

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-202

CHEMISTRY REVIEW(S)

Zipsor (diclofenac potassium soft gelatin capsules)

NDA 22-202

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Xanodyne Pharmaceuticals, Inc.
One Riverfront Place Newport
KY 41071-4563

Indication: Zipsor™ is indicated for the relief of mild to moderate pain. (b) (4)

Presentation: White, 120cc HDPE bottles, containing 100 capsules and sealed with a heat induction seal, and a child resistant closure.

EER Status: Acceptable (March 06, 2008)

Consult:	EA:	Categorical exclusion provided in the NDA
	Pharm. Tox.:	Pending (approvable) 06/23/2008
	Clin. Pharm.:	Acceptable 06-20-2008
	Biometrics:	Acceptable 06-12-2008
	Methods Validation	Not recommended
	Microbiology:	N/A

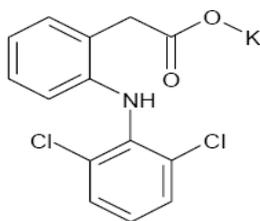
Original Submission: 09-21-2007

Re-submissions: N/A

Post-Approval Agreements: None beyond the typical stability commitment.

Drug Substance

The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid monopotassium salt. The molecular weight is 334.24. Its molecular formula is C₁₄H₁₀Cl₂NKO₂. Chemical structure is provided below.



Chemical names:

Benzene acetic acid, 2-[(2,6-dichlorophenyl)amino]-, monopotassium salt.

Potassium [o-(2,6-dichloroanilino)phenyl]acetate

The drug substance is chemically synthesized, as described in DMF (b) (4) and is purchased commercially under the DMF (Type II DMF (b) (4)). The DMF has been reviewed and found to be adequate in support of this NDA.

Conclusion

Drug substance: The drug substance is satisfactory.

Drug Product

Zipsor (diclofenac potassium) Soft Gelatin Capsules are available as liquid-filled, soft gelatin capsules containing 25 mg of diclofenac potassium for oral administration. The inactive ingredients in Zipsor include ProSorb® (a proprietary combination of polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, and hydrochloric acid), isopropyl alcohol, and mineral oil. The capsule shells contain gelatin, sorbitol, isopropyl alcohol, glycerin, and mineral oil. The imprinting on the gelatin capsules is black edible ink. The gelatin NF and glycerin USP used in the capsules and formulation, respectively, are certified to be BSE free and are sourced from bovine sources.

The drug product is a liquid formulation of diclofenac potassium encapsulated in soft gelatin capsules. The patented technology, ProSorb®, used in the formulation is designed to improve absorption characteristics and reduce time to onset of activity for pain relief. The principle behind the ProSorb technology is the use of selected dispersing agents that are designed to facilitate more rapid, consistent, and complete absorption of NSAIDs from the gastrointestinal tract. The applicant indicated that the speed and consistency of absorption is expected to be advantageous in the treatment of mild to moderate pain.

CMC portion of the application is generally considered adequate and acceptable to support a market approval of the product pending issue with some impurities which need toxicology studies and subsequent evaluation.

Additional Items: 30 months of expiry dating is granted for Zipsor™ capsules in HDPE bottles, stored at 25°C/60%RH. An expiry period of 15 months is granted for Zipsor™ capsules in blisters, stored at 25°C/60%RH.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending satisfactory conclusion from the Pharmacology/Toxicology reviewer.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim
8/19/2008 01:26:20 PM
CHEMIST

NDA 22-202

Zipsor
(diclofenac potassium soft gelatin capsules)

Xanodyne Pharmaceuticals, Inc.
One Riverfront Place
Newport, KY 41071-4563

John C. Hill, Ph.D.
ONDQA/DPMA-I and DAARP(HFD-170)

Chemistry Review #2

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9

Chemistry Review Data Sheet

1. NDA 22-202
2. REVIEW #2
3. REVIEW DATE: 03-JUN-2008
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

(N) Original NDA Filing

Document Date

21-SEP-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

BZ Supplement (Response to 74 day letter)

Document Date

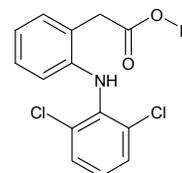
10-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Xanodyne Pharmaceuticals, Inc.
Address: One Riverfront Place
Newport, KY 41071-4563
Representative: Arthur C. Ilse, Director Regulatory Affairs
Telephone: 859-342-2076

