CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022396Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022396	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Dyloject Established/Proper Name: diclofenac sodium Dosage Form: IV Strengths: 37.5 mg/mL		
Applicant: Hospira		
Date of Receipt: December 3, 2009, June 28, 2013, October 31, 2014		
PDUFA Goal Date: October 3, 2010, December 28, 2013, April 30, 2015	Action Goal Date (if different): October 1, 2010, December 23, 2013, Dec. 23 2014	
Proposed Indication(s): **management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20142	**Nonclinical section of labeling**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA/BE studies

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Cataflam	20142	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Cataflam,

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
This application provides for a change in dosage form, (b) (4) to IV and a new indication for management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

NDA 020142, Cataflam
NDA 021234, Flector
NDA 022202, Zipsor
NDA 022165, Cambia
NDA 022122, 020037, and 020254 (Voltaren and Voltaren XR)
NDA 021005, Solaraze
NDA 020947, Pennsaid
NDA 0204623 Pennsaid
NDA 204592 Zorvolex
And approved generics

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 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). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of ☐

approval

APPEARS THIS WAY ON ORIGINAL

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

/s/

SWATI A PATWARDHAN
12/23/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 022396
Product Name:

PMR/PMC Description: 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

PMR/PMC Schedule Milestones:

Final Protocol Submission:	06/2017
Study/Trial Completion:	03/2019
Final Report Submission:	09/2019
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics and safety of Dyloject Injection in pediatric patients ages 2 to less than 17 years with acute pain) for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed because an age-appropriate formulation needs to be developed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To obtain adequate data to describe the dosing and safety of Dyloject Injection in pediatric patients ages 2 to less than 17 years with acute pain.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics and safety of Dyloject Injection in pediatric patients ages 2 to less than17 years with acute pain. The study can be open label in design.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022396
Product Name:	Dyloject (diclofenac sodium) Injection
PMR/PMC Description:	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 is completed.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2019
	Study/Trial Completion:	05/2020
	Final Report Submission:	11/2020
	Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the efficacy, pharmacokinetics, and safety of Dyloject Injection in pediatric patients ages 1 to less than 2 years with acute pain) for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed because an age-appropriate formulation needs to be developed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To obtain adequate data to describe the dosing, efficacy, and safety of Dyloject Injection in pediatric patients ages 1 to less than 2 years with acute pain.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics, safety, and efficacy of Dyloject in pediatric patients 1 to less than 2 years of age. Efficacy must be evaluated using an adequate and well-controlled design.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 022396

PMR/PMC Description: 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 to less than 2 years of age.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	05/2017
	Study Completion:	03/2018
	Final Report Submission:	07/2018
	Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The drug substance, diclofenac sodium, has not been approved for pediatric use. In addition, hydroxypropyl-β-cyclodextrin (HPβCD), an excipient, is in FDA-approved intravenous drug products, but none of these products have been approved for pediatric use. In general toxicology studies, this excipient showed kidney findings in mature rats (mild renal tubular vacuolation) and mature monkeys (mild granular appearance of the renal tubular cells in the medullary rays), but was not associated with impairment of renal function or progressive renal disease, and was cleared with full histological reversibility. However, there is no safety information available that addresses the potential effect of this excipient on a developing kidney of the pediatric population aged 1-2 years old.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The pediatric studies will be completed as PMRs. The studies will include children down to 1 year of age. The nonclinical study is required prior to address the safety of the drug product in pediatric population aged 1-2 years of age, as the kidney is not fully formed until about 1 year of age and is a potentially uniquely vulnerable target organ of toxicity for both diclofenac and the hydroxypropyl beta-cyclodextrin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a nonclinical toxicology study to support the safety of administering the drug product to pediatric population aged 1-2 years old.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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/s/

SWATI A PATWARDHAN
12/22/2014

JUDITH A RACOOSIN
12/22/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 17, 2014

To: Swati Patwardhan, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 022396
OPDP labeling comments for Dyloject™ (diclofenac sodium) Injection, for intravenous use
Labeling Review

OPDP has reviewed the proposed package insert (PI) for Dyloject (diclofenac sodium) Injection for intravenous use (Dyloject) that was submitted for consult on November 28, 2014. Comments on the proposed PI are based on the version sent via email from Swati Patwardhan (RPM) on December 8, 2014 entitled "NDA 022396 draft-labeling.doc".

Comments regarding the PI are provided on the marked version below.

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
12/17/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 10, 2013

To: Swati Patwardhan, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 022396
OPDP labeling comments for Dyloject™ (diclofenac sodium) Injection for intravenous use
Labeling Review

OPDP has reviewed the proposed package insert (PI) for Dyloject (diclofenac sodium) Injection for intravenous use (Dyloject) that was submitted for consult on July 24, 2013. Comments on the proposed PI are based on the version sent via email from Swati Patwardhan (RPM) on November 26, 2013 entitled "NDA 022396 draft-labeling.doc".

Comments regarding the PI are provided on the marked version below.

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
12/10/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 7, 2013
Reviewer:	Rachna Kapoor, Pharm.D. Division of Medication Error Prevention and Analysis
Acting Team Leader:	Morgan Walker, Pharm.D., M.B.A. Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Dyloject (diclofenac sodium) Injection 37.5 mg/mL
Application Type/Number:	NDA 22396
Applicant/sponsor:	Hospira, Inc.
OSE RCM #:	2013-1696

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and package insert for Dyloject (diclofenac sodium) Injection for NDA 22396 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Dyloject (diclofenac sodium) Injection NDA 22396 is a parenteral NSAID indicated for the management of acute moderate to severe pain in adults. It is the only injectable form of diclofenac sodium.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 22, 2009 request for proprietary name review.

- Active Ingredient: diclofenac sodium
- Indication of Use: the management of (b) (4) moderate to severe pain alone or in combination with opioid analgesics in adults
- Route of Administration: intravenous
- Dosage Form: solution for injection
- Strength: 37.5 mg/mL
- Dose and Frequency: 37.5 mg administered by intravenous bolus injection. (b) (4) Frequency of administration is every 6 hours as needed
- How Supplied: 1 mL fill in a clear 2 mL glass vial with an orange tamper-evident top. Comes in a carton of 25 vials
- Storage: store at controlled room temperature 20-25°C (68-77°F). Do not freeze. Protect from light

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 28, 2013 (Appendix B)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton Labeling submitted June 28, 2013 (Appendix C)
- Package Insert submitted June 28, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Dyloject for proprietary name review RCM #2010-639 and found the name to be acceptable on July 29, 2010. This was a re-assessment of the proposed proprietary name that was found acceptable in OSE Review #2009-2488 dated March 19, 2010. A labeling review RCM #2009-2489 was completed on September 10, 2010. Some of the recommendations were implemented whereas others were not. This review will address those that were not.

3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Division

a. Package Insert

i. FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations. As part of this campaign, the FDA agreed not to approve error prone abbreviations in labeling because they are carried on to the prescribing practice. Therefore, we request you revise the abbreviation 'IV' to read 'Intravenous' throughout the package insert. The abbreviation 'IV' is considered error-prone[2] as it can be misinterpreted for other routes of administration.

ii. In the Dosage and Administration Section (Highlights and Full Prescribing Information) include the statement, "For Intravenous Administration Only".

B. Comments to the Applicant

a. Container Labels

i. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors such as the font weight, pursuant to 21 CFR 201.10(g)(2)

[2] Institute of Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2007). Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

ii. Revise the proposed proprietary name "DYLOJECT" from all upper case to title case (i.e. Dyloject) for improved readability.

iii. Remove the [redacted] (b) (4) information, [redacted] (b) (4) from the principal display panel, as it is not required by small label regulations and crowds the label, making it difficult to read other required product information

iv. Revise and increase the prominence of the route of administration statement, [redacted] (b) (4) to read, 'For Intravenous Use Only'.

b. Carton Labeling

i. See Comments B(a)(i) and B(a)(ii) above and apply to carton labeling

ii. Include the statement, 'Single-Use Vials, Discard Unused Portion' on the principal display panel

iii. Relocate the net quantity statement, '25 x 1 mL Vials', to appear below the statement, 'For Intravenous Use' to move it away from the strength statement to prevent confusion between the strength and number of vials

If you have further questions or need clarifications, please contact Vaishali Jarral, project manager, at 301-796-4248.

APPENDICES

Appendix A. Database Descriptions

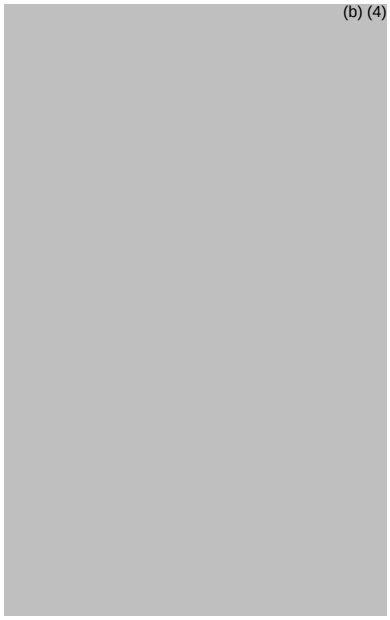
FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix B: Container Labels



Appendix C: Carton Labeling

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/s/

RACHNA KAPOOR
11/07/2013

MORGAN A WALKER
11/08/2013

KELLIE A TAYLOR
11/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

DATE:	September 10, 2010
APPLICATION TYPE/NUMBER:	NDA 022396
TO:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products
THROUGH:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, Pharm D. Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
FROM:	Walter Fava, RPh, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
SUBJECT:	Label and Labeling Review
DRUG NAME(S):	Dyloject (Diclofenac Sodium) Injection 37.5 mg/mL
APPLICANT/SPONSOR:	Hospira, Inc.
OSE RCM #:	2009-2489

1 INTRODUCTION

This review responds to a request from the Division of Anesthesia and Analgesia Products for assessment of the labels and labeling for Dyloject (Diclofenac Sodium) Injection, 37.5 mg/mL.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted June 17, 2010 (see Appendices A and B). We also evaluated the package insert labeling submitted on December 2, 2009.

