

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204767Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ellen Fields, MD, MPH
Subject	Deputy Division Director Summary Review
NDA #	204767/ 017 and 018
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	April 30, 2015
PDUFA Goal Date	October 30, 2015
Proprietary Name	Acetaminophen Injection
Dosage Forms / Strength	Injection, 10 mg/mL
Proposed Indication(s)	1. Management of mild to moderate pain 2. management of moderate to severe pain with adjunctive opioid analgesics 3. reduction of fever
Action	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Carlic Huynh, PhD; Newton Woo, PhD; Dan Mellon, PhD
CMC Review/OBP Review	Julia Pinto, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
OPDP	N/A
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	N/A
OSE/DDRE	N/A
OSE/DRISK	N/A
Other	N/A

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

1. Introduction

Fresenius Kabi USA submitted this New Drug Application for a new presentation of an intravenous acetaminophen product via the 505(b)(2) pathway, relying on the Agency's previous findings of safety and efficacy for the Listed Drug, Ofirmev (NDA 22450), for the same indication, the management of mild-to-moderate pain, management of moderate-to-severe pain with adjunctive opioid analgesics, and reduction of fever. This is the second review cycle for this application following a Complete Response action in 2013.

2. Background

The Applicant submitted their original NDA on September 12, 2012. A Complete Response action was taken on July 25, 2013, due to inadequate leachable data at multiple time points, and inadequate safety justification for levels of leachables from the container/closure system. The referenced Master File (26696) supporting the safety of the FreeFlex (b)(4) was also found inadequate and a deficiency letter was sent to the Master File holder.

Ofirmev was approved on November 2, 2010 and has exclusivity that expires on November 2, 2013. There are also two active patents listed in the Orange Book due to expire on August 5, 2017 and June 6, 2021.

3. CMC/Device

The CMC review was conducted by Julia Pinto, PhD, Acting Branch Chief, OPQ/ONDP/Division II.

The original NDA submission was recommended as a Complete Response from the CMC perspective, in April 2013, due to a lack of data to support the leachable/extractables from the Freeflex (b)(4) container closure system. In the current submission, the Applicant submitted a leachable/extractable assessment of the drug product stored in the proprietary FreeFlex (b)(4)

Stress tests at 60°C were performed over the pH range of 5 to 7. The drug product samples were taken after four weeks. (b)(4)

however none of the observed levels were out of specifications.

Photostability data demonstrated the product does not degrade upon direct exposure to light.

As stated in Dr. Pinto's review:

The current resubmission, has adequately addressed these concerns by providing updated leachable assessment of the drug product and stress testing for potential extractables. No changes are proposed from the original submission, in terms of formulation, manufacture or controls. Therefore this NDA is recommended for approval, from the CMC perspective, with a 24 month expiry for the drug product.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Carlie Huynh, PhD, with secondary concurrence by Newton Woo, PhD and R. Daniel Mellon, PhD.

The deficiency identified during the first review cycle for this product was lack of nonclinical data supporting the safety of three identified leachables from the container closure system. The current submission included the following nonclinical data: a 4-week IV toxicity study with (b) (4) in rats and a 4-week IV toxicity study with (b) (4) in rats in order to qualify the safety of both substances. The Applicant also submitted 18 and 24-month time points for stability which included updated leachable data and revised toxicological risk assessments as requested (for (b) (4)) in the complete response letter.

Dr. Huynh stated in his review:

In the 4-week IV toxicology studies, rats were dosed via intravenous administration daily with (b) (4). Adverse local and systemic findings were noted in both repeat-dose toxicity studies with a systemic NOAEL of (b) (4)/day and (b) (4)/day identified for (b) (4), respectively, which confer exposure margins of (b) (4) based on a body surface area comparison, respectively. The Applicant also submitted the results of an Ames assay with (b) (4) and with (b) (4). Both leachables tested negative in an Ames assay and therefore are not considered mutagenic under the conditions tested. Review of the revised toxicological risk assessments showed that there is adequate coverage of the leachables (b) (4) to support the proposed 24-month shelf-life.

Taken together, the Applicant has provided adequate nonclinical data to support the safety of the identified leachables from the container closure system and therefore we recommend approval from the nonclinical pharmacology toxicology perspective.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted in this review cycle. The Applicant had requested a waiver for in-vivo bioavailability/ bioequivalence studies. The proposed drug product is identical to the referenced drug with the exception of the concentration of the

inactive ingredients and the elimination of the buffer from the product under review. The information submitted in support of the request was found adequate and the biowaiver was granted during the first cycle.

6. Clinical Microbiology

No clinical microbiology review was required for this application.

7. Clinical/Statistical-Efficacy

No clinical efficacy studies were submitted in support of this application. As a 505(b)(2) application for an acetaminophen solution of the same concentration and tonicity as the referenced product and with no novel or unusual excipients, there was no need for additional clinical efficacy studies.

8. Safety

No clinical safety studies were submitted in support of this application. As a 505(b)(2) application for an acetaminophen solution of the same concentration and tonicity as the referenced product and with no novel or unusual excipients, there was no need for additional clinical safety studies.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. There were no scientific or regulatory issues that required discussions from an AC.

10. Pediatrics

This NDA does not trigger any of the requirements of the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

In the Summary Review for the first cycle, Dr. Sharon Hertz stated:

Ofirmev was approved on November 2, 2010 and has exclusivity that expires on November 2, 2013. There are also two active patents listed in the Orange Book due to expire on August 5, 2017 and June 6, 2021. The Applicant filed the application under 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted (Paragraph IV certification). The Applicant notified the owners of the referenced product, Ofirmev, that this b(2) application was filed [21 CFR 314.52(b)] and submitted documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. In response, the Applicant has been sued for patent infringement.

The Applicant submitted a Patent Amendment to the Agency on August 11, 2015, stating that the litigation has been dismissed, and Fresenius Kabi has a license to launch its product before patent expiration.

There are no unresolved relevant regulatory issues.

12. Labeling

- Labeling was addressed during the first review cycle, and the Applicant responded to all comments provided. The label is similar to the Listed Drug, Ofirmev, and differences pertain to the new presentation and configuration of the product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Approval

- Risk Benefit Assessment

The Applicant has provided adequate data to address all deficiencies in the Complete Response letter. This product is a new presentation of IV APAP in a FreeFlex ^{(b) (4)} and relies on the Agency's prior findings of safety and efficacy for Ofirmev. The risk benefit balance is expected to be the same as Ofirmev. There are no outstanding issues that would preclude approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None
- Recommendation for other Postmarketing Requirements and Commitments
None

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/s/

ELLEN W FIELDS
10/28/2015