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zipsor
- b) Non-Proprietary Name (USAN): diclofenac potassium
- c) Code Name/# (ONDC only): DPSGC (diclofenac potassium soft gelatin capsules)



Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2)

Listed drug: Cataflam Immediate-Release Tablets (Novartis Pharmaceuticals)

10. PHARMACOL. CATEGORY:

Relief of mild to moderate pain

11. DOSAGE FORM:

Soft gelatin capsule

12. STRENGTH/POTENCY:

25 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM	CODE ¹	STATUS ²	DATE	COMMENTS

Chemistry Review Data Sheet

#		REFERENCED		REVIEW COMPLETED	
(b) (4)	III	(b) (4)	1,4	Adequate*	15-APR-2004 LOA: 05-FEB-2007
	III		1,4	Adequate*	07-DEC-2006 LOA: 08-FEB-2007
	III		1,4	Adequate*	06-DEC-2004 LOA: 19-FEB-2007
	III		1,4	Adequate*	09-DAC-2004 LOA: 05-FEB-2007
	III		1,4-	Adequate*	01-OCT-2003 LOA: 05-FEB-2007
	III			Adequate*	02-OCT-2007 LOA: 05-FEB-2007
	III		1,4	Adequate*	30-JAN-2007 LOA: 13-FEB-2007
	III		1,4	Adequate*	07-JUN-2007 LOA: 06-MAR-2007
	II		1,4	Adequate	11-DEC-2008 LOA: 01-MAR-2007

Chemistry Review Data Sheet

(b) (4)	(b) (4)	(b) (4)				
			1,4	Adequate	13-SEP-1999	LOA: 11-APR-2007
			1,4	Adequate	28-JAN-2008	LOA: 19-FEB-2007
			IV	Adequate	14-JUN-2007	LOA: 20-FEB-2007
			IV	Adequate	31-OCT-2001	LOA: 21-FEB-2007
IV	Adequate	06-FEB-2008	LOA: 24-AUG-2007			

*Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	(b) (4)
IND	63,308	Diclofenac Potassium Soft Gelatin Capsules
NDA	20-142	Cataflam (diclofenac potassium immediate-release tablets), approved November 24, 1993

18. STATUS:

ONDC:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER
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CHEMISTRY REVIEW



Chemistry Review Data Sheet

RELATED REVIEWS			
Biometrics			
EES	Acceptable	06-MAR-2008	S. Ferguson
Pharm/Tox	Pending		
Biopharm			
LNC			
Methods Validation	Adequate	28-JAN-2008	John C. Hill, Ph.D.
OPDRA			
EA	Adequate	28-JAN-2008	John C. Hill, Ph.D.
Microbiology			

The Chemistry Review for NDA 22-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the provided data, this application remains approvable from a CMC viewpoint. Appropriate toxicology studies of impurity (b) (4) are outstanding.

An expiry period of 30 months is granted for Zipsor™ capsules in HDPE bottles, stored at 25°C/60%RH.

An expiry period of 15 months is granted for Zipsor™ capsules in blisters, stored at 25°C/60%RH.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Zipsor (diclofenac potassium) Soft Gelatin Capsules are available as liquid-filled, soft gelatin capsules containing 25 mg of diclofenac potassium for oral administration. The inactive ingredients in Zipsor include ProSorb® (a proprietary combination of polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, and hydrochloric acid), isopropyl alcohol, and mineral oil. The capsule shells contain gelatin, sorbitol, isopropyl alcohol, glycerin, and mineral oil. The imprinting on the gelatin capsules is black edible ink. The gelatin NF and glycerin USP used in the capsules and formulation, respectively, are certified to be BSE free and are sourced from bovine sources

Drug Substance

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic properties. The diclofenac molecule has been available for medicinal use since the mid 1970s in Japan and the mid 1980s in the United States. It has been approved for marketing in more than 120 countries and is one of the most recognized NSAID analgesics for a variety of painful conditions, including osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. In addition to generic formulations of diclofenac, there are several delayed and extended release formulations currently marketed. The pharmacology, pharmacokinetics, and toxicology of oral diclofenac have been well described by the innovator (Ciba-Geigy, now Novartis) and in the published literature.

The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl) amino] benzenecetic acid monopotassium salt. The molecular weight is 334.24. Its molecular

Executive Summary Section

formula is $C_{14}H_{10}Cl_2NKO_2$. This drug substance is purchased commercially under Type II DMF (b). This DMF has been reviewed and found to be adequate in support of this NDA.

