

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022396Orig1s000

SUMMARY REVIEW



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
 Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Ave.
 Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	December 23, 2014
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	022396/000
Applicant Name	Javelin Pharmaceuticals / Hospira, Inc.
Date of Original Submission	December 2, 2009 Complete Response letter issued October 1, 2010
Date of First Complete Response Submission	June 28, 2013 Complete Response letter issued December 23, 2013
Date of Second Complete Response Submission	October 31, 2014
PDUFA Goal Date	April 30, 2015
Proprietary Name / Established (USAN) Name	Dyloject / diclofenac sodium
Dosage Forms / Strength	Solution for intravenous injection / 37.5 mg/mL
Proposed Indications	<ol style="list-style-type: none"> 1. Management of acute mild to moderate to pain 2. Management of acute moderate to severe pain alone or in combination with opioid analgesics
Action	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
CDTL Review	Josh Lloyd, MD
Pharmacology Toxicology Review	Armaghan Emami, PhD / Jay Chang, PhD / Dan Mellon, PhD
ONDQA Review	Julia Pinto, PhD
Project Management Staff	Swati Patwardhan
OMP/OPDP	L. Shenee Toombs
OMPQ/DGMPA/NDMAB	Juandria Williams, PhD / Mahesh Ramanadham

CDTL = Cross-Discipline Team Leader
 DGPC = Division of Good Clinical Practice Compliance
 DGMPA = Division of GMP Assessment
 NDMAB = New Drug Manufacturing Assessment Branch
 OMP = Office of Medical Policy

OMPQ = Office of Manufacturing and Product Quality
 OND = Office of New Drugs
 ONDQA = Office of New Drug Quality Assessment
 OPDP = Office of Professional Drug Promotion

1. Introduction

Dyloject, is an injectable formulation of diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) that is an inhibitor of both isoforms of cyclooxygenase (COX-1 and COX-2). It exhibits analgesic, anti-inflammatory and antipyretic effects. Diclofenac is approved and marketed in the United States in immediate-release and modified-release oral formulations, as well as a topical formulation. There are no approved intravenous formulations in the United States.

This formulation was originally developed by Javelin Pharmaceuticals, Inc., under IND 65,048. The company was acquired by Hospira, Inc. (the Applicant), and a new drug application (NDA) was submitted on December 2, 2009, under section 505(b)(2) of the federal Food, Drug, and Cosmetic Act. The referenced drug was Cataflam (NDA 020142). This is the third review cycle for this application. The first two review cycles resulted in two Complete Response letters (issued on October 1, 2010, and on December 23, 2013). This submission consists of the Applicant's response to the second Complete Response letter.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

As noted in Dr. Lloyd's review during the second review cycle, the supporting data for the original NDA included 16 clinical studies, two of which were Phase 3 efficacy trials (DF-004 and DFC-005), and one Phase 3 open-label safety study (DFC-010). The review team's conclusion at the end of the first review cycle was that adequate information had been submitted to evaluate the drug product's efficacy and safety. No concerns were identified related to the efficacy of the product. There was concern that the safety profile of one of the doses proposed by the Applicant did not result in a favorable risk:benefit assessment; however, the team concluded that the data supported the risk:benefit assessment of a lower dose regimen.

From a drug quality perspective, the review team concluded that there was a lack of assurance of an acceptable manufacturing process.

Both of these issues resulted in the NDA not being approved during the first review cycle. The Complete Response letter issued on October 1, 2010, identified two deficiencies as the reasons for the action:

CLINICAL

1. Data submitted do not support the proposed (b) (4)



(b) (4)

CHEMISTRY, MANUFACTURING AND CONTROLS

2. (b) (4)

(b) (4)

Based on the currently available data provided in the amendment dated September 23, 2010, we are recommending a “For Cause Inspection” of the drug product manufacturer’s facility (b) (4)

(b) (4)

An inspection must be performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance prior to marketing of this product.

In the second submission, the Applicant addressed the clinical deficiency (b) (4)

addressed the (b) (4) concern The Applicant (b) (4)

Although the clinical information in the application was deemed to be sufficient for approval, the inspection of the manufacturing facilities identified continuing issues with the manufacturing process. The deficiency noted in the December 23, 2013 letter indicated the following:

FACILITY INSPECTIONS AND ASSESSMENT

During a recent inspection of the [REDACTED] (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

This submission is a response to that deficiency.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The drug product is an aqueous solution, presented in a 1-mL fill volume in a 2- mL USP Type I flint glass vial. The stopper is a 13-mm [REDACTED] (b) (4) rubber stopper, and there is an aluminum overseal.

Specific Issues Identified in the Course of the Review

No new data related to the drug substance or drug product were submitted in this application. The primary issue that needed to be evaluated during this review cycle was whether the Applicant had adequately addressed the concerns [REDACTED] (b) (4)

In Dr. Pinto's current review, she has noted the following:

In the current Submission, dated October 31, 2014, Javelin again, submits a complete response to the NDA, to address the inspection issues [REDACTED] (b) (4) at the [REDACTED] (b) (4) Facility (a contract manufacturer).