- Container Label
    - 37.5 mg/mL (1 mL vials)
- Carton Labeling
    - 37.5 mg/mL (25 x 1 mL vials)
- Package insert (no image)

3 RECOMMENDATIONS

Our evaluation noted areas where information on the labels and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the Package Insert Labeling in Section 3.1 (*Comments to the Division)* for discussion during the review team's label and labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the labels and labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Abolade Adeolu, at 301-796-4264.

3.1 COMMENTS TO THE DIVISION

A. Package Insert

1. General Comments
    a. FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations. As part of this campaign, the FDA agreed not to approve error prone abbreviations in labeling because they are carried on to the prescribing practice. Therefore, we request you revise the abbreviation 'IV' to read 'Intravenous' throughout the package insert. The abbreviation 'IV' is considered error-prone[1] as it can be misinterpreted for other routes of administration.
2. Dosage and Administration Section (Highlights and Full Prescribing Information)
    a. Include the statement, 'For Intravenous Administration Only'.

[1] Institute of Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2007). Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

3. Dosage Form and Strengths Section (Highlights and Full Prescribing Information)

   a. Revise to read, [redacted]

3.2 COMMENTS TO THE APPLICANT

A. General Comments

Pursuant to the change in ownership of this NDA to Hospira Inc., please revise all labels and labeling accordingly to reflect this change and submit for our review along with the any changes made in response to our recommendations below.

B. Container Labels (37.5 mg/mL, 1 mL vials)

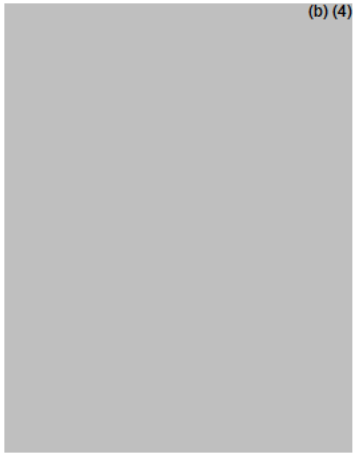
1. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors such as the font weight, pursuant to 21 CFR 201.10(g)(2).
2. Remove the [redacted] information, [redacted] from the principal display panel, as it is not required by small label regulations and crowds the label, making it difficult to read other required product information.
3. Revise and increase the prominence of the route of administration statement, [redacted] to read, 'For Intravenous Use Only'.

C. Carton Labeling (25 x 1 mL vials)

1. See Comments B1, and B3 above and apply to carton labeling.
2. Remove the statement [redacted] from the principal display panel as it is duplicative and crowds the principal display panel.
3. Include the statement, 'Single-Use Vials, Discard Unused Portion' on the principal display panel.
4. Relocate the net quantity statement, '25 x 1 mL Vials', to appear away from the strength statement.

APPENDICES

Appendix A: Container Label



Appendix B: Carton Labeling (25 x 1 mL)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

WALTER L FAVA
09/10/2010

CARLOS M MENA-GRILLASCA
09/10/2010

DENISE P TOYER
09/10/2010

CAROL A HOLQUIST
09/10/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: August 24, 2010

To: Kathleen Davies – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 022396 Dyloject (diclofenac sodium) INJECTION

DDMAC has reviewed the proposed product labeling (PI), and Carton and Container label for Dyloject (diclofenac sodium) INJECTION (Dyloject), submitted for DDMAC review on February 03, 2010.

The following comments are provided using the draft PI as of August 20, 2010. If you have any questions about DDMAC's comments, please do not hesitate to contact me at 6-3692 or mathilda.fienkeng@fda.hhs.gov.

Carton and Container Label

DDMAC has reviewed the carton and container labels for the 1 mL glass vials and has no comment.

12 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/ TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

MATHILDA K FIENKENG
08/24/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22396
Brand Name	Dyloject
Generic Name	Diclofenac sodium injection
Sponsor	Javelin Pharmaceuticals, Inc.
Indication	Treatment of short term management of acute moderate to severe pain
Dosage Form	Parenteral
Drug Class	Non-Steroidal Anti-Inflammatory Drug (NSAID)
Therapeutic Dosing Regimen	37.5 mg every 6 hours (b) (4) (b) (4)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	75 mg/ml
Submission Number and Date	SDN 001 /3 Dec 2009
Review Division	DAARP / HFD 170

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of DIC075V (37.5 mg and 75 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between DIC075V (37.5 mg and 75 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 6, indicating that assay sensitivity was established.

In this randomized, double-blind, placebo-controlled and open label active-controlled, four-period crossover study, 70 healthy subjects were received DIC075V 37.5 mg , DIC075V 75 mg, moxifloxicin 400 mg, and placebo. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for DIC075V (37.5 mg and 75 mg) and the Largest Lower Bound for Moxifloxicin 400 mg (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
DIC075V 37.5 mg	1	1.6	(-0.4, 3.7)
DIC075V 75 mg	1	1.4	(-0.7, 3.4)
Moxifloxicin 400 mg*	4	10.7	(8.6*, 12.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.8 ms.

The supratherapeutic dose (75 mg) produces mean C_{max} values of 2-fod higher than the mean C_{max} for the therapeutic dose (37.5 mg). These concentrations are above those for the predicted worst case scenario. DIC075V follows linear PK over doses ranging from 18.75 to 75 mg. Diclofenac (the active ingredient of DIC075V) is metabolized in the liver by conjugation to hydroxylated forms, principally 4-hydroxydiclofenac, approximately 65% of which is excreted in the urine and approximately 35% in the bile. 4-hydroxydiclofenac has very weak pharmacologic activity. The pharmacokinetics of diclofenac in hepatically and renally impaired subjects are not altered. Intrinsic factors (such as age, race and gender) have not been identified to affect DIC075V pharmacokinetics. Drug interaction studies did not suggest DIC075V pharmacokinetic alteration.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

In the draft label, the sponsor proposed the following language regarding QT/QTc.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

(b) (4)

2.2 QT-IRT TEAM PROPOSED LABEL

The sponsor proposed a brief description in the PI for QTc effects. We have the following recommendations which are suggestions only. We defer all final labeling decisions to the review division.

The effect of DYLOJECT on QTc prolongation was evaluated in a randomized, double-blind, positive (moxifloxacin 400 mg)- and placebo-controlled crossover study in healthy subjects. A total of 70 subjects were administered diclofenac sodium 37.5 mg and 75 mg. In a study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Dyloject™ (diclofenac sodium) Injection, is a parenteral formulation intended for the management of acute moderate to severe pain in adults.

The dosage regimen is 37.5 mg every six hours (b) (4)

3.2 MARKET APPROVAL STATUS

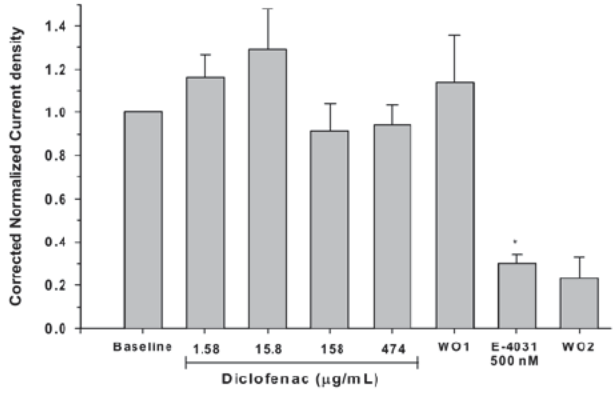
Diclofenac sodium is approved in other (non-parenteral) dosage forms currently on the U.S. market.

Dyloject has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and is currently on the market in the U.K.

3.3 PRECLINICAL INFORMATION

None of the diclofenac concentrations tested inhibited the hERG current when compared to baseline current density measured (n = 7). Paired student's t-tests confirmed that the difference in normalized current density measured in the baseline and in the presence of all concentrations of diclofenac tested did not reach the selected threshold for statistical significance, $p \leq 0.05$ (Figure 1). The four concentrations of HPβCD (vehicle) tested respectively caused 22.5, 39.3, 43.5 and 36.5% of inhibition of the hERG tail current density.

Figure 1: Effect of Diclofenac on hERG Currents from Transfected HEK 293 Cells



Source: Study 800213-1, Figure 1

Reviewer's comments: diclofenac does not block hERG currents at concentrations as high as 30-fold the human C_{max} exposure achieved with a single dose of 75-mg IV bolus.

3.4 PREVIOUS CLINICAL EXPERIENCE

From module 2 CTD summaries and ISS

Overall, in the clinical program, a total of 1888 subjects were exposed to the proposed to-be- marketed formulation of DIC075V and 263 subjects were exposed to earlier formulations of Dyloject, including 257 subjects exposed to DIC075V and 6 subjects exposed to DIC075T. Of the 1888 subjects exposed to DIC075V, 1156 were exposed to DIC075V (b) (4) dose of 37.5 mg and 50 mg in the multiple dose studies in acute moderate to severe postoperative pain (DFC-004, DFC-005, and DFC-010). The safety profile of DIC075V in these 1156 subjects is the primary focus of this overview. Exposure to (b) (4) 37.5-mg and 50-mg doses of DIC075V is summarized in Table 2.

Among the 1156 DIC075V-treated subjects, the median number of doses received was 8, with the number of doses ranging from 1 to 21. A total of 365 subjects were exposed to DIC075V for > 2 days, with 254 subjects exposed to DIC075V for 3 days (9 to 12 doses), 78 subjects exposed to DIC075V for 4 days (13 to 16 doses), and 33 subjects exposed to DIC075V for 5 days (17 to 21 doses). The mean total dose received was 367.1 mg, ranging from 38 mg to 1000 mg.

