CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 200403	Submission Date(s): April 29, 2010
Brand Name	N/A
Generic Name	Hydromorphone HCl Injection, USP
Reviewer	Wei Qiu, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	DCPII
OND division	DAAP
Sponsor	Hospira
Relevant IND(s)	N/A
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	solutions; 1, 2, and 4 mg/mL
Route of Administration	IV, SC, or IM injection
Indication	Management of pain in patients where an opioid analgesic is appropriate.

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed this submission dated April 29, 2010 and finds it acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Sponsor submitted a 505(b)(2) NDA 200534 for hydromorphone Hydrochloride solutions for injection, 1, 2, and 4 mg/mL for the management of pain where use of an opioid analgesic is appropriate. Dilaudid® Injection (NDA 19034) is the reference listed drug (b) (4)

No new clinical pharmacology or clinical studies were conducted with the proposed products. Sponsor requested a biowaiver and ONDQA Biopharmaceutics group evaluated the biowaiver request and concluded that the sponsor's biowaiver request is acceptable and that biowaiver is granted (see review by Dr. Angelica Dorantes dated October 26, 2010 for details).

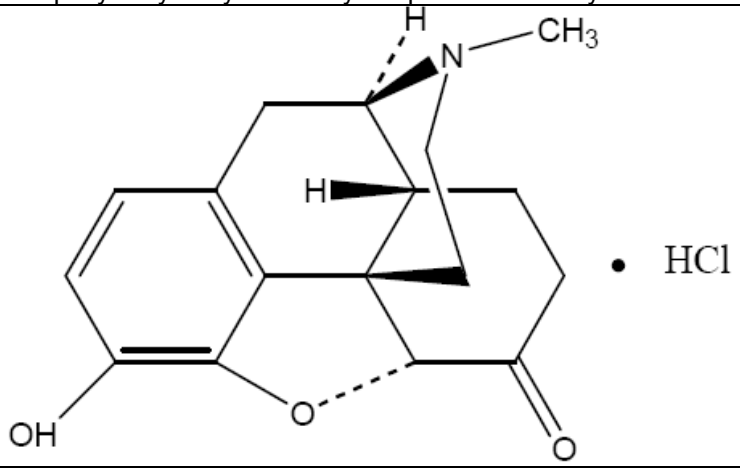
With respect to pediatrics, sponsor requested waiver of pediatric studies justifying the waiver request citing the applicable regulations. Since this NDA is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, the requirements of 21CFR314.55 do not apply and a waiver will be granted by the Agency.

2 Question Based Review

2.1 General Attributes of the Drug

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulations of the drug product?*

Table 1 Physical-Chemical Properties of Hydromorphone Hydrochloride

Drug Name	Hydromorphone Hydrochloride
Chemical Name	4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride
Structure	
Molecular Formula	$C_{17}H_{19}NO_3$•HCl
Molecular Weight	321.80
Solubility	Freely soluble in water, sparingly soluble in alcohol, and practically insoluble in ether.

Hydromorphone hydrochloride Injection is available as a sterile aqueous solution, which is intended for intravenous, subcutaneous or intramuscular administration. The drug product is comprised of a clear, colorless to nearly colorless solution. The components and composition of the drug products, hydromorphone hydrochloride solutions 1, 2, and 4 mg/mL are listed in **Table 2**.

Table 2 Components and Composition of Hydromorphone Hydrochloride Injection Solutions

Component	Strength	Strength	Strength	Function	Reference to Standards
	1 mg/mL	**2 mg/mL**	**4 mg/mL**		
Hydromorphone Hydrochloride USP	1.0 mg	2.0 mg	4.0 mg	Active ingredient	USP
Sodium Lactate (b) (4) USP	(b) (4)				USP
(b) (4)					USP
Sodium Chloride USP, EP, BP					USP
(b) (4)					USP
					NF
Lactic Acid USP					USP
Sodium Hydroxide (b) (4)					NF
(b) (4)					NF

qs = Quantity Sufficient, AR = As Required

(b) (4)

[2] The final pH range of the finished drug product is 3.5 – 5.5.