B. Description of How the Drug Product is Intended to be Used

Zipsor™ is indicated for the (b) (4) and for the relief of mild to moderate pain.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the drug substance characterization data, the drug product pharmaceutical and manufacturing development data, and the accelerated, stressed and real-time stability data. The applicant has demonstrated lot-to-lot consistency in the manufacture and consistent quality of the drug product.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

John C. Hill, Ph.D., Review Chemist/Date: Same date as review
Ali Al-Hakim, Ph.D., Branch Chief/Date: Same date as review

C. CC Block

Tanya Clayton, ProjectManager/Date: Same date as review

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/s/

John C. Hill
6/3/2008 07:20:25 AM
CHEMIST

Ali Al-Hakim
6/3/2008 03:24:44 PM
CHEMIST

NDA 22-202

Zipsor
(diclofenac potassium soft gelatin capsules)

Xanodyne Pharmaceuticals, Inc.
One Riverfront Place
Newport, KY 41071-4563

John C. Hill, Ph.D.
ONDQA/DPMA-I and DAARP(HFD-170)

DRAFT
Chemistry Review #1

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [diclofenac potassium, (b) (4) Co., Ltd.] (<i>Adequate</i>).....	10
P DRUG PRODUCT [Zipsor™, Soft Gelatin Capsules, 25 mg] (<i>Adequate</i>).....	16
A APPENDICES	78
R REGIONAL INFORMATION	79
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	83
A. Labeling & Package Insert	83
B. Environmental Assessment Or Claim Of Categorical Exclusion	84

Chemistry Review Data Sheet

1. NDA 22-202
2. REVIEW #1
3. REVIEW DATE: 28-JAN-2008
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
(N) Original NDA Filing

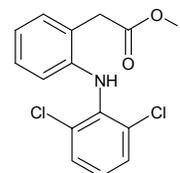
Document Date
21-SEP-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Xanodyne Pharmaceuticals, Inc.
Address:	One Riverfront Place Newport, KY 41071-4563
Representative:	Arthur C. Ilse, Director Regulatory Affairs
Telephone:	859-342-2076

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zipsor
- b) Non-Proprietary Name (USAN): diclofenac potassium
- c) Code Name/# (ONDC only): DPSGC (diclofenac potassium soft gelatin capsules)



Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2)

Listed drug: Cataflam Immediate-Release Tablets (Novartis Pharmaceuticals)

10. PHARMACOL. CATEGORY:

Relief of mild to moderate pain

11. DOSAGE FORM:

Soft gelatin capsule

12. STRENGTH/POTENCY:

25 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: Rx OTC**15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)** SPOTS product – Form Completed Not a SPOTS product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:****17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF	TYPE	HOLDER	ITEM	CODE ¹	STATUS ²	DATE	COMMENTS
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Chemistry Review Data Sheet

#			REFERENCED			REVIEW COMPLETED	
(b) (4)	III	(b) (4)	(b) (4)	1,4	Adequate*	15-APR-2004	LOA: 05-FEB-2007
	III			1,4	Adequate*	07-DEC-2006	LOA: 08-FEB-2007
	III			1,4	Adequate*	06-DEC-2004	LOA: 19-FEB-2007
	III			1,4	Adequate*	09-DAC-2004	LOA: 05-FEB-2007
	III			1,4-	Adequate*	01-OCT-2003	LOA: 05-FEB-2007
	III				Adequate*	02-OCT-2007	LOA: 05-FEB-2007
	III			1,4	Adequate*	30-JAN-2007	LOA: 13-FEB-2007
	III			1,4	Adequate*	07-JUN-2007	LOA: 06-MAR-2007
	II			1,4	Adequate	03-MAY-1999	LOA: 01-MAR-2007

Chemistry Review Data Sheet

	(b) (4)						
	(b) (4)		(b) (4)	1,4	Adequate	13-SEP-1999	LOA: 11-APR-2007
							LOA: 19-FEB-2007
	IV			1,4	Adequate	14-JUN-2007	20-FEB-2007
	IV			1,4	Adequate	31-OCT-2001	LOA: 21-FEB-2007
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² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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IND	63,308	Diclofenac Potassium Soft Gelatin Capsules
NDA	20-142	Cataflam (diclofenac potassium immediate-release tablets), approved November 24, 1993

18. STATUS:

ONDC:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER
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CHEMISTRY REVIEW



Chemistry Review Data Sheet

RELATED REVIEWS			
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm	Pending		
LNC			
Methods Validation	Pending		
OPDRA			
EA	Adequate	28-JAN-2008	John C. Hill, Ph.D.
Microbiology			

The Chemistry Review for NDA 22-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable from a CMC viewpoint pending completion of manufacturing facilities inspections and clin/pharm evaluation of the biowaver request.