Dr. Juandria Williams, Ph.D. from the Office of Manufacturing and Product Quality in a review memo dated 18-DEC-2014 (Filed in Panorama), has made a recommendation that the application be approved since all issues [REDACTED] (b) (4) at that [REDACTED] (b) (4) Facility have been resolved. The Office of Compliance has provided an overall acceptable recommendation for all facilities.

Conclusion: Therefore since all outstanding inspection issues have been adequately resolved, and no additional CMC changes have been submitted, this NDA is recommended for approval, from the CMC perspective.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Dr. Pinto that there are no manufacturing issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data submitted during this review cycle.

However, discussion about the Applicant's proposed pediatric plan raised concerns about the safety of the proposed formulation for the pediatric patients in the youngest age range. In particular, the potential for diclofenac and hydroxypropyl- β -cyclodextrin (HPBCD) to cause renal toxicity in the context of the developing kidney was in question.

This concern was conveyed to the Applicant and they agreed to conduct a juvenile animal study as a postmarketing requirement (PMR) prior to the initiation of the clinical study in the youngest age cohort. It was noted in the discussion with the Applicant that they also had the option of submitting a literature-based justification for the safety of their pediatric formulation, which if deemed adequate upon review, could potentially release them from this PMR.

Outstanding or Unresolved Issues

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/Biopharmaceutics

There were no new clinical pharmacology data submitted during this review cycle.

Outstanding or Unresolved Issues

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

6. Clinical Microbiology

Dyloject is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

There were no new clinical data submitted during this review cycle. As noted in my review of December 23, 2013, the review team concluded that the Applicant had submitted adequate data to support efficacy of the product during the review cycle.

Outstanding or Unresolved Issues

There are no outstanding clinical issues or concerns that would preclude approval.

8. Safety

There were no new clinical data submitted during this review cycle. The Applicant noted that there have been no significant changes or findings in the safety profile of the product since the Applicant's submission of June 28, 2013.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant has not conducted any clinical trials in pediatric patients. At present, the Applicant's proposed pediatric plan is to request a waiver from studying pediatric patients between the ages of birth and 12 months of age, and a deferral for studying pediatric patients between the ages of 1 year and 17 years of age. The Applicant's plan included the following studies:

Study 1:

A pharmacokinetic and safety study in pediatric patients between the ages of 2 and 17 years of age.

Study 2:

A pharmacokinetic, safety, and efficacy study in pediatric patients between the ages of 1 to 2 years of age.

The first study will be

(b) (4)

Efficacy from the adult studies will be extrapolated to the pediatric patients older than 2 years of age, which is consistent with the Division's policy regarding NSAIDs.

The Applicant's pediatric study plan was presented to the Pediatric Research Committee (PeRC) during the second review cycle (on November 6, 2013). The following text, which was reproduced from Dr. Lloyd's review, was included in my review of December 23, 2013, and it summarized the committee's recommendations at that time:

PeRC noted that the variability in development of metabolic pathways for this product have not been clearly established and would not preclude studies in pediatric patients birth to <12 months of age. Therefore, PeRC did not agree with the Applicant's partial waiver request in that age group. However, due to the theoretical concerns associated with immature metabolic pathways, PeRC recommended that even though the Applicant will be required to conduct studies in all pediatric age ranges, that studies should be conducted sequentially in older age groups first. If studies in older age groups reveal safety concerns, studies in younger age groups could be waived at that time. Additionally, if more commonly used NSAIDs (e.g., ibuprofen) receive approval down to birth, a waiver in patients less than one year of age could be considered at that time. PeRC recommended that the postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) be issued such that each pediatric age group has sequential, non-overlapping protocol submission and study completion dates.

The Division has had additional internal discussions regarding the Applicant's request for a waiver of the studies in the youngest pediatric age group (i.e., less than 1 year of age), and we have concluded that, due to the specific circumstances related to this product, it is appropriate to grant the Applicant's request for a waiver in this age group. The following paragraphs, reproduced from Dr. Lloyd's review, summarize our rationale:

The Division's policy has been to waive pediatric studies in patients less than one year of age for diclofenac-containing products because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric age group. This NDA was initially discussed at a meeting of the Pediatric Research Committee (PeRC) on September 1, 2010, where the variability in pharmacokinetics in the youngest patients due to immaturity of enzymatic pathways was discussed. PeRC agreed with the partial waiver in patients less than one year of age.

There are two characteristics of the metabolism and clearance of diclofenac that have implications for evaluation of this product in patients less than one year of age. Formation of the major diclofenac metabolite, 4'-hydroxy-diclofenac is primarily mediated by CYP2C9. Current data suggest that adult activity of CYP2C9 is not attained until some time between one and six months of age. Furthermore, the clearance of diclofenac appears to be dependent on bodyweight with lower clearance associated with lower body weight. As noted by Dr. Nallani in his Aug. 17, 2010 review, as an extension to this observation, clearance of diclofenac might be significantly lower in pediatric patients down to neonates. The concern regarding bodyweight will at least partially be addressed by conducting pediatric studies sequentially, starting with older age groups first. However, given the variability in maturation of metabolic pathways, the safety concern in the youngest age groups persists.