(b) (4)

2. *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Hydromorphone hydrochloride is a pure mu receptor opioid agonist whose principle therapeutic action is analgesia.

The proposed indication is for the management of pain in patients where an opioid analgesic is appropriate.

3. *What are the proposed dosage form and routes of administration?*

Dosage form of the proposed hydromorphone products are injectable and the route of administration is injection (intravenous, subcutaneous and intramuscular).

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of hydromorphone in general?

Sponsor did not conduct any PK studies in support of this product. Instead, approval is sought based on biowaiver referring to NDA 19034 and relying on the labeling language of the reference product. Hydromorphone is approximately 8-19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume of distribution is 302.9 liters. Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amount of 6-hydroxy reduction metabolites. Only a small amount of hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites. The systemic clearance is approximately 1.96 liters/minute. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours. Pharmacokinetic information for intrinsic and extrinsic factors such as hepatic impairment, renal impairment, geriatric, gender, pregnancy and nursing mothers are available for Dilaudid® and the same information will also be in the package insert of this product.

2.3 Intrinsic Factors

N/A

2.4 Extrinsic Factors

N/A

2.5 General Biopharmaceutics

N/A

2.6 Analytical Section

N/A

3 Detailed Labeling Recommendations

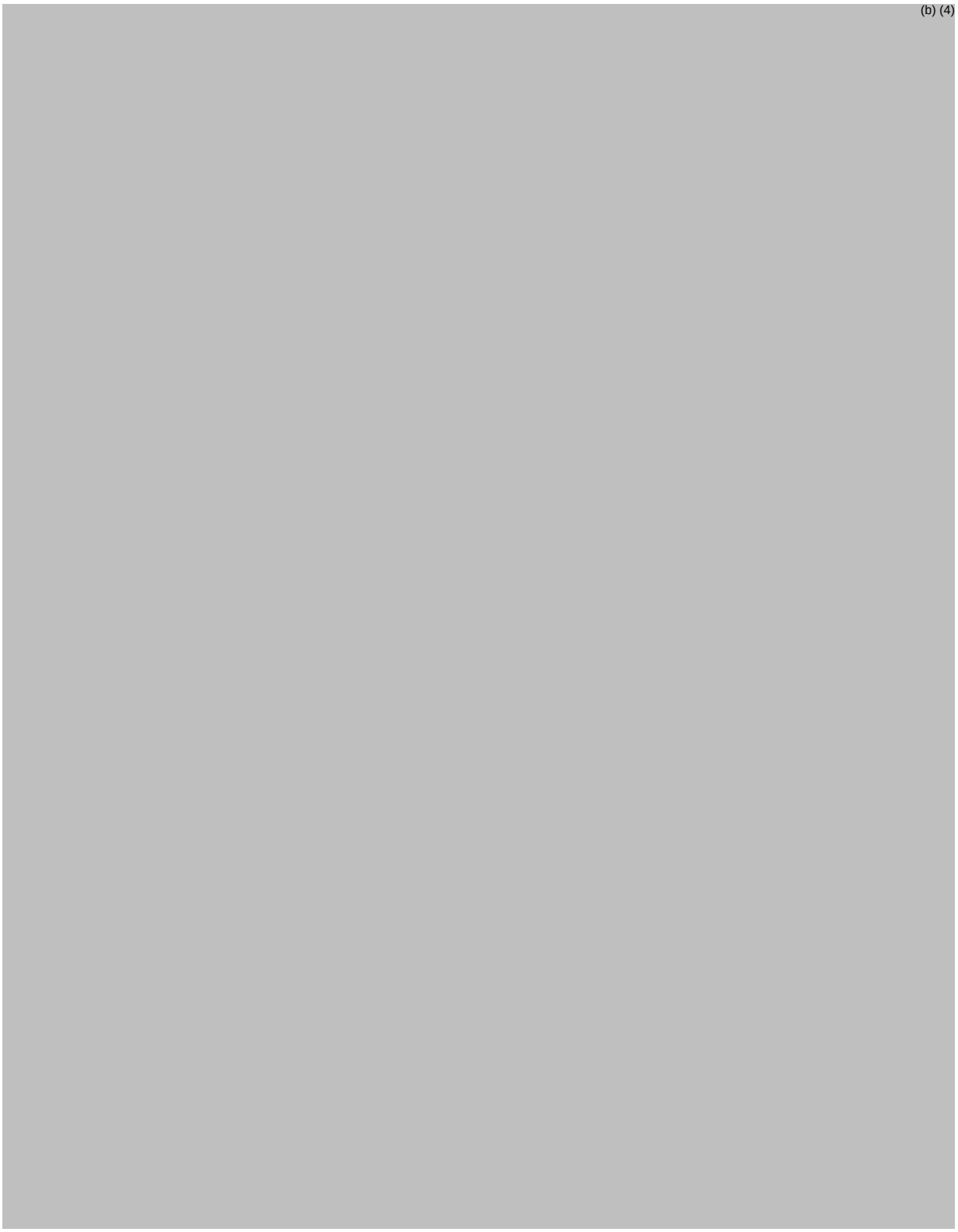
Currently, labeling supplement S-021/NDA 19034 submitted on 02/19/10 proposing PLR conversion of package insert for Dilaudid® is under review. Since Dialudid is the reference product for this NDA, the labeling recommendations for this product proposed below by this reviewer are based on the most recent labeling language incorporated in the package insert of Dilaudid® in supplement S-021.

