

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022396Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22, 2014
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA#	22396
Applicant	Hospira, Inc.
Date of Submission	October 31, 2014
PDUFA Goal Date	April 30, 2015
Proprietary Name / Established (USAN) names	Dyloject/ Diclofenac sodium
Dosage forms / Strength	Solution for IV injection, 37.5 mg/ml
Proposed Indication(s)	1. Management of mild to moderate pain 2. Management of moderate to severe pain alone or in combination with opioid analgesics
Recommended:	Approval

1. Introduction

Javelin Pharmaceuticals, Inc., (subsequently purchased by Hospira; also referred to as “the Applicant”) developed Dyloject, an injectable drug product containing diclofenac sodium, under IND 65,048, for the short-term management of acute moderate to severe pain. The Applicant submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, on December 2, 2009 (received December 3, 2009), referencing the Agency’s prior findings of effectiveness and safety for diclofenac potassium (Cataflam; NDA 20142). The Applicant received a Complete Response (CR) letter on October 1, 2010, detailing deficiencies related to the clinical and the chemistry, manufacturing, and controls (CMC) disciplines, as well as labeling. The Applicant submitted a response to the initial CR letter on June 28, 2013, and, at that time, the Division determined that the Applicant submitted adequate information and data to demonstrate the safety and effectiveness of the product. However, continued issues were noted at the inspection of the manufacturing facilities, and a second CR letter was issued on December 23, 2013. The main deficiency cited in the CR letter is reproduced below:

FACILITY INSPECTIONS AND ASSESSMENT

During a recent inspection of the (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 review will predominantly focus on the pediatric study requirements for Dyloject, as the Division’s pediatric requirements for diclofenac-containing products were evolving during the

second review cycle, and the outstanding inspection issues. I have concluded that this application should receive an Approval action.

2. Background

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities and is a potent inhibitor of both COX-1 and COX-2. Diclofenac is approved and marketed in the United States as various salt and free acid forms in oral (immediate-release and modified-release) and topical formulations for multiple painful conditions. There are no approved intravenous (IV) formulations of diclofenac in the United States.

The original NDA for Dyloject was submitted on December 2, 2009. The basis for the NDA was 16 clinical studies including two Phase 3 efficacy trials (DFC-004 and DFC-005) and one Phase 3 open-label safety study (DFC-010). Details regarding the safety and efficacy reviews are available in Dr. Larissa Lapteva's combined CDTL-Division Deputy Director memo dated October 1, 2010. Also refer to Dr. Lapteva's review for a discussion of the relevant pre-submission regulatory history. Please refer to my CDTL memo dated December 11, 2013, for details surrounding the second cycle review.

3. CMC/Device

Dr. Pinto noted in her review that

In the current Submission, dated October 31, 2014, Javelin again, submits a complete response to the NDA, to address the inspection issues (b) (4)

(b) (4) at the (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 (b) (4) at that (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.

I concur with the CMC recommendation.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Armaghan Emami, PhD, with secondary concurrence by Jay Chang, PhD, and Dan Mellon, PhD. Although no new nonclinical pharmacology/toxicology data were submitted with this CR submission and there were no pharmacology/toxicology issues that precluded approval during the first and second review cycle, the pharmacology/toxicology team recommends a postmarketing requirement for a juvenile animal study (refer to the discussion under Section 10 Pediatrics below).

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics data were submitted with this CR submission.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

No new efficacy data were submitted with this CR submission.

8. Safety

No new safety data were submitted with this CR submission. The Applicant reports that “[n]o significant change or findings in the safety profile have been identified for Dyloject since the last safety update provided in our June 28, 2013 response to the [C]omplete [R]esponse.”

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

No studies have been carried out in pediatric patients.

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 CPY2C9. Current data suggest that adult activity of CYP2C9 is not attained until some time between one and six months of age.¹ 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.

¹ Blake MJ, Castro L, Leeder SJ, Kearns GL, Ontogeny of drug metabolizing enzymes in the neonate. *Seminars in Fetal & Neonatal Medicine* (2005) 10, 123-138.

The discussion of conducting pediatric studies in the youngest age groups raised concerns about the safety of the proposed formulation (specifically the potential for diclofenac and HPβCD present in the formulation to cause renal toxicity in the context of the developing kidney) in the youngest age ranges. Therefore, the pharmacology/toxicology team is recommending a PMR to evaluate the general toxicology of the Dyloject pediatric formulation prior to initiation of the clinical study in pediatric patients one year to less than two years of age, and I concur with that recommendation.

The pediatric study requirements were discussed over a teleconference with the Applicant on December 4, 2014, and the Applicant submitted a revised pediatric study plan that included the following studies and proposed timelines with a request for deferral of studies in patients 1 to less than 17 years of age:

- Study 1: Safety and PK in pediatric patients between the ages of 2 through less than 17 years
Final Protocol Submission: 06/2017
Study/Trial Completion: 03/2019
Final Report Submission: 09/2019
- Study 2: Efficacy, safety, and PK in pediatric patients one through less than two years of age
Final Protocol Submission: 04/2019
Study/Trial Completion: 05/2020
Final Report Submission: 11/2020

Pediatric studies will be conducted sequentially starting with the oldest age groups first (b) (4)

The proposed studies are consistent with the Division's current policy to allow extrapolation of efficacy from adults to pediatric patients two years of age and older for NSAIDs. The Applicant provided synopses of the proposed studies in the pediatric study plan; however, the full protocols will need to be reviewed before each study can begin. Some aspects of the proposed study designs would not fully satisfy the Division's requirements (b) (4)

As such, I recommend that all protocols and statistical analysis plans be submitted and agreed upon by the Agency before the respective pediatric studies begin.

The Applicant's timeline for the proposed pediatric program is based on the Applicant requiring 24 months for formulation development. Discussions regarding the appropriateness and acceptability of this timeline are ongoing amongst the review team at this time.

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.

11. Other Relevant Regulatory Issues

This application was presented at a 505(b)(2) clearance meeting on December 9, 2014, and it was cleared for action from their perspective.

12. Labeling

The Applicant submitted proposed labeling with minor editorial changes and an additional change to the Dosage and Administration section to give the intravenous bolus injection **over 15 seconds** (emphasis added to highlight the additional proposed language). This administration procedure is acceptable, as it is consistent with what was done in the Phase 3 clinical trials.

The Office of Prescription Drug Promotion (OPDP) evaluated the proposed labeling and had comments as detailed in their consult response dated December 17, 2014.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant submitted this NDA on October 31, 2014, in response to a CR action taken by the Division on December 23, 2013. The main deficiency during the last review cycle was related to facility inspections and assessment. The Applicant has adequately responded to this deficiency outlined in the CR letter, and I recommend approval of this product.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and 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. Conduct the study or studies after the juvenile animal toxicology study of Dyloject.
 - Conduct 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 <2 years of age.
- Recommended Comments to Applicant

Submit the pediatric protocols and statistical analysis plans for review and agreement by the Agency before starting the respective study in children

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/s/

JOSHUA M LLOYD
12/22/2014