Table 2: Treatment Exposure in Placebo and DIC075V 37.5 mg and 50 mg Treatment Groups: Safety Population: Multiple-dose Studies in Subjects with Postoperative Pain

		DIC075V 37.5 mg and 50 mg[a]		
Number of Exposure Days	Placebo[b] (N=126)	DFC-004/ DFC-005 (N=187)	DFC-010 (N=969)	Total (N=1156)
n (%)				
1 (≤ 4 doses)	53 (42.1)	68 (36.4)	41 (4.2)	109 (9.4)
2 (5 - 8 doses)	58 (46.0)	76 (40.6)	606 (62.5)	682 (59.0)
3 (9 - 12 doses)	12 (9.5)	35 (18.7)	219 (22.6)	254 (22.0)
4 (13 - 16 doses)	3 (2.4)	7 (3.7)	71 (7.3)	78 (6.7)
5 (17 - 21 doses)	0	1 (0.5)	32 (3.3)	33 (2.9)
Mean (SD)	1.7 (0.7)	1.9 (0.9)	2.4 (0.8)	2.3 (0.8)
Median	2.0	2.0	2.0	2.0
Min-Max	1-4	1-5	1-5	1-5

Source: ISS Table 2.2 (CTD 5.3.5.3.2).

ECGs were performed in 12 of the studies at screening, and 9 studies had at least one post-baseline ECG assessment: during treatment, at discharge, or at the follow-up visit. The ECG parameters included in the ISS are heart rate, QTc, QT, QRS, and PR. The overall ECG interpretation is also summarized with respect to the 3 responses: normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). It should be noted that for all studies except DFC-004 and DFC-005, Bazett's correction formula was used to derive the QTc intervals. For DFC-004 and DFC-005 Fridericia's formula was used. Independent third party blinded analysis of ECG was conducted (b) (4) for DFC-004 and DFC-005, which focused on QTcB/QTcF interval central tendency analysis, QTcB/QTcF interval categorical changes from baseline, and analysis of new potentially meaningful clinical events. Although an option for investigators in study DFC-010, independent third party analysis was not conducted of automated ECG assessments.

Because of the limited availability of ECG data, the analysis of ECG overall interpretation was only performed for the multiple-dose studies (Analysis Population 1).

The incidence of treatment-emergent arrhythmic events was generally low in all treatment groups. With the exception of tachycardia, which was reported for 3.3% of subjects who received DIC075V 37.5 mg or 50 mg in study DFC-010, 1.1% of subjects who received DIC075V 37.5 mg or 50 mg in studies DFC-004 and DFC-005, and 4.8% of subjects who received placebo, no arrhythmic events were reported for >1% of subjects in any treatment group.

Most arrhythmic events reported were mild or moderate in severity and unrelated to study treatment. A total of 3 severe arrhythmic events were reported in 2 subjects in study DFC-010 who received DIC075V 50 mg. One subject (Subject 47-014) had an event of syncope reported as severe and unrelated to study treatment and one subject (Subject 31-034) had 2 arrhythmic events, tachycardia and atrial fibrillation, reported as severe and unrelated to study treatment; the outcome of these events were reported as fatal. This subject also had an SAE of sepsis reported with a fatal outcome.

Four subjects in study DFC-010 had arrhythmic events that were reported as SAEs, including 2 subjects who received DIC075V 37.5 mg with atrial fibrillation assessed as moderate in severity (Subject 47-046 and Subject 58-017), and 2 subjects who received DIC075V 50 mg, one with cardio-respiratory arrest (Subject 47-055), and one with ECG QT prolonged (Subject 61-001). All SAEs were assessed as unrelated to study treatment. The cardio-respiratory arrest, which was the result of a morphine patient controlled analgesia (PCA) overdose, responded promptly and completely to naloxone (Mu opioid antagonist) and resuscitation. However study treatment was discontinued. Two other subjects in study DFC-010, one each who received DIC075V 37.5 mg and DIC075V 50 mg, discontinued treatment due to arrhythmic events, including moderate bradycardia in Subject 28-025 and moderate atrial fibrillation in Subject 69-020.

Table 3: Overall Incidence of Arrhythmic Events in Placebo and DIC075V 37.5 mg and 50 mg Treatment Groups: Multiple-dose Studies in Subjects with Acute Moderate to Severe Pain (Safety Population)

		DIC075V 37.5 mg and 50 mg[a]		
MedDRA Preferred Term	Placebo[b] (N=126) n (%)	DFC-004/DFC-005 (N=187) n (%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Tachycardia	6 (4.8)	2 (1.1)	32 (3.3)	34 (2.9)
Bradycardia	1 (0.8)	1 (0.5)	10 (1.0)	11 (1.0)
Atrial fibrillation	0	0	9 (0.9)	9 (0.8)
Sinus tachycardia	0	0	4 (0.4)	4 (0.3)
Sinus bradycardia	0	0	3 (0.3)	3 (0.3)
Syncope	0	0	3 (0.3)	3 (0.3)
Palpitations	0	1 (0.5)	1 (0.1)	2 (0.2)
Arrhythmia	0	0	2 (0.2)	2 (0.2)
Supraventricular extrasystoles	0	0	2 (0.2)	2 (0.2)
Electrocardiogram QT prolonged	0	0	2 (0.2)	2 (0.2)
Heart rate irregular	0	0	2 (0.2)	2 (0.2)
Bundle branch block left	0	0	1 (0.1)	1 (0.1)
Bundle branch block right	0	0	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	0	0	1 (0.1)	1 (0.1)
Heart rate increased	1 (0.8)	0	1 (0.1)	1 (0.1)
Loss of consciousness	0	0	1 (0.1)	1 (0.1)
Heart rate abnormal	1 (0.8)	0	0	0

Source: Appendix 13.5, Table 3.11.2.4

a The DIC075V 37.5 mg and 50 mg dose groups are included in this analysis (b) (4) (b) (4)

b Includes subjects in the placebo group that match subjects in the DIC075V group who received the proposed dose.

Source: Table 4-48, ISS, page 158

Reviewer's comments: No seizures, sudden death or ventricular arrhythmias were reported in these trials. In study DFC-010, syncope and QT prolongation were reported in subjects treated with diclofenac and none in the placebo group. However, the incidence was ≤1 %.

3.5 Clinical Pharmacology

Appendix 6.1 summarizes the key features of DIC075V's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 Overview

The QT-IRT reviewed the protocol (conducted under IND 65048) prior to conducting this study. The sponsor submitted the study report DFC-001 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Single-Dose, Comparative, Positive and Placebo Controlled, Four-way, Four-period, Cross-Over Study to Evaluate the Effect of DIC075V on QTc Intervals in Healthy Subjects

4.2.2 Protocol Number

DFC-011

4.2.3 Study Dates

First Subject Enrollment: 20, May 2009
Last Subject Enrollment: 07, July 2009

4.2.4 Objectives

Primary Objectives:

- Evaluate the effect of DIC075V (diclofenac sodium injection) on ventricular repolarization in healthy subjects compared to placebo after a single dose of DIC075V administered intravenously (IV).
- Evaluate electrocardiogram (ECG) assay sensitivity of the study by evaluating the baseline-adjusted effect of a single 400 mg oral (PO) dose of moxifloxicin (moxifloxacin hydrochloride) on ventricular repolarization in healthy subjects compared to placebo.

Secondary Objectives:

- Evaluate the effect of DIC075V on ventricular repolarization in healthy subjects compared to placebo at the T_{max} of diclofenac and hydroxypropyl-beta-cyclodextrin (HPβCD).
- Determine if there is a pharmacokinetic/pharmacodynamic (PK/PD) relationship between the duration of the QTc intervals and diclofenac or HPβCD plasma concentrations.
- Obtain additional PK information on diclofenac and HPβCD in healthy subjects.
- Provide additional safety information.

4.2.5 Study Description

4.2.5.1 Design

A single center, randomized, positive and placebo controlled, 4-way, 4-period, crossover study. Enrollment was planned for approximately 72 subjects to receive study drug; 70 subjects actually received study drug.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxicin) controls.

4.2.5.3 Blinding

The positive (moxifloxicin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects received each of the following 4 study drugs:

- DIC075V 37.5 mg-dose administered IV over 30 seconds (Therapeutic Dose)
- DIC075V 75 mg-dose administered IV over 30 seconds (Supra-therapeutic Dose)
- DIC075V placebo dose administered IV over 30 seconds (Placebo)
- Moxifloxicin 400-mg dose administered with water (Positive Control).

4.2.6.2 Sponsor's Justification for Doses

DIC075V 37.5 mg is the proposed therapeutic dose. A Supra-therapeutic dose of DIC075V, 75 mg, was chosen because it was the highest dose tested in the clinical program. There is no prior experience or exposure data for DIC075V at doses greater than 75 mg. Moreover, there is a concern about the potential for acute renal toxicity or gastric irritation with higher concentrations.

Reviewer's Comment: The sponsor's dose justification is acceptable. According to the sponsor's Summary of Clinical Pharmacology and the proposed labeling text, the PK of DIC075V is dose proportional over the range of 18.75 to 75 mg. Diclofenac (the active ingredient of DIC075V) is metabolized in the liver by conjugation to hydroxylated forms, principally 4-hydroxydiclofenac, approximately 65% of which is excreted in the urine and approximately 35% in the bile. 4-hydroxydiclofenac has very weak pharmacologic activity. The pharmacokinetics of diclofenac in hepatically and renally impaired subjects are not altered. Intrinsic factors (such as age, race and gender) have not been identified to affect DIC075V pharmacokinetics. Drug interaction studies did not suggest DIC075V pharmacokinetic alteration. The exposure of the supratherapeutic dose (75 mg) in the current TQT study is 2-fold higher than the therapeutic dose (37.5 mg), which should cover the expected high clinical exposure scenario.