As such, the following labeling changes are proposed by this reviewer to the labeling language proposed by Hospira for this product (Deletion is shown by Red ~~Strike through~~, addition is shown by blue underline)

Section 8 USE IN SPECIFIC POPULATIONS

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



4 Appendix

4.1 Clinical Pharmacology Filing and Review Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**200403**	**Brand Name**	**Hydromorphone HCl Injection, USP**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	
Medical Division	**DAAP**	**Drug Class**	**Opioid analgesic**
OCP Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Management of pain in patients where an opioid analgesic is appropriate.**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Solution 1, 2, and 4 mg/mL**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**April 29, 2010**	**Route of Administration**	**IV, SC, or IM Injection**
Estimated Due Date of OCP Review	**Jan 10, 2011**	**Sponsor**	**Hospira**
Medical Division Due Date	**Jan 24, 2011**	**Priority Classification**	**Standard**
PDUFA Due Date	**Feb 28, 2011**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		**1**	**0**	**Sponsor requests a biowaiver and the biowaiver is granted by ONDQA.**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**This application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, so sponsor believes the requirement of 21CFR314.55 do not apply.**
Literature References				
Total Number of Studies		**1**	**0**	

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/s/

WEI QIU
01/25/2011

SURESH DODDAPANENI
01/25/2011

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 200-403	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	April 29, 2010	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DDOP	**Date Assigned:**	May 5, 2010
Sponsor:	Hospira, Inc.	**Date of Review:**	October 25, 2010
Trade Name:	Hydromorphone HCl Injection 1, 2, 4 mg/ml	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Hydromorhone Hydrochloride		
Indication:	Hydromorphone injection is indicated for management of pain in patients where an opioid analgesic is appropriate.		
Formulation/ strengths	Hydromorphone Hydrochloride Injection, USP, 1, 2 and 4 mg/mL is available in ampules, Carpuject™ and iSecure™ syringes and single dose vials for parenteral administration. *The ampules are 1 ml capacity. The vials are 2 ml capacity. The cartridges consist of 2.5 ml capacity Carpuject cartridges and 1.5 ml capacity iSecure cartridges*		
Route of Administration	Intended for intravenous and intramuscular administration.		
Type of Review:	**BIOWAIVER REQUEST**		

BACKGROUND:

Hydromorphone Hydrochloride (HCl) is a potent Schedule II opioid agonist.