An expiry period of 30 months is granted for Zipsor™ capsules in HDPE bottles, stored at 25°C/60%RH.

An expiry period of 15 months is granted for Zipsor™ capsules in blisters, stored at 25°C/60%RH.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

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The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl) amino] benzenecetic acid monopotassium salt. The molecular weight is 334.24. Its molecular

Executive Summary Section

formula is $C_{14}H_{10}Cl_2NKO_2$. This drug substance is purchased commercially under Type II DMF (b) (4). This DMF has been reviewed and found to be adequate in support of this NDA.

B. Description of How the Drug Product is Intended to be Used

Zipsor™ is indicated for the relief (b) (4) of mild to moderate pain.
Diclofenac.

C. Basis for Approvability or Not-Approval Recommendation**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

76 pp withheld in full immed. after this page as (b)(4) CCI/TS.

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/s/

John C. Hill
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CHEMIST

Ali Al-Hakim
1/28/2008 11:56:05 AM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-202	
Applicant:	Xanodyne	
Stamp date:	September 21, 2007	
PDUFA Date:	July 21, 2007	
Trademark:	Zipsor [®]	
Established Name:	Diclofenac Potassium	
Dosage Form:	Soft gelatin capsules (25 mg)	
Route of Administration:	Oral	
Indication:	Management of mild to moderate pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	___
Comments for 74-Day Letter:	<u>√</u>	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2) with Reference Listed Drug, Cataflam® (diclofenac potassium) tablets, NDA 20-141.

The drug product Zipsor® is formulated as diclofenac potassium 25 mg in a proprietary soft gelatin capsule, intended to provide consistent delivery and rapid absorption of the NSAID for use in treating mild and moderate pain. This formulation provides also a reduction in strength from the 50 mg tablets (Cataflam®) to 25 mg. Since the soft gelatin capsules are formulated with a liquid fill, diclofenac potassium in solution, the particle size, hydration state, morphic form and other solid properties of the drug substance are not expected to impact bioavailability of the drug.

Zipsor® (diclofenac potassium) soft gelatin capsules, 25 mg, will be marketed in 120 cc white HDPE bottles, containing 100 capsules, sealed with a heat induction seal, and a child resistant closure. The drug product will also be packaged in (b) (4) blister cards, with aluminum foil lidding stock, and a dual adhesive child-resistant label applied to the back of each blister card.

B. Review, Comments and Recommendations

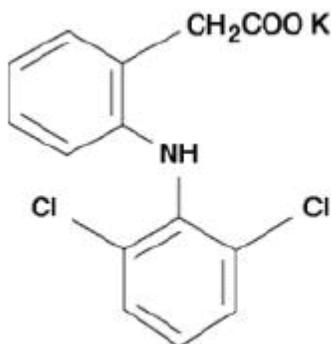
Drug Substance

The drug substance manufacturing process is described in DMF (b) (4) (LoA provided).

Sections pertaining to characterization, general properties, reference standards and stability data (5 years) are also described in the DMF. The DMF holder is the drug substance manufacturer, (b) (4) Three other facilities, (b) (4)

(b) (4) in the US and Canada, perform alternate release testing of the drug substance.

DMF (b) (4), type II, (b) (4) should be reviewed and evaluated. The applicant claimed no impact of physical properties of the drug substance, e.g., drug substance solubility, polymorphism, particle size distribution, etc., on the formulation (liquid fill), however homogeneity of the solution, (b) (4) through the shelf-life of the drug product and impact on dissolution should be reviewed and assessed accordingly.



Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Molecular formula: C₁₄H₁₀Cl₂KNO₂

Molecular Weight: 334.24 g/mol

Drug Substance Specifications

(b) (4)



The applicant stated that residual solvents testing is not performed, since the solvents listed in the USP monograph are not used in the manufacturing process of potassium diclofenac. This statement should be verified during the review of the drug substance DMF (b) (4). With respect to impurities, (b) (4) is observed at levels (b) (4)% in the drug substance and drug product. This impurity is a structural alert for mutagenicity (b) (4). The specification for this impurity should be assessed per the EMEA guideline (NMT 1.5 mcg total daily intake), in consultation with the Toxicology Division. Finally, the specification for (b) (4) As NMT (b) (4), and the observed levels of (b) (4) should be evaluated as per the EMEA guideline on heavy metals in consultation with the Toxicology Division.