4.2.6.3 Instructions with Regard to Meals

On Study Days -1, +1, +4, +7, and +10 during the hours of frequent ECG collection in the morning, the subjects were to be kept fasting. A mid-day meal could be given between 4 and 6 hours post-dose and concluded within 30 minutes, allowing for 1.5 hours before the next ECG acquisition at 6 hours post-dose. The evening meal was scheduled between 8 and 12 hours post-dose.

Identical lunches were served to each subject on all Dosing Days. On Washout Days (Study Days +2, +3, +5, +6, +8, and +9), standard meals and beverages were provided as per the clinic's usual policy. On these days, the subjects could have these meals at their preferred times.

Subjects could not consume caffeine-containing food and beverages between 3 days prior to admission to the clinic on Study Day -2 (Admission to Clinic) and Clinic Discharge. Tobacco and alcoholic beverages were prohibited throughout the study.

Reviewer's Comment: Not applicable. DIC075V is administered intravenously.

4.2.6.4 ECG and PK Assessments

On each of the Dosing Days (Study Days +1, +4, +7, and +10), ECGs were acquired from a continuous Holter recording flashcard at selected nominal timepoint intervals relative to dosing. The ECGs were 15 seconds in duration and were extracted in triplicate at various intervals. These extraction intervals were at approximately -1.5, -1.0, and -0.5 hours (pre-dose), and 5, 10, 15, and 30 minutes (2-minute window) and 1, 2, 4, 6, 8, 12, and 23.5 hours (5-minute window).

Blood was drawn for the determination of diclofenac (DIC075V), HPβCD (used (b) (4) in the DIC075V formulation), and moxifloxacin plasma concentrations at Time 0 (pre-dose), and approximately 5, 10, 15, 20, and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8,12, 18, and 23.5 hours after dosing.

Reviewer's Comment: The timings of the ECGs and the PK are acceptable. DIC075V is administered intravenously. The sampling schedule is adequate to cover the T_{max} of diclofenac and HPβCD (right after the injection) and the potential delayed effect up to 24 hours.

4.2.6.5 Baseline

Baseline data were calculated based on the average of the ECGs at -1.5, -1.0, and -0.5 hours (pre-dose) at each study period.

4.2.7 ECG Collection

ECGs for QTc analysis at Study Days -1, +1, +4, +7, and +10 were acquired from a continuous Holter ECG recording flashcard at various timepoints relative to anticipated subject-specific dosing. The ECGs were 15 seconds in duration and extracted in triplicate.

The subjects were to be kept resting in the supine position for 10 minutes before the intense cluster of the ECG Holter recordings at the nominal timepoints during the first hour postdosing. After the first hour, the subjects were to resume supine resting for 10 minutes prior to each ECG nominal timepoint.

ECG data were extracted and analyzed (b) (4) The central ECG laboratory used a limited number of skilled ECG readers. All ECGs were interpreted in a blinded fashion without knowledge of therapy or sequence including the active control. All ECGs from a particular subject were read by a single, qualified cardiologist.

The QT interval measurements were to be obtained by averaging 3 to 5 QT intervals measured from raw waveforms in a single lead, preferably lead II. All ECG measurements, baseline and on-treatment, for an individual subject were to be based on the same lead.

Every attempt was made to obtain all ECGs measurements for an individual subject on the same lead; however, it was not always possible to maintain 100% lead consistency using this approach. Factors such as noise, artifacts, or a change in the T wave morphology precluding accurate QT assessment in the selected lead mandated the use of an alternative lead. For 47 (67%) subjects, a percentage of measurements were based on a lead(s) other than the primarily selected lead. In 43 of the 47 subjects, fewer than 5% of

measurements were from a second or third lead. In 3 of 47 subjects, 5% to fewer than 10% of measurements were taken from a second or third lead. In 1 subject, 20% of measurements were taken from a second lead.

A semiautomatic or manual adjudication approach was to be used. In the semiautomatic method, the fiducial points were to be initially placed by a computer algorithm and, thereafter, adjusted as appropriate by the reader. PR and QRS interval data has been provided in a dataset. Each ECG has undergone a focused evaluation of the T and U wave morphology and appropriately categorized by diagnosis. These data are also provided.

The Screening, Check-In, Safety, and Clinic Discharge / Early Termination electrocardiograms will be acquired using a standard 12-lead electrocardiograph providing a print out display of the 12-lead tracing, and a lead II rhythm strip recorded at a sampling frequency of 1000 Hz, at 25 mm/sec at a standard duration of 10 seconds.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Of the 171 screened subjects, 74 were randomized and 70 were dosed. All 70 dosed subjects completed the study per protocol. The most common reasons that subjects were precluded from participation included positive toxicology screens (19 subjects), abnormal ECGs (18 subjects), and out of range laboratory results (14 subjects).

Four female subjects (01-208, 01-211, 01-225, 01-230) were randomized to a treatment sequence but withdrew just prior to dosing. The reasons for withdrawal were: withdrew consent (2 subjects), abnormal vital sign assessment, and abnormal laboratory result.

Among the 70 dosed subjects, there were more males (39 subjects, 55.7%) than females (31, 44.3%), the mean age was 23.3 years, and the mean BMI was 24.67 kg/m^2.

Table 4: Subject Disposition

	Treatment Sequence ABCD n (%)	Treatment Sequence BDAC n (%)	Treatment Sequence CADB n (%)	Treatment Sequence DCBA n (%)	All Subjects n (%)
Screened					171
Randomized	19	18	18	19	74
Withdrawn (Not dosed)	1	2	1	0	4[e]
Safety Population[a]	18	16	17	19	70
QT Population[b]	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
PK Population[c]	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
Concentration-QT Population[d]	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
Treatment Received					
DIC075V 37.5 mg (Regimen A)	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
DIC075V 75 mg (Regimen B)	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
DIC075V Placebo (Regimen C)	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
Avelox 400 mg (Regimen D)	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)
Completed Study	18 (100)	16 (100)	17 (100)	19 (100)	70 (100)

a All randomized subjects who received at least 1 dose of study drug and have at least 1 post-dose safety assessment.
b All randomized subjects who completed all 4 treatment periods and have QTc values for all treatment arms.
c All randomized subjects who received DIC075V and have sufficient data for PK analysis.
d All randomized subjects who received DIC075V and DIC075V placebo and have at least 1 set of post-dose QT assessments and corresponding plasma diclofenac and/or HPβCD concentrations.
e Four female subjects (01-208, 01-211, 01-225, 01-230) withdrew just prior to dosing. Reasons for withdrawal were: withdrew consent (2 subjects), abnormal vital sign assessment, and abnormal laboratory result.
Note: All percentages are based on the number of subjects in the Safety population.
Source: Table 14.1.1.1

Source; CSR, table 10-1

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the time-matched baseline-adjusted mean differences between DIC075V (37.5 mg and 75 mg) and placebo in QTcF. The sponsor used ANOVA model including treatment and period as fixed effect, and subject as a random effect. Table 5 presented the maximum time point of ΔΔQTcF for DIC075V 37.5-mg, DIC075V 75-mg, and moxifloxacin 400-mg groups. The maximum upper bounds of the 2-sided 90% CIs for the mean differences between DIC075V (37.5 mg and 75 mg) and placebo at one hour post-dosing were below 10 ms. For moxifloxicin 400-mg group, the largest lower bound of the 2-sided 90% CI for the mean differences was greater than 5 ms (see Figure 2).

Table 5: Sponsor's Analysis Results of Maximum Mean Baseline and Placebo-adjusted QTcF for DIC075V 37.5 mg , DIC075V 75 mg, and Moxifloxicin 400 mg

	DIC075V 37.5 mg n = 70	DIC075V 75 mg n = 70	Avelox 400 mg n = 70
Nominal Time After Dosing	1 hour	1 hour	4 hours
Change from Baseline[a], ms			
Mean (SD)	-2.60 (6.777)	-2.89 (6.566)	5.97 (7.926)
Median	-2.70	-3.20	5.95
Minimum, Maximum	-22.8, 12.1	-16.8, 14.8	-14.9, 30.3
Difference from Placebo, ms			
Mean (SD)	1.62 (9.406)	1.33 (9.135)	10.63 (10.925)
Median	1.95	1.20	11.05
Minimum, Maximum	-18.3, 22.1	-17.2, 19.3	-15.5, 39.9
Adjusted Mean[b]	1.62	1.36	10.62
Standard Error	1.249	1.248	1.281
90% CI[b]	-0.45, 3.68	-0.70, 3.42	**8.50**, 12.73

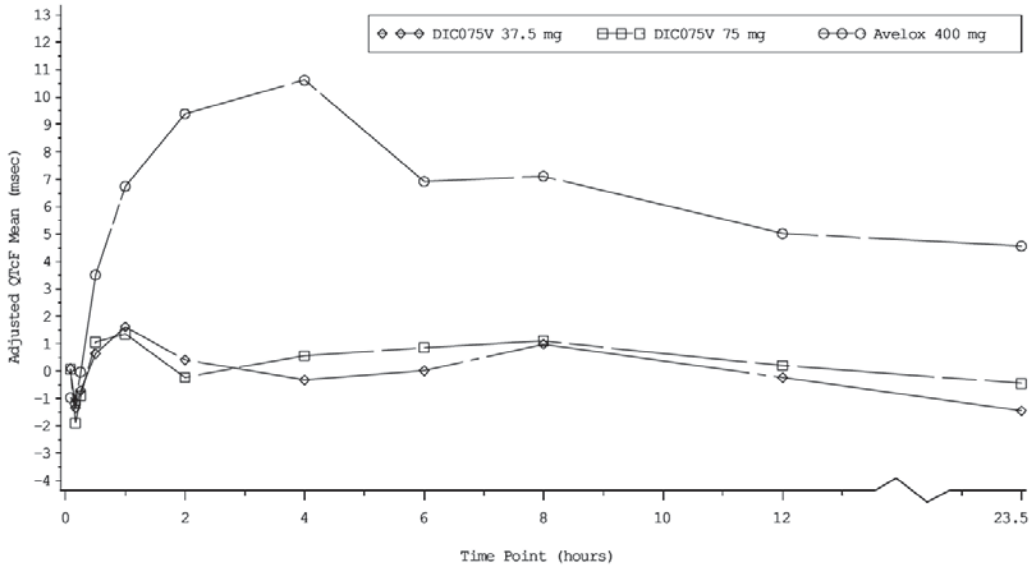
ms = milliseconds; SD = standard deviation; CI = confidence interval

a Baseline = average of QTcF at -1.5, -1.0, and -0.5 hours pre-dose.

b Adjusted mean (baseline–adjusted QTcF for active - baseline–adjusted QTcF for placebo), standard error, and 90% CI were obtained from an ANOVA model with effects for subject, period, and treatment, with subject as a random effect.