The application was discussed at PeRC again on November 6, 2013, during the second review cycle, where PeRC expressed concerns about waiving studies in patients less than one year based solely on the safety concerns about immature enzymatic pathways and recommended requiring studies in that age group. PeRC recommended that the Division issue discrete PMRs with sequential, non-overlapping protocol submission and study completion dates for each pediatric age group, starting with the oldest groups first, to address the Division's safety concerns.

Although the Division's discussions surrounding pediatric study requirements for diclofenac-containing products with the Center's pediatric groups were ongoing during the last review cycle, a requirement for conducting pediatric studies in all pediatric age ranges, including those patients less than one year of age, was communicated to the Applicant in the CR letter dated December 23, 2013. However, the Applicant's pediatric study plan in the current submission continued to only include studies in pediatric patients 1 to less than 17 years of age.

The pediatric study requirements for this product were further discussed internally within the Division during the current review cycle. Although waiving studies in the youngest pediatric patients may not be appropriate for all drugs, there are serious safety concerns associated with the use of NSAIDs. Given that the risk is potentially greater and more unpredictable in the context of immature metabolic pathways in the youngest pediatric patients and that alternative therapies are available in the marketplace (e.g., opioids) with dosing recommendations for these products in widely accepted clinical resources, an intravenous diclofenac does not represent the best clinical option in the youngest patients. Therefore, in this context, it is appropriate to waive pediatric studies less than one year. This reasoning may not be applicable to all drugs, and the decision to grant any waiver of pediatric studies should be considered in the clinical context that a particular product will be used.

Dr. Lloyd's recommendation regarding the pediatric development plan is noted below:

In summary, I recommend that studies in pediatric patients less than one year of age be waived because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric age group and that the pediatric postmarketing study requirements listed in Section 13 of this review be required for approval. Pediatric studies in patients 1 year to less than 17 years may be deferred because the product is ready for approval for use in adults and the pediatric studies have not been completed.

I concur with Dr. Lloyd's recommendation that studies should be waived in the youngest pediatric age group (birth to less than 1 year old), that studies in pediatric patients between the ages of 1 and 17 years may be deferred on the basis that studies in adults have been completed and the drug development program has progressed to the point that the drug is ready for approval, and that efficacy may be extrapolated from adults to pediatric patients two years of age and older.

I also concur with the Applicant's proposal to divide the 1 to 17 year-old cohort (b) (4) and to conduct the studies in a sequential fashion, with the older age groups being enrolled first.

Dr. Lloyd's review noted that the Applicant's proposed timeline for the pediatric program was under internal discussion, particularly with respect to the assertion that they would need 24 months for pediatric formulation development. Due to the Applicant's explanation regarding the steps that would be required to develop, manufacture, and generate stability data on the new formulation, their proposed timeline is deemed acceptable.

11. Other Relevant Regulatory Issues

The Division of Good Manufacturing Practice Assessment (DGMPA) reviewed the Applicant's response to the observation cited in the FDA Form 483 that was issued on October 22, 2013, upon the completion of the pre-approval inspection of the manufacturing facility that was conducted by the Office of Compliance (b) (4). The inspection identified (b) (4)

As noted above, the conclusion was that the Applicant has adequately qualified (b) (4)

Outstanding or Unresolved Issues

The review by DGMPA has determined that the concern (b) (4) has been adequately addressed and, therefore, this application can be approved at this time.

12. Labeling

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.

The Office of Prescription Drug Products (OPDP) provided comments on the package insert during this review cycle, and their recommendations have been incorporated.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
Approval.

Risk:Benefit Assessment

The Applicant has submitted adequate information and data to demonstrate the safety and effectiveness of the product when used as directed in the package insert. The concerns [REDACTED] (b) (4) [REDACTED] have also been adequately addressed, therefore, the risk:benefit assessment is favorable and this application can be approved at this time.

Recommendation for Postmarketing Risk Management Activities
None.

Recommendation for other Postmarketing Study Commitments

- An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of Dyloject (diclofenac sodium) Injection in pediatric patients 2 to less than 17 years of age with acute pain.
- A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of Dyloject (diclofenac sodium) Injection in pediatric patients 1 to less than 2 years of age with acute pain. The study or studies are to be conducted after the juvenile animal toxicology study of Dyloject is completed.
- A juvenile animal study to evaluate the general toxicology of the Dyloject (diclofenac sodium) Injection pediatric formulation to support the safe use of the pediatric formulation prior to initiation of the clinical study in pediatric patients 1 through less than 2 years of age.

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/s/

RIGOBERTO A ROCA
12/23/2014