Drug product

Zipsor® 25 mg soft gelatin capsules is an immediate release dosage form. Quantitative composition is provided below.

DRUG PRODUCT QUANTITATIVE COMPOSITION

COMPONENT	REFERENCE TO QUALITY STANDARD	FUNCTION	mg per Capsule	% w/w
FILL SOLUTION				
DICLOFENAC POTASSIUM	In-house	Active	25.0 ¹	(b) (4)
Polyethylene Glycol 400	NF			(b) (4)
Glycerin (b)	USP			
Sorbitol Solution 70%	USP			
Povidone (b) (4)	USP			
Polysorbate 80	NF			
Hydrochloric Acid (b) (4) (b) (4)	In-house			
(b) (4)	NF			
(b) (4)	(b) (4)			
Gelatin (b) (4) (b) (4)	NF		(b) (4)	See Footnote ²
Sorbitol (b) (4)	In-house			
Glycerin (b)	USP			
(b) (4)	USP			
(b) (4)	(b) (4)			
(b) (4)	USP		(b) (4)	(b) (4)
(b) (4)	USP			
(b) (4)	In-house			
Total				400.00

¹ The actual amount of diclofenac potassium used is corrected for its purity.

(b) (4)

The actual overage of diclofenac potassium should be assessed e.g., from executed batch records of registration batches. The purity factor should be confirmed from batch analyses and reference standards in the DMF (b) (4)

The amounts of the gelatin capsule excipients are proprietary and referenced to DMF (b) (4) Gelatin NF is described as (b) (4) BSE certification by the supplier should be confirmed. All excipients with the exception of Sorbitol (b) (4) and the imprinting ink are pharmacopeial. Specifications and grade of excipients are included in the NDA. Certain physical properties of the excipients, e.g., viscosity, should be assessed for suitability and impact on the homogeneity of the solution and stability throughout the proposed shelf life (b) (4)

(b) (4) however, this material has no USP monograph and is referenced to DMF (b) (4) holder (b) (4) This DMF should be referenced for necessary complementary information not provided in the NDA. Specifications for Sorbitol (b) (4) are provided in the NDA. Similarly, specifications for (b) (4) Black Ink (b) (4) are provided in the NDA.

(b) (4)

Manufacturing Process:

(b) (4) is the manufacturer of the drug product. (b) (4) and (b) (4) perform testing and packaging of the drug product. The commercial batch size is either (b) (4) or (b) (4) capsules. Scale up is within (b) (4) of the clinical batches.

Components/Composition of the drug product is provided in the following table.

4 pp withheld following this page as (b)(4) CCI/Trade Secret.

(contd.)

(b) (4)

The manufacturing process and process controls are described in sufficient detail. Hold times of the liquid fill solution, intermediates and bulk capsules (capsules are shipped from the manufacturer to the packager in different sites) should be assessed and supported by stability data. Photostability of the drug substance in solution has been performed and should be considered.

The commercial process is representative of the clinical process. One registration batch used in pivotal clinical trials has been manufactured by the commercial process.

NDA Registration batches:

Clinical Stability Batches

Product Description	Lot Number	Use	Capsules
25 MG PLACEBO	PDS1307	CLINICAL STABILITY	(b) (4)
25 mg DPSGC	PDS1436	Stability	
25 mg DPSGC	PDS1457	Stability	
25 mg DPSGC	PDS1304	Clinical Stability	

Stability data:

PDS 1436, PDS 1457: 9 month under normal and 6 month under accelerated storage (bottles/blisters)

PDS 1304: 24 month under normal storage in bottles and 6 month in blisters

Supporting batches: 36 months under normal storage in bottle and blisters

During pre-formulation (Phase 1 and 2) a crossover study between diclofenac sodium and diclofenac potassium was conducted to demonstrate bioequivalence of the two salts. An optimized formulation/process with diclofenac potassium was used in Phase 3 studies.