Source: Sponsor's CSR Table 11-2 on Page 66/272.

Figure 2: Sponsor's Mean and 90% CI ΔΔQTcF Time Course



Source: Sponsor's CSR Figure 11-1 on Page 65/272.

Reviewer's Comments: We will provide our independent analysis results in section 5.2.

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc>450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc > 60 ms.

4.2.8.3 Safety Analysis

No subject discontinued or withdrew after dosing began.

The most frequently occurring TEAEs were Nervous System Disorders. These events were primarily mild dizziness and were concentrated in the DIC075V 75-mg and moxifloxicin 400-mg groups.

Administration Site Conditions were the second most common TEAEs. These consisted of catheter site and vessel puncture site events (irritation, hematoma, inflammation, pain, swelling, reaction [nos]) and were comparably distributed across the treatment arms.

Table 6: Treatment-emergent Adverse Events in More Than 1 Subject by Treatment, Safety Population

MedDRA SOC Preferred Term	DIC075V Placebo n = 70 n (%)	DIC075V 37.5 mg n = 70 n (%)	DIC075V 75 mg n = 70 n (%)	AVELOX® 400 mg n = 70 n (%)
Any TEAE	6 (8.6)	6 (8.6)	7 (10.0)	9 (12.9)
Gastrointestinal Disorders	0	1 (1.4)	4 (5.7)	3 (4.3)
Upper abdominal pain	0	1 (1.4)	1 (1.4)	0
Nausea	0	0	3 (4.3)	3 (4.3)
General Disorders & Administration Site Conditions	4 (5.7)	2 (2.9)	3 (4.3)	2 (2.9)
Catheter site pain	1 (1.4)	1 (1.4)	0	0
Vessel puncture site hematoma	2 (2.9)	0	1 (1.4)	0
Vessel puncture site pain	0	1 (1.4)	2 (2.9)	0
Nervous System Disorders	2 (2.9)	3 (4.3)	3 (4.3)	4 (5.7)
Dizziness	1 (1.4)	1 (1.4)	2 (2.9)	4 (5.7)
Headache	1 (1.4)	2 (2.9)	1 (1.4)	1 (1.4)
Reproductive System and Breast Disorders	0	1 (1.4)	0	1 (1.4)
Dysmenorrhea	0	1 (1.4)	0	1 (1.4)

TEAE = treatment-emergent adverse event; defined as not present before exposure to the study drug or already present and worsening in either intensity or frequency following exposure to study drug
Source: Table 14.3.1.1.

Source: CSR, Table 12-2

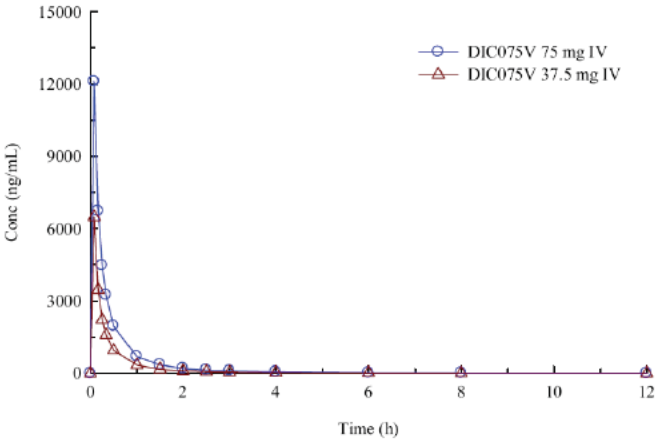
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

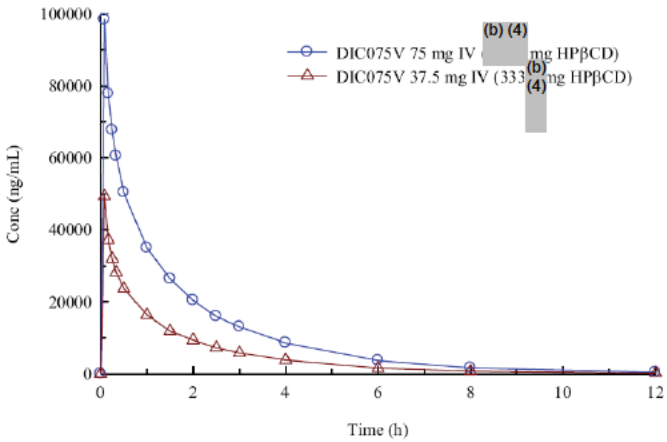
Mean concentrations of DIC075V and HPβCD are presented in Figure 3. Mean PK parameters are shown in Table 7 and Table 8. The dose proportionality is demonstrated.

Figure 3: Mean Concentration-time Profiles of DIC075V (Left) and HPβCD (Right)

DIC075V



HPβCD



(Source: Sponsor's Clinical Study Report, Figure 11-6/7 on Page 76/77)

Table 7: Summary of Plasma Pharmacokinetic Parameters for DIC075V

Parameter[1]	DIC075V 37.5 mg	DIC075V 75 mg
Cmax (ng/mL)	6,493 ± 1,363 (70)	12,102 ± 2,146 (70)
Tmax (h)	0.083 (70)	0.083 (70)
AUC(0-t) (h×ng/mL)	1,984 ± 399 (70)	3,943 ± 788 (70)
AUC(inf) (h×ng/mL)	2,017 ± 397 (66)	3,967 ± 789 (70)
λz (h^{-1})	0.4209 ± 0.075 (66)	0.3887 ± 0.067 (70)
t½ (h)	1.70 ± 0.33 (66)	1.84 ± 0.35 (70)
CL (mL/min)	299 ± 57.9 (66)	304 ± 62.1 (70)
Vz (L)	43.4 ± 9.32 (66)	48.1 ± 11.2 (70)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) is reported.

(Source: Sponsor's Clinical Study Report, Table 11-8 on Page 76)

Table 8: Summary of Plasma Pharmacokinetic Parameters for HPβCD

Parameter[1]	DIC075V 37.5 mg (333 (b) (4) mg HPβCD)	DIC075V 75 mg ((b) (4) mg HPβCD)
Cmax (ng/mL)	49,570 ± 11,553 (70)	99,039 ± 21,709 (70)
Tmax (h)	0.083 (70)	0.083 (70)
AUC(0-t) (h×ng/mL)	59,571 ± 10,737 (70)	130,497 ± 27,384 (70)
AUC(inf) (h×ng/mL)	60,355 ± 10,563 (69)	131,163 ± 27,377 (70)
λz (h^{-1})	0.4044 ± 0.045 (69)	0.3820 ± 0.059 (70)
t½ (h)	1.74 ± 0.23 (69)	1.86 ± 0.32 (70)
CL (mL/min)	95.1 ± 18.5 (69)	88.2 ± 17.3 (70)
Vz (L)	14.3 ± 3.47 (69)	14.1 ± 3.22 (70)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) is reported.

(Source: Sponsor's Clinical Study Report, Table 11-9 on Page 77)

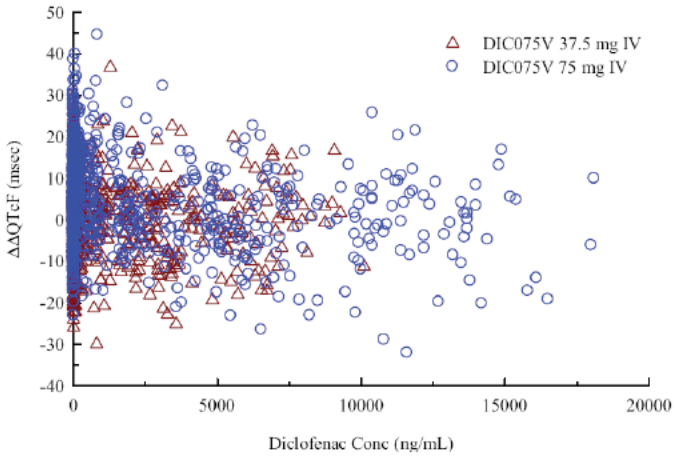
Reviewer's Analysis: The sampling strategy is acceptable to characterize the time course of DIC075V and HPβCD.

