advil Liqui-Gels was approved in the United States for OTC use in April 1995 under NDA 20402. Advil Liqui-Gels is listed in the FDA's Orange Book as a reference listed drug.

8. Safety

The reader is referred to the MO review by Dr. Priscilla Callahan-Lyon for a detailed analysis of the safety data provided. In general, the primary reviewer concluded that there are no new safety signals noted. The available data continue to support a positive risk-benefit analysis for this product. I agree.

The safety data submitted provided an update to the safety information included in the original NDA submission and included post-marketing data from four databases:
1. Pfizer internal safety database
2. World Health Organization (WHO) database
3. FDA Adverse Event Reporting System (AERS)
4. American Association of Poison Control Centers database (AAPCC)

For each database, Pfizer reviewed the serious case reports as well as topics of special interest including: deaths, drug interactions (particularly warfarin and lithium), drug overdose, drug abuse or misuse, experience during pregnancy or lactation, use in pediatric and geriatric populations, and experience in patients with renal insufficiency or cirrhosis.

The medical officer concludes that Pfizer Consumer Healthcare has provided adequate post-marketing data supporting the safety of ibuprofen. No new safety signals were identified. In addition, although the exposure has been less for ibuprofen sodium as compared to standard ibuprofen, there is no evidence of unexpected safety concerns associated with ibuprofen sodium.

9. Advisory Committee Meeting

No advisory committee meeting was held for this product.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable. After discussions it was determined that a new salt is a new active ingredient and therefore triggers PREA.

The reader is referred to my previous review as well as the MO and CDTL reviews for a discussion of pediatric issues. In summary, PREA is triggered and there was no information presented by PCH to support a waiver for the less than 12 year old population. Therefore, during the first review cycle the Agency recommended that a pharmacokinetic bioequivalence study evaluating an Na IBU pediatric formulation in adult subjects may be adequate to establish the safety and efficacy of Na IBU in the targeted pediatric population. To address this, PCH will develop an oral solution (b) (4). This formulation is intended to provide (b) (4) of the active ingredient, ibuprofen (IBU), in a salt form per (b) (4). The pharmacokinetic profile of this formulation will be assessed in a single-dose, randomized, open-label, in-patient, two-way crossover bioequivalence study (b) (4)

The proposed timeline is as follows:

Final Protocol Submission:	07/13
Final Report Submission:	04/14

As ibuprofen has been adequately studied and labeled in children from 6 months to 17 years of age, the proposal of a PK program in adults using bioequivalence to an approved product for children is acceptable to the clinical and clinical pharmacology reviewers. This approach was presented to PeRC on April 6, 2011 and also found to be acceptable. A waiver for less than 6 months of age was also acceptable. I agree with this approach.

11. Other Relevant Regulatory Issues

No issues.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Nonprescription Regulation Development (DNRD) provided labeling reviews.
The label conforms to the currently approved Advil label. There were no changes submitted. The DNRD reviewer previously recommended approval and I agree. I also agree with the proprietary name, Advil.

13. Decision/Action/Risk Benefit Assessment

Based on the information presented in this submission, the applicant has provided adequate data to support approval of this product. The PK studies demonstrate equivalence to the reference listed product and the chemistry review did not identify any specific issues. The safety information does not suggest that ibuprofen sodium would have a safety profile that differs from any other approved ibuprofen formulations. The 483 issues have been satisfactorily resolved. The applicant has agreed to the pediatric plan.

Therefore, I recommend approval with the PREA PMR as described.

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

/s/

JOEL SCHIFFENBAUER
06/12/2012