SUBMISSION:

In this application dated April 29, 2010, Hospira submitted NDA 200-403 for Hydromorphone Hydrochloride Injection 1, 2, 4 mg/ml under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug. The proposed drug product contains the same active ingredient [redacted] (b) (4), as the Reference Listed Drug, Dilaudid® Injection. Dilaudid is available in ampules for parenteral administration. Each 1 mL of sterile solution contains 1 mg, 2 mg, or 4 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution.

BIOPHARMACEUTICS:

Description and Composition of Drug Product: Hydromorphone Hydrochloride Injection, USP is available as a sterile aqueous solution, which is intended for intravenous, subcutaneous or intramuscular administration. The drug product is comprised of a clear, colorless to nearly colorless solution, free from visible particulates, presented in USP [redacted] (b) (4) glass ampules, vials and cartridges. The pH range is 3.5-5.5. This is an [redacted] (b) (4) product containing no antimicrobial preservatives. The ampules are 1 mL capacity. The vials are 2 mL capacity. The cartridges consist of 2.5 mL capacity Carpuject cartridges and 1.5 mL capacity iSecure cartridges. Both cartridge configurations incorporate 22 gauge Luer Lock needle assemblies. The quantitative composition on a per mL and per concentration basis are provided in the next Table.

Quantitative Composition

Component	Strength	Strength	Strength	Function
	1 mg/mL	2 mg/mL	4 mg/mL	
Hydromorphone Hydrochloride USP	1.0 mg	2.0 mg	4.0 mg	Active ingredient
Sodium Lactate (b) (4) USP	(b) (4)			(b) (4)
Sodium Chloride USP, EP, BP	(b) (4)			
Lactic Acid USP				
Sodium Hydroxide (b) (4)				
(b) (4)				

(b) (4)).

2 The final pH range of the finished drug product is 3.5 – 5.5.

(b) (4)

None of the inactive ingredients exceed the IIG limits for maximum daily dose and route of administration.

Comparison Between Reference Listed Drug and Generic Drug: The following table compares the reference and proposed drug products.

Comparison Between Reference Listed Drug and Generic Drug

	Reference Listed Drug	**Generic Equivalent**
	Purdue Pharma, L.P. **Dilaudid®**	**Hospira, Inc.** **Hydromorphone HCL Injection**
Conditions of Use	Management of pain in patients where an opioid analgesic is appropriate.	Management of pain in patients where an opioid analgesic is appropriate
Active Ingredient(s)	Hydromorphone Hydrochloride	Hydromorphone Hydrochloride
Inactive Ingredient(s)	- 0.2% sodium citrate - 0.2% citric acid	- (b) (4) sodium lactate solution, - lactic acid - sodium chloride
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	1, 2, 4 mg/ml	1, 2, 4 mg/ml

The conditions of use (indication), route of administration, dosage form, and strength for the subject drug, Hydromorphone HCl Injection, USP, are the same as prescribed and recommended for the use of the Reference Listed Drug. The proposed drug product contains the same active ingredient (b) (4), as the

Reference Listed Drug. The proposed drug product will be available in the same configuration as the RLD as well as in a vial, and Carpuject and iSecure syringes. The only differences in the formulation are the inactive ingredients. Hospira's proposed Hydromorphone Hydrochloride Injection, USP uses [redacted] (b) (4) and sodium chloride for tonicity, whereas Dilaudid® (Purdue Pharma, L.P) uses [redacted] (b) (4).

BIOWAIVER REQUEST:

In this submission, Hospira Inc. is requesting that the Agency's waives the requirement for the submission of in vivo BA/BE data to support the approval of Hydromorphone HCl Injection 1, 2, and 4 mg/ml. Information supporting this request was provided by Hospira.