4.2.8.4.2 Exposure-Response Analysis

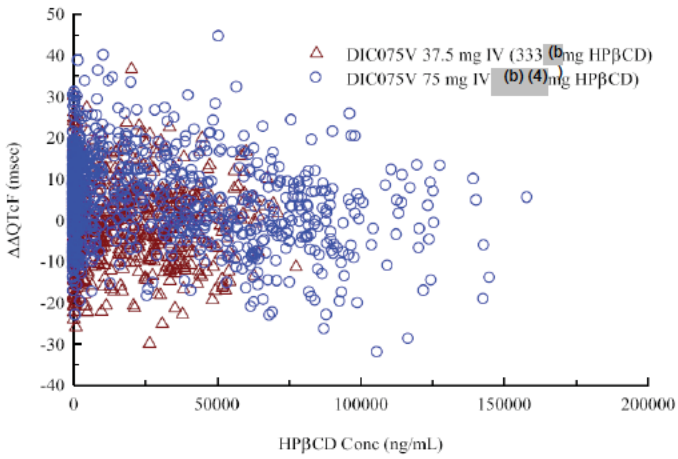
Relationships between ΔΔQTcF (Figure 4) and the plasma concentrations of diclofenac and HPβCD were explored graphically. There were no apparent relationships between the changes in any ΔΔQTcF and the corresponding plasma concentrations of diclofenac or HPβCD.

Figure 4: Change (ms) from Placebo in QTcF versus DIC075V (Left) and HPβCD (Right) Concentrations

DIC075V



HPβCD



(Source: Sponsor's Clinical Study Report, Figure 11-9/12 on Page 79/80)

Reviewer's Comments: Plots of reviewer's ΔΔQTcF vs. diclofenac and HPβCD concentrations are presented in Figure 7. Consistent with the sponsor's results, the slope of the concentration-response relationship is not positive.

5 REVIEWERS' ASSESSMENT

5.1 Evaluation of the QT/RR Correction Method

5.2 Statistical Assessments

We evaluated the appropriateness of the correction methods (QTcP and QTcF). Baseline values were excluded in the validation. Ideally, a good correction method for QT would not be affected by changes in RR intervals. We used the mixed model of the pooled post-dose data of QTcP and QTcF distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included gender, baseline, RR, correction type (QTcP or QTcF), and the interaction term of RR and correction type. The slopes of QTcP and QTcF versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 9, it appears that QTcF had smaller absolute slopes than QTcP. Therefore, QTcF is a better correction method for the study data.

Table 9: Comparison of QTcP and QTcF Using the Mixed Model

Treatment Groups	Slope of QTcP	Slope of QTcF	Dff_p_value
DIC075V 37.5 mg	0.0067	0.0005	0.0989
DIC075V 75 mg	0.0100	-0.0016	0.0005
Placebo	-0.0001	0.0023	0.4320
Moxifloxicin 400 mg	0.0173	0.0109	0.0588
All	0.0071	0.0043	0.0241

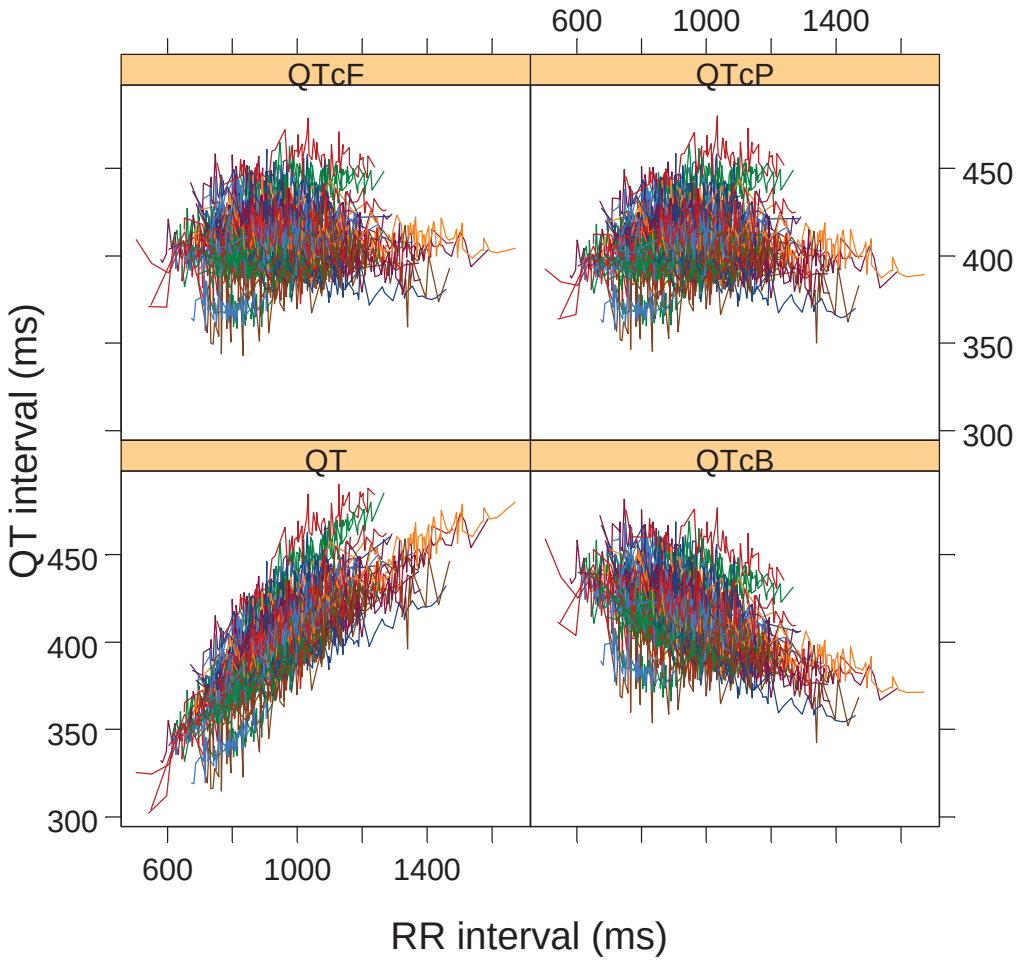
We also confirmed this conclusion by evaluating the Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc values versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 10, it also appears that QTcF is the best correction method. Therefore, the FDA reviewer used QTcF for the analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 10: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcP	
	N	MSSS	N	MSSS	N	MSSS
DIC075V 37.5 mg	70	0.0051	70	0.0011	70	0.0016
DIC075V 75 mg	70	0.0058	70	0.0010	70	0.0014
Placebo	70	0.0058	70	0.0009	70	0.0012
Moxifloxicin 400 mg	70	0.0061	70	0.0012	70	0.0018
All	70	0.0048	70	0.0005	70	0.0010

The QT-RR interval relationship is presented in **Error! Reference source not found.**, together with the Bazett's (QTcB), Fridericia (QTcF), and Population-specific correction (QTcP).

Figure 5: QTcF, QTcP, QT, and QTcB vs. RR (Each Subject's Data Points are Connected with a Line)



5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model included TIME, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. The model also included the baseline and gender as covariates. The analysis results are presented in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between DIC075V 37.5 mg and placebo, and between DIC075V 75 mg and placebo are 3.7 ms and 3.4 ms, respectively.

Table 11: Analysis Results of ΔQTcF and ΔΔQTcF for DIC075V 37.5 mg, DIC075V 75 mg, and Moxifloxicin 400 mg

		Treatment Group									
		DIC075V 37.5 mg			DIC075V 75 mg			Moxifloxicin 400 mg			
	Placebo	ΔQTc	ΔΔQTc		ΔQTc	ΔΔQTc		ΔQTc	ΔΔQTc		
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	Adj.* 90% CI
5 min	-0.7	-0.6	0.1	(-1.8, 2.1)	-0.6	0.1	(-1.8, 2.1)	-1.6	-0.9	(-2.8, 1.1)	(-3.5, 1.8)
10 min	-0.2	-1.5	-1.3	(-3.1, 0.4)	-2.0	-1.8	(-3.6, -0.1)	-1.2	-1.1	(-2.8, 0.7)	(-3.5, 1.3)
15 min	-1.6	-2.3	-0.7	(-2.6, 1.2)	-2.5	-0.8	(-2.7, 1.1)	-1.6	0.1	(-1.8, 1.9)	(-2.5, 2.6)
30 min	-2.6	-2.0	0.7	(-1.3, 2.6)	-1.5	1.1	(-0.9, 3.1)	1.0	3.6	(1.6, 5.5)	(0.9, 6.3)
1	-4.2	-2.6	1.6	(-0.4, 3.7)	-2.8	1.4	(-0.7, 3.4)	2.6	6.8	(4.7, 8.8)	(4.0, 9.6)
2	-4.0	-3.5	0.4	(-1.4, 2.3)	-4.2	-0.2	(-2.0, 1.7)	5.5	9.5	(7.6, 11.4)	(6.9, 12.0)
4	-4.6	-4.9	-0.3	(-2.4, 1.8)	-4.0	0.6	(-1.5, 2.7)	6.1	10.7	(8.6, 12.8)	(7.8, 13.5)
6	-8.8	-8.7	0.1	(-1.6, 1.8)	-7.8	1.0	(-0.7, 2.7)	-1.6	7.1	(5.4, 8.8)	(4.8, 9.5)
8	-8.1	-7.1	1.1	(-0.7, 2.8)	-6.9	1.2	(-0.6, 3.0)	-0.8	7.3	(5.5, 9.1)	(4.8, 9.7)
12	-6.0	-6.1	-0.2	(-2.0, 1.7)	-5.6	0.4	(-1.5, 2.2)	-0.7	5.2	(3.4, 7.1)	(2.8, 7.7)
23.5	-1.4	-2.8	-1.4	(-3.5, 0.6)	-1.8	-0.4	(-2.4, 1.6)	3.3	4.6	(2.6, 6.7)	(1.8, 7.4)

*The lower bound of the 90% CI is 7.8 ms after Bonferroni adjustment for 4 time points.