A comparative bioavailability study conducted with three different diclofenac potassium formulations (25 mg/mL solution and 25 mg soft gelatin capsules – old and new process) was successful in establishing bioequivalence. Despite differences in Tmax, all three formulations were comparable with respect to AUC and Cmax.

Tables below show the comparison between the two processes (the new and the old formulations).

Registration and Clinical Batch Process Comparison



Composition of New and Old Formulation of DPSGC, 25 mg

	New Formulation	Intermediate Formulation	Old Formulation
	New Process		Old Process
Ingredient	PDS-1304, PDS-1436, PDS-1457 %w/w	PDS-1214, PDS-1216 and PDS-1216 %w/w	PDS-1025, PDS-1027 and PDS-1029 %w/w

(b) (4)



New formulation



(b) (4)

Old formulation



(b) (4)

Drug Product Specifications:

The analytical methods used for control of Zipsor® SGC are based on compendial procedures. The dissolution method, apparatus II, paddles, phosphate buffer, pH 6.8, 50 rpm should be evaluated for discriminatory ability and robustness, e.g., by supporting data on developmental formulations.

Drug Product Release Specification

(b) (4)



Batch analysis data:

Release data on the registration batches show impurities (b) (4) below (b) (4) %. The proposed specification limits for identified and unidentified impurities (exceed ICH) should be assessed. Justification should be based on ICH Q3 guidelines and the EMEA guideline for structural alerts (A) as discussed in the drug substance section. Specifications and qualification levels should be assessed in consultation with the Toxicology Division.

Container Closure:

Five packaging DMFs (Type III) are supporting the container closure system, i.e., HDPE bottles, bottle and cap resins, (b) (4) white CRC cap with (b) (4). Since this is an oral dosage form, review of the packaging DMFs is not required.

Stability:

Stability testing on Zipsor® SGC, 25 mg is performed under standard ICH conditions at (b) (4). Stability protocols are provided. Tests performed are: Appearance, pH, assay, impurities, dissolution and microbial limits. Summary of the stability data on the registration batches:

Lot Number	Packaging	Stability start	Data Available
PDS1304 (05036A) (gel aged: 12-24 hours)	100 ct/120cc white HDPE/35 mm cap w/ induction seal	25 Apr 2005	24 mo. 25°C/60% RH 12 mo. 30°C/65% RH 6 mo. 40°C/75% RH
PDS1436A (gel aged: 12-24 hours)	100 ct/120cc white HDPE/35 mm cap w/ induction seal	18 JUL 2006	9 mo 25°/60%RH 9 mo 30°/65%RH 6 mo 40°/75% RH
PDS1436B (gel type: gel aged: 24-30 hours)	100 ct/120cc white HDPE/35 mm cap w/ induction seal	18 JUL 2006	9 mo 25°/60%RH 9 mo 30°/65%RH 6 mo 40°/75% RH
PDS1457X (gel aged: 12-24 hours)	100 ct/120cc white HDPE/35 mm cap w induction seal	18 JUL 2006	9 mo 25°/60%RH 9 mo 30°/65%RH 6 mo 40°/75% RH
PDS1457Y (gel aged 24-30 hours)	100 ct/120cc white HDPE/35 mm cap w induction seal	18 JUL 2006	9 mo 25°/60%RH 9 mo 30°/65%RH 6 mo 40°/75% RH
PDS1458 (gel type: R00101 gel aged: 12-30 hours)	100 ct/120cc white HDPE/35 mm cap w/ induction seal	18 JUL 2006	9 mo 25°/60%RH 9 mo 30°/65%RH 6 mo 40°/75% RH

Physician samples (4 batches): Longest data: 9 month under normal and six month under accelerated storage in (b) (4) blisters.

Supporting data (6 batches, 10 configurations in bottles and blisters): Longest data: 36 months under normal storage. Batches: PDS1025, PDS 1027, PDS 1029, PDS 1214, PDS 1216, PDS 1218.

The proposed shelf-life of (b) (4) should be evaluated and assessed based on the available stability test data. The applicant did not provide statistical analysis. The expiration dating is proposed based on significant extrapolation of real time data on the registration batches and real time stability data on supporting batches.

Several trends are observed on stability and should be assessed for impact on drug product quality and performance:

- Increase in impurities (b) (4) mostly under accelerated conditions.
- Cross-linking of the capsules and increase in disintegration times, requiring Level II and III testing using enzymes, under accelerated conditions
- Appearance change, described as “sticking” of the capsules, under accelerated conditions, which the applicant deemed insignificant.
- Dissolution data throughout the shelf life have not been included in module 3.