Reviewer Comments:

- ***Hospira has provided information showing that their proposed formulation, route of administration, dosage form and indications of their product, Hydromorphone HCl Injection 1, 2, 4 mg/ ml are similar to those of the Referenced Listed Drug (RLD) product, Dilaudid® (hydromorphone HCl) Injection of Purdue Pharma.***
- ***Although, the inactive ingredients are different than those of the reference product, there are no safety concerns because the proposed product is a true solution and the inactive ingredients function as a buffer, isotonic agent, and pH adjuster. None of them exceed the IIG limits for maximum daily dose and route of administration.***
- ***Any difference in the pH range with respect to the RLD product will not have an effect on the bioavailability of the proposed Hydromorphone HCl Injection product.***

RECOMMENDATION:

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 200-404 for Hydromorphone Hydrochloride Injection 1, 2, and 4 mg/ml. Based on the provided information showing that **1)** their product contains the same active ingredient. The only differences in the formulation are the inactive ingredients. Hospira's proposed Hydromorphone HCl Injection, USP uses [redacted] (b) (4) and sodium chloride for tonicity, whereas Dilaudid® (Purdue Pharma, L.P.) uses [redacted] (b) (4), and **2)** the route of administration, dosage form and indications of their product are the same as the RLD product, ONDQA-Biophamaceutics considers that the in vivo BA/BE of Hydromorphone HCl Injection is self-evident. Therefore, the sponsor's request for a biowaiver for Hydromorphone HCl Injection 1, 2, and 4 mg/ ml is acceptable and the biowaiver is granted.

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

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/s/

ANGELICA DORANTES
10/25/2010

PATRICK J MARROUM
10/26/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**200403**	**Brand Name**	**Hydromorphone HCl Injection, USP**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	
Medical Division	**DAAP**	**Drug Class**	**Opioid analgesic**
OCP Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Management of pain in patients where an opioid analgesic is appropriate.**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Solution 1, 2, and 4 mg/mL**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**April 29, 2010**	**Route of Administration**	**IV, SC, or IM Injection**
Estimated Due Date of OCP Review	**Jan 10, 2011**	**Sponsor**	**Hospira**
Medical Division Due Date	**Jan 24, 2011**	**Priority Classification**	**Standard**
PDUFA Due Date	**Feb 28, 2011**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				**Sponsor requests a biowaiver.**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**This application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, so sponsor believes the requirement of 21CFR314.55 do not apply.**
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	No clinical study was conducted with the proposed product.
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		Sponsor requests a biowaiver.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			x	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	This application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, so sponsor believes the requirement of 21CFR314.55 do not apply.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and			x	

	biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Hospira Inc. submitted a 505(b)(2) NDA 200403 for Hydromorphone Hydrochloride Injection. This product is a marketed but unapproved product. The RLD is Dilaudid® (hydromorphone hydrochloride), NDA 19-034, held by Purdue Pharma. The indication and route of administration are the same as prescribed and recommended for the use of the RLD.

The proposed drug product is a sterile aqueous solution. It contains the same dosage form and active ingredient [redacted (b) (4)] as the RLD, Dilaudid®, and is intended for intravenous, subcutaneous or intramuscular administration. Sponsor stated that the proposed drug product will be available in the same configuration as the RLD in vials as well as in Carpuject™ and iSecure™ syringes. Sponsor stated that the only differences in the formulation are the inactive ingredients. The proposed product used [redacted (b) (4)] and sodium chloride for tonicity whereas Dilaudid® uses [redacted (b) (4)].

Sponsor requests a waiver of the in vivo study requirements based on 21CFR320.22. This biowaiver request will be reviewed by ONDQA. Since this application is not for a new active ingredient, new indication, new dosage form, new dosing regiment, or new route of administration, sponsor believe the requirements of 21CFR314.55 with regards to pediatric use information do not apply.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200403	ORIG-1	HOSPIRA INC	Hydromorphone Hydrochloride Injection 1,2,4 mg/mL

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/s/

WEI QIU
06/18/2010

SURESH DODDAPANENI
06/18/2010