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APPLICATION NUMBER:

204957Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader and Division Director Summary Review

Date	(electronic stamp)
From	Ning Hu, MD MS, Cross-Discipline Team Leader, Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Rigoberto A Roca, MD, Division Director, DAAP
NDA#	204957
Applicant	B. Braun Medical, Inc.
Date of Original Submission	December 13, 2016 Complete Response letter issued September 28, 2017
Date of First Complete Response Submission	September 27, 2018 Complete Response letter issued March 27, 2019
Date of Second Complete Response Submission	October 24, 2019 Complete Response letter issued April 24, 2020
Date of Third Complete Response Submission	August 27, 2020
PDUFA Goal Date	February 26, 2021
Proprietary Name /Established or Proper Name	Acetaminophen Injection in the PAB® Container
Dosage Form(s) / Strength	Solution for injection 10 mg/mL in 50mL and 100mL PAB® containers
Proposed Indications	1. Management of mild to moderate pain, 2. Management of moderate to severe pain with adjunctive opioid analgesics 3. Reduction of fever
Regulatory Action	Approval

Material Reviewed/Consulted

OND Action Package, including:			
Cross-Discipline Team Leader	Ning Hu, MD, MS		
Project Manager	Jaimin Patel, PharmD		
Pharmacology Toxicology Review	Carlic Huynh, PhD, Jay Chang, PhD, R. Daniel Mellon, PhD		
OPQ Review	Discipline	Primary Assessment	Secondary Assessment
	Manufacturing	Yoon Oh	Jonathan Swoboda
	Regulatory Business Process Manager	Anika Lalmansingh	
	Application Technical Lead	Valerie Amspacher	
Clinical Pharmacology Review	David Lee, PhD; Yun Xu, PhD		
OSE/ DMEPA	Cameron Johnson, PharmD; Otto L. Townsend, PharmD		

OND=Office of New Drugs; CDTL=Cross-Discipline Team Leader; OPQ=Office of Pharmaceutical Quality; OSE=Office of Surveillance and Epidemiology; DMEPA=Division of Medication Errors Prevention.

1. Introduction

The Applicant has submitted a complete response to the Complete Response action taken on April 24, 2020 for Acetaminophen Injection in the Partial Additive Bag (PAB). This is the fourth review cycle for this application. Following completion of the third cycle review, the only deficiency preventing approval of the NDA was the facility inspection issues and withhold recommendation by the OPQ review team.

2. Background

The NDA was originally submitted on December 13, 2016 as a 505(b)(2) application relying in part on the Agency's previous findings of safety and efficacy for Ofirmev (Mallinckrodt NDA 22450). Ofirmev is injectable solution in100 mL glass vials containing 1000 mg acetaminophen (10 mg/mL). The proposed product has two configurations, 1000mg/ 100mL and 500 mg/100 mL that was packaged in PAB containers.

To support approval, the Applicant submitted Chemistry, Manufacturing, and Controls (CMC), nonclinical, and bioequivalence information to bridge their product to Ofirmev. No clinical studies were required or conducted. The proposed indications and dosing regimen are the same as Ofirmev.

3. CMC/Device

Following review of the inspection documentation, the Office of Manufacturing Assessment (OPMA) in the Office of Pharmaceutical Quality (OPQ) concluded that the previous facility issues that precluded approval have been resolved. The following is a summary of the manufacturing review, taken verbatim from Integrated Quality Review dated on December 8, 2020.

> *Following review of the inspection documentation and application documents, the main finished dosage form manufacturing facility for NDA 204957 Resubmission 32 has been found acceptable. Resubmission 32 due to the OAI[1] classification of previous inspection at the main, finished dosage form production site. This inspection occurred 06/22/2020 to 7/23/2020 and as documented under WA 344468, this inspection has been classified as VAI[2]. Facilities are acceptable to perform proposed responsibility for this application.*

The drug product, drug substance, biopharmaceutics and microbiology remain adequate from previous review cycles. Refer to integrated quality review dated on December 8, 2020 for details regarding CMC considerations.

I concur with the conclusions reached by the product quality review team that there are no CMC issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There had not been nonclinical issues identified during the first three review cycles that would have precluded approval. There had been adequate information from nonclinical perspective to bridge the proposed product to the listed drug, Ofirmev.

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[1] Official Action Indicated
[2] Voluntary Action Indicated

However, there were two nonclinical comments communicated in the March 27, 2019 complete response letter (second cycle review) that were not approvability issues. The Applicant addressed both of these comments in the 3rd cycle resubmission. Refer to nonclinical review (April 8, 2020, third cycle) and combined nonclinical/Division director review (March 22, 2019, second cycle) regarding the Nonclinical Pharmacology/Toxicology considerations.

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology

There had not been clinical pharmacology issues identified during the first three review cycles that would have precluded approval. The pharmacokinetic data indicated that the bioequivalence was established between the proposed product and Ofirmev. Refer to clinical pharmacology review (September 1, 2017, original NDA review cycle) regarding the clinical pharmacology considerations.

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the previous review cycles, and there are none during this review cycle.

6. Pediatrics

The Pediatric Research Equity Act (PREA) is not triggered for this application because the NDA is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

7. Other Relevant Regulatory Issues

- Patent issue

  On September 7, 2017, the Applicant notified the Agency of a Notice of Litigation from Mallinckrodt IP and Mallinckrodt Hospital Products against B. Braun for patent infringements on Ofirmev.

  During the second and third review cycle, the Agency requested the applicant to provide “updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved” and “documentation of notices of patent certifications”.

  The applicant provided required documentations. The 505(b)(2) committee reviewed the documentations and cleared the application for the current action.

8. Labeling/DMEPA Review

The Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling during the previous review cycles. Refer to DMEPA’s labeling review dated on May 15, 2017 (original review cycle), January 31, 2019 (second review cycle) and November 10, 2020 (fourth review cycle) regarding detailed labeling considerations. The

applicant's responses to the previous recommendations as well as their revisions to the container label and carton labeling are deemed acceptable by DMEPA.

The applicant submitted the literature summary during the 2nd review cycle to support the proposed labeling revisions for sections 8.1 Pregnancy and 8.2 Lactation. The proposed revisions were not tracked in the updated labeling at this resubmission. The review of literature and revised labeling will require additional time. Considering that the applicant requested for expedited review for this application given the increased demand of acetaminophen injection under the COVID-19 pandemic, the following labeling communication was sent to applicant, along with other suggested revisions.

> *Although this new information was included in the literature summary in the NDA, it has not yet been reviewed by the Division of Pediatric and Maternal Health. This review will require additional time. Alternatively, you may opt to remove this proposed language for now and, should this application be approved, submit these changes later as a proposed supplemental labeling revision to the approved label.*

The Applicant has accepted all the suggested revisions and agreed to remove the additions in sections 8.1 and 8.2. The Office of Prescription Drug Products (OPDP) reviewed and agreed the final version of the label.

9. Decision/Action

Regulatory Action: Approval

The facility inspection issues that precluded approval of this NDA has been adequately addressed and resolved. The applicant submitted pertinent documentations that adequately addressed patent related legal issues.

The submitted information provided adequate scientific bridge to the reference listed drug, Ofirmev, to support a favorable benefit and risk profile of the Acetaminophen Injection in the PAB Container.

- Risk Evaluation and Management Strategy (REMS)
  None

- Postmarketing Requirements and Commitments (PMRs)
  None

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/

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02/09/2021 09:54:02 PM

RIGOBERTO A ROCA
02/18/2021 02:57:51 PM