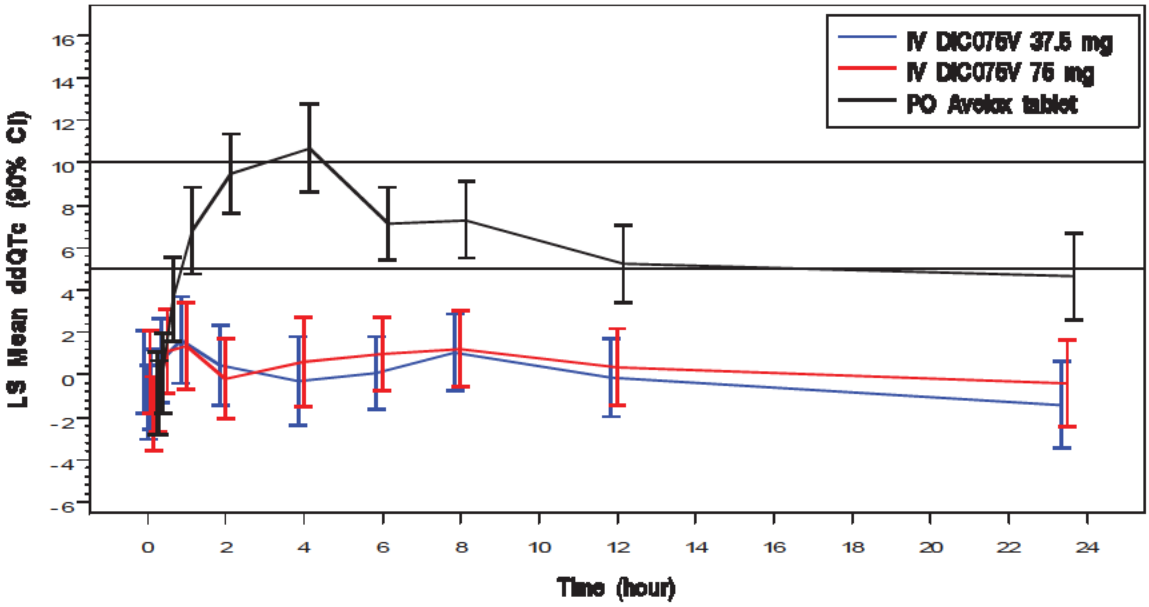
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxicin and placebo data. The results are presented in Table 11. The largest unadjusted 90% lower confidence interval is 8.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.8 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 6: Mean and 90% CI ΔΔQTcF Time Course



(Note: CIs are all unadjusted including moxifloxicin treatment group)

5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 12: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
DIC075V 37.5 mg	70	68 (97.1%)	2 (2.9%)
DIC075V 75 mg	70	67 (95.7%)	3 (4.3%)
Placebo	70	67 (95.7%)	3 (4.3%)
Moxifloxicin 400 mg	70	65 (92.9%)	5 (7.1%)

Table 13 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 13: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
DIC075V 37.5 mg	70	70 (100%)	0 (0.0%)
DIC075V 75 mg	70	70 (100%)	0 (0.0%)
Placebo	70	70 (100%)	0 (0.0%)
Moxifloxicin 400 mg	70	69 (98.6%)	1 (1.4%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper bounds of 2-sided 90% CI for the PR mean differences between DIC075V 37.5 mg and placebo, and between DIC075V 75 mg and placebo are 2.7 ms and 2.8 ms, respectively. There are no subjects who experienced absolute PR interval greater than 200 ms in DIC075V (doses of 37.5 mg and 75 mg) treatment groups.

Table 14: Analysis Results of ΔPR and ΔΔPR for DIC075V 37.5 mg, DIC075V 75 mg, and Moxifloxicin 400 mg

		Treatment Group					
		DIC075V 37.5 mg			DIC075V 75 mg		
	Placebo	ΔQTc	ΔΔQTc		ΔQTc	ΔΔQTc	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
5 min	-0.8	0.3	1.0	(-0.5, 2.6)	-0.1	0.7	(-0.9, 2.2)
10 min	-1.1	-0.8	0.3	(-1.0, 1.7)	-1.0	0.2	(-1.1, 1.5)
15 min	-1.4	-0.8	0.7	(-0.7, 2.0)	-0.4	1.0	(-0.3, 2.4)
30 min	-2.1	-1.0	1.1	(-0.3, 2.5)	-1.6	0.6	(-0.9, 2.0)
1	-2.5	-1.3	1.2	(-0.3, 2.7)	-2.4	0.0	(-1.4, 1.5)
2	-3.4	-3.2	0.1	(-1.4, 1.6)	-3.2	0.2	(-1.3, 1.7)
4	-3.5	-3.3	0.1	(-1.4, 1.6)	-4.1	-0.6	(-2.1, 0.9)
6	-10.1	-10.1	-0.0	(-1.5, 1.4)	-9.5	0.6	(-0.8, 2.1)
8	-9.7	-9.8	-0.1	(-1.4, 1.3)	-9.1	0.6	(-0.7, 2.0)
12	-8.0	-7.8	0.1	(-1.1, 1.4)	-6.4	1.5	(0.3, 2.8)
23.5	-0.4	-0.7	-0.3	(-1.9, 1.3)	-0.7	-0.3	(-1.9, 1.3)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper bounds of 2-sided 90% CI for the QRS mean differences between DIC075V 37.5 mg and placebo, and between DIC075V 75 mg and placebo are 1.1 ms and 0.9 ms, respectively. There are

seven subjects who experienced absolute QRS interval greater than 110 ms in DIC075V treatment groups. Table 16 presents the categorical analysis of QRS.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for DIC075V 37.5 mg, DIC075V 75 mg, and Moxifloxicin 400 mg

		Treatment Group					
		DIC075V 37.5 mg			DIC075V 75 mg		
	Placebo	ΔQTc	ΔΔQTc		ΔQTc	ΔΔQTc	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
5 min	-0.3	-0.1	0.2	(-0.3, 0.7)	-0.3	-0.0	(-0.5, 0.5)
10 min	-0.4	-0.3	0.1	(-0.4, 0.7)	-0.4	-0.0	(-0.6, 0.5)
15 min	-0.5	-0.2	0.3	(-0.2, 0.8)	-0.3	0.1	(-0.3, 0.6)
30 min	-0.5	-0.3	0.2	(-0.3, 0.7)	-0.4	0.1	(-0.4, 0.6)
1	-0.8	-0.5	0.3	(-0.2, 0.8)	-0.4	0.4	(-0.2, 0.9)
2	-0.7	-0.4	0.3	(-0.2, 0.8)	-0.4	0.3	(-0.2, 0.8)
4	-0.9	-0.3	0.6	(0.1, 1.1)	-0.7	0.3	(-0.2, 0.8)
6	-0.8	-0.8	-0.1	(-0.6, 0.4)	-1.2	-0.5	(-1.0, 0.1)
8	-1.1	-0.7	0.4	(-0.1, 0.9)	-0.8	0.3	(-0.3, 0.8)
12	-0.1	0.0	0.1	(-0.5, 0.8)	-0.4	-0.3	(-1.0, 0.3)
23.5	-0.3	-0.3	0.0	(-0.6, 0.6)	-0.4	-0.0	(-0.6, 0.6)

Table 16: Categorical Analysis of QRS

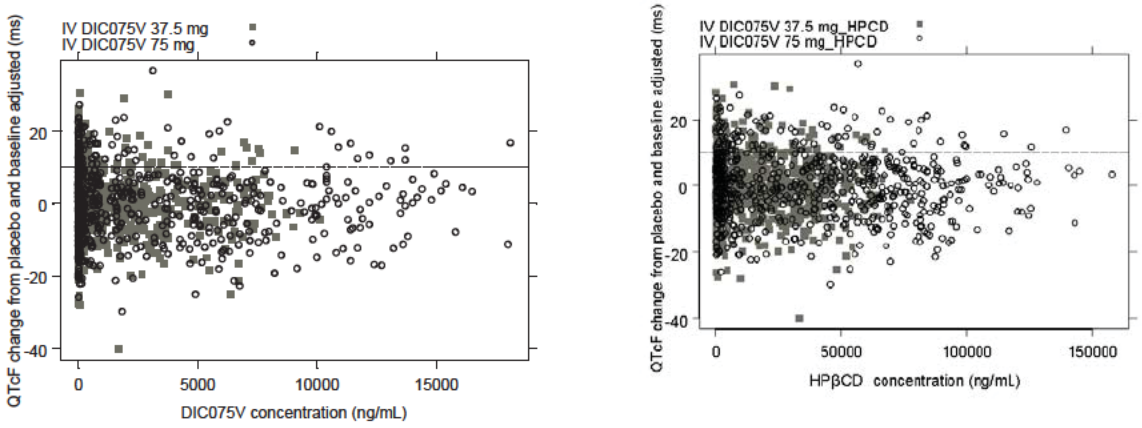
Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
IV DIC075V 37.5 mg	70	63 (90.0%)	7 (10.0%)
IV DIC075V 75 mg	70	65 (92.9%)	5 (7.1%)
Placebo	70	65 (92.9%)	5 (7.1%)
Moxifloxicin 400 mg	70	66 (94.3%)	4 (5.7%)

5.3 Clinical Pharmacology Assessments

The mean DIC075V and HPβCD concentration-time profiles are illustrated in Figure 3.

The relationship between ΔΔQTcF and DIC075V concentration and the relationship between ΔΔQTcF and HPβCD concentration are visualized in Figure 7 with no evident exposure-response relationship.

Figure 7: ΔΔ QTcF vs. DIC075V (left) and HPβCD (right) Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in multiple leads (Led II and V2 in the majority of cases), with less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

DIC075V does not affect PR and QRS duration.

There are no subjects who experienced absolute PR interval greater than 200 ms in DIC075V (doses of 37.5 mg and 75 mg) treatment groups.