Labeling

Labeling information on the container labels and packaging insert should be assessed with respect to CMC requirements.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF (b) (4) should be reviewed and evaluated.
2. The excipient described in DMFs (b) (4) and (b) (4) should be referenced and reviewed only for necessary information not provided in the NDA.
3. Impact of physical properties of the drug substance, e.g., solubility, polymorphism, particle size distribution, etc., on the formulation (liquid fill), on the homogeneity of the solution, (b) (4).
4. Specification of (b) (4) a structural alert for mutagenicity (b) (4). As per EMEA guideline the total daily intake should be NMT 1.5 mcg. This issue should be discussed/consulted with the Toxicology Division.
5. Specification for (b) (4) As NMT (b) (4), and the observed levels of (b) (4) per the EMEA guideline on heavy metals in consultation with the Toxicology Division.
6. Certain physical properties of the excipients, e.g., viscosity, for suitability and impact on the homogeneity and stability of the solution throughout the proposed shelf life (b) (4).
7. Hold times of the liquid fill solution, intermediates and bulk capsules as supported by stability data including photostability of the drug substance in solution.
8. The dissolution method, apparatus II, paddles, phosphate buffer, pH 6.8, 50 rpm should be evaluated for discriminatory ability and robustness, e.g., by supporting data on developmental formulations; the proposed dissolution specification as supported by registration and supporting stability data.
9. Expiration dating and justification in the absence of statistical analysis should the applicant does not amend it (statistical analysis).
10. Specifications and proposed limits for identified and unidentified impurities (exceed ICH) Justification should be based on ICH Q3 guidelines and the EMEA guideline for structural alerts (A) as discussed in the drug substance section. Specifications and qualification levels should be assessed in consultation with the Toxicology Division.
11. Trends in stability data, i.e.:
 - Increase in impurities (b) (4) mostly under accelerated conditions.
 - Cross-linking of the capsules and increase in disintegration times, requiring Level II and III testing using enzymes, under accelerated conditions
 - Appearance change, described as “sticking” of the capsules, under accelerated conditions, which the applicant deemed insignificant.

D. **Comments for 74-day Letter:**

- The applicant should provide statistical analysis of the stability test data (SAS format) during early stages of the review cycle (10-month clock).
- The applicant should provide dissolution profiles and stability data for the registration and supporting batches or indicate the NDA module in which they have been included.

E. **Recommendation for fileability:** The NDA is fileable based on sufficient number of registration and clinical batches, 9-24 month long term stability data on the proposed commercial and 36-month long term data on supporting batches. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review, since it is a 505(b)(2) application, the drug substance is not an NME, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues and the commercial process is representative of the pilot scale (clinical Phase 3) process.

Consults

The requested biowaiver (module 1, data in module 5) should be evaluated in consultation with the biopharmaceutics reviewer and/or biopharmaceutics experts in ONDQA.

Specifications for impurities including heavy metals and structural alerts should be evaluated in consultation with the Toxicology reviewer.

The primary reviewer, in conjunction with the project manager, should initiate the following consults/requests as soon as possible (see fileability template below).

<u>Danae D Christodoulou, Ph.D.</u>	<u>10/29/2007</u>
Pharmaceutical Assessment Lead	Date

<u>Ali Al-Hakim, Ph.D.</u>	<u>10/30/2007</u>
Branch II Chief	Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested per 21CFR 23.31(a)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided without statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	N/A		Solid oral dosage form/ immediate release
16	Have all consults been identified and initiated?	√ √ √ N/A N/A √ N/A		Pharm/Tox Biopharm Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ()

DMF #	Holder	Description	LoA Included	Status
	(b) (4)	Diclofenac Potassium	Yes	pending
	(b) (4)	Gelatin mass (b) (4)	Yes	pending
	(b) (4)	Sorbitol Special	Yes	pending
	(b) (4)	HDPE bottle	Yes	NA
	(b) (4)	Bottle Resin: (b) (4)	Yes	NA
	(b) (4)	white CRC cap (b) (4)	Yes	NA
	(b) (4)	Cap Resin: (b) (4)	Yes	NA
	(b) (4)		Yes	NA

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this page is the manifestation of the electronic signature.**

/s/

Danae Christodoulou
10/30/2007 02:25:37 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
10/30/2007 02:31:27 PM
CHEMIST