Seven subjects who experienced absolute QRS interval greater than 110 ms in DIC075V treatment groups, three of them had QRS baseline values > 100 ms and in all cases QRS increases were ≥4 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	DIC075V 37.5 mg	
Maximum tolerated dose	Unknown – the maximum dose tested in the DIC075 clinical program was 75 mg.	
Principal adverse events	The most common side effects include: ▪ Nausea (upset stomach) ▪ Vomiting ▪ Pain after surgery ▪ Intestinal gas ▪ Headache ▪ Constipation Less common side effects include: ▪ Dizziness ▪ Injection site pain ▪ Throat pain ▪ Swelling or redness at the surgery site ▪ Swelling ▪ Difficulty sleeping	
Maximum dose tested	Single Dose	DIC075V 75 mg, <5 sec IV bolus)
	Multiple Dose	DIC075V 37.5 mg (<15 sec IV bolus) q6h, up to 5 days [DFC-004, DFC-005]
Exposures Achieved at Maximum Tested Dose	Single Dose	DIC075V 75 mg, <5 sec IV bolus (mean ± SD) [DFC-PL1] ▪ Cmax: 15,862 ± 2,896 ng/ml ▪ AUC: 3,524 ± 476 ng·h/ml
	Multiple Dose	DIC075V 37.5 mg (<15 sec IV bolus) x 4 doses [DFC-PK-006] ▪ Cmax: 5,617 ± 1,799 ng/ml ▪ AUC: 1,839 ± 506 ng·h/ml
Range of linear PK	DIC075V 37.5 mg (<15 sec IV bolus) x 4 doses [DFC-PK-006]	
Accumulation at steady state	No accumulation observed [DFC-PK-006]	
Metabolites	According to the Cataflam package insert, five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy; 5-hydroxy; 3'-hydroxy; 4', 5-dihydroxy; and 3'-hydroxy-4'-methoxy diclofenac. One diclofenac metabolite 4'-hydroxy-diclofenac has very weak pharmacologic activity.	

		Renal Impairment: No differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal impairment. In patients with renal impairment (inulin clearance 60-90, 30-60, and < 30 ml/min; n=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects. (Cataflam PI)
Extrinsic Factors	Drug interactions	As described in the Cataflam PI, the known drug interactions for diclofenac include aspirin, methotrexate, cyclosporine, ACE inhibitors, furosemide, lithium, and warfarin.
	Food Effects	The effect of food on DIC075V PK has not been evaluated. However, as DIC075V is administered IV, food should have no effect on the absorption of DIC075V.
Expected High Clinical Exposure Scenario	DIC075V is an NSAID, and acute high clinical exposure would be expected to cause acute renal and gastrointestinal effects, such as acute renal insufficiency and gastrointestinal bleeding, as well electrolyte imbalances. However, the potential for a high clinical exposure with DIC075V is remote for the following reasons: 1. DIC075V is an injectable product that is administered in a medical setting by a healthcare professional. The patient does not self-administer DIC075V, thus avoiding any potential patient-induced administration errors. 2. DIC075V is only available in one concentration. Thus, it will be impossible for a healthcare professional to administer the wrong dose due to using a different concentration formulation. 3. DIC075V will be available only 1 ml vials, in which the contents of the entire vial represent a single dose. A high dose can only occur if the healthcare professional inadvertently administered a dose that was taken from more than 1 vial of DIC075V. With proper training, this scenario should not occur. However, if a high clinical exposure were to occur, there are inherent safeguards with DIC075V that should minimize danger to the patient: 1. DIC075V 75 mg has already been shown to be safe and is the approved dose in the United Kingdom. Thus, there is a two-fold margin of safety for the proposed 37.5 mg therapeutic	

Absorption	Absolute Bioavailability	100% - this product is administered via IV bolus injection
	Tmax	0.083 h [Study DFC-PK-006]
Distribution	Vd/F or Vd	DIC075V 37.5 mg at steady state [DFC-PK-006] Vz = 83.4 ± 127 L
	% bound	Diclofenac is more than 99% bound to human serum proteins, primarily to albumin (Cataflam PI).
Elimination	Route	Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine.
	Terminal t½	DIC075V 37.5 mg at steady state [DFC-PK-006] t½ = 2.29 ± 0.63 h
	CL/F or CL	DIC075V 37.5 mg at steady state [DFC-PK-006] CL = 387 ± 394 ml/min
Intrinsic Factors	Age	Clearance of DIC075V is not affected by age. The mean plasma diclofenac concentration-time curves were comparable among the three age cohort (≥55 and ≤65 years, n=12; ≥55 and ≤65 and < 75 years, n=13; and ≥75 years, n=3) as were the mean values for the pharmacokinetic parameters.
	Sex	Effect of gender on DIC075V PK has not been evaluated
	Race	Effect of race on DIC075V PK has not been evaluated
	Hepatic & Renal Impairment	Effect of hepatic & renal impairment on DIC075V PK is currently being evaluated. <u>Hepatic Impairment:</u> According to the Cataflam package insert, hepatic metabolism accounts for almost 100% of Cataflam elimination, so patients with hepatic disease may require reduced doses of Cataflam compared to patients with normal hepatic function.

	dose, in the event that a patient accidentally received a 75 mg dose. 2. DIC075V has a short half-life, approximately 2.3 hours. Thus, most patients should be able to eliminate >95% of DIC075V in approximately 12 hours. Additionally, DIC075V is metabolized to generally inactive metabolites.

6.2 TABLE OF STUDY ASSESSMENTS

LIST OF ACTIVITIES	Screen	Check-In Study Day -2	Study Day -1	Dosing Day 1	Wash-Out Days	Dosing Day 2	Wash-Out Days	Dosing Day 3	Wash-Out Days	Dosing Day 4	Clinic Discharge / Early Termination	Follow-Up (7 ± 3 Days after Discharge)[a]
Study Days	-21 to -3	-2	-1	+1	+2, +3	+4	+5, +6	+7	+8, +9	+10	+11	
Days of Confinement	---	1	2	3	4, 5	6	7, 8	9	10, 11	12	13	---
Informed Consent	X											
Review Inclusion/ Exclusion Criteria	X	X										
Demographics and Medical History	X											
Physical Examination	X										X	
Admission to Clinic		X										
Safety12-lead ECG	X	X		X[b]		X[b]		X[b]		X[b]	X	
Randomization[c]				X								
Vital Signs[d]	X	X		X		X		X		X	X	
Clinical Laboratory Tests	X	X									X	
HIV, Hepatitis B and C Screens	X											
Serum Pregnancy Test	X	X					X				X	
Urine Alcohol, Tobacco, and Drug Screens	X	X										
Administration of Study Drug				X		X		X		X		
12-lead ECG from Holter Monitor[e]			X	X		X		X		X		
Blood samples for PK analyses[f]				X		X		X		X		
Monitor for Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Current medications	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from Clinic											X	
Follow-up on any clinically significant abnormal findings from Clinic Discharge/Early Termination												X

Notes: Subjects were confined to the clinic from Study Day -2 to Study Day +11. Subjects were not discharged during the Washout periods.

a If there were no clinically significant abnormal findings upon discharge from the clinic, the Follow-up visit could be conducted with the appropriate study staff by phone.

b Safety 12-Lead ECGs at approximately 1 hour pre-dose (-1 hour) and 4 and 6 hours post-dose

c Subjects who met all eligibility criteria and were willing to participate were randomized to a 4-treatment sequence in accordance with a Williams Square design.

d Vital Signs: Heart rate, respiratory rate, blood pressure, and temperature (Screening only) were measured. Vital signs were recorded on Dosing Days at pre-dose and approximately 1 and 6 hours post-dose.

e 12-lead ECGs extracted from Holter Monitor: ECGs were extracted on Study Day -1 and were time-matched with the expected ECG extractions on each of the Dosing Days: approximately -1.5, -1.0, and -0.5 hours pre-dose, and 5, 10, 15, and 30 minutes (2-min window) and 1, 2, 4, 6, 8, 12, and 23.5 hours (5-min window) post-dose.

f Blood for PK analyses: pre-dose and approximately 5, 10, 15, 20, and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 and 23.5 hours post-dose.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	JAVELIN PHARMACEUTICALS INC	diclofenac sodium injection

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

/s/

MOH JEE NG
04/19/2010

JOANNE ZHANG
04/19/2010

JIANG LIU
04/19/2010

HAO ZHU
04/19/2010

MONICA L FISZMAN
04/19/2010

NORMAN L STOCKBRIDGE
04/19/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022396 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Dyloject Established/Proper Name: diclofenac sodium injection Dosage Form: 37.5 mg (b) (4) Strengths:		
Applicant: Javelin Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: 12/2/2009 Date of Receipt: 12/3/2009 Date clock started after UN:		
PDUFA Goal Date: October 3, 2010	Action Goal Date (if different):	
Filing Date: 2/1/2010	Date of Filing Meeting: 1/20/2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): management of acute moderate to severe pain in adults		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): IND 065048				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?		X		
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** **Consult sent to QT IRT on 1/12/10**	X			

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 4/21/06 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 3/10/08 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 20, 2010

BLA/NDA/Supp #: 022396

PROPRIETARY NAME: Dyloject

ESTABLISHED/PROPER NAME: diclofenac sodium injection

DOSAGE FORM/STRENGTH: 37.5 (b) (4)

APPLICANT: Javelin Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of acute moderate to severe pain in adults

BACKGROUND: Related IND 65048

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Sara Stradely	Y
Cross-Discipline Team Leader (CDTL)	Jeff Siegel		Y
Clinical	Reviewer:	Rosemarie Neuner	Y
	TL:	Jeff Siegel	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	
Biostatistics	Reviewer:	Jon Norton	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Armaghan Emami	Y
	TL:	Adam Wasserman	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Martin Haber	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalf	Y
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

APPEARS THIS WAY ON ORIGINAL

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Rigoberto Roca **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	JAVELIN PHARMACEUTICALS INC	diclofenac sodium injection

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

/s/

JESSICA M BENJAMIN
03/24/2010