CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-315

CHEMISTRY REVIEW(S)

NDA 22-315

Posurdex (dexamethasone intravitreal implant) 0.35 and 0.7 mg

Allergan, Inc.

George Lunn, Ph.D.
Division of Anti-Infective and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 22-315

2. REVIEW #: 1

3. REVIEW DATE: 26-MAY-2009

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-0000 (Non-clinical presubmission)	12-DEC-2007
N-0002 (Quality presubmission)	27-AUG-2008
N-0003	23-DEC-2008
N-0008	19-MAR-2009
N-0010	06-MAY-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Allergan, Inc.
Address:	2525 Dupont Drive Irvine, CA 92612

Chemistry Review Data Sheet

Representative:	Elizabeth Bancroft Senior Director, Regulatory Affairs
Telephone:	(714) 246-4391

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Posurdex
b) Non-Proprietary Name (USAN): Dexamethasone intravitreal implant
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of macular edema secondary to central retinal vein occlusion or branch retinal vein occlusion

11. DOSAGE FORM: Intravitreal implant

12. STRENGTH/POTENCY: 0.35 and 0.7 mg

13. ROUTE OF ADMINISTRATION: Intravitreal

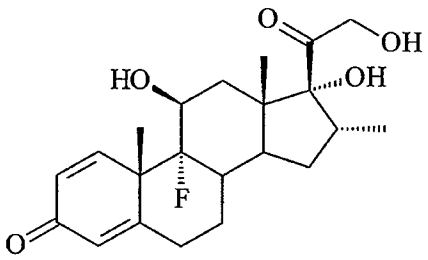
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

(11α,16β)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-1,4-diene-3,20-dione



Molecular Formula: $C_{22}H_{29}FO_5$
Molecular weight: 392.47

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Dexamethasone micro USP	1	Adequate	5/26/09	Reviewed by G. Lunn
	IV			1	Adequate	3/4/09	Reviewed by G. Lunn
				1	Adequate	4/23/09	Reviewed by G. Lunn

b(4)

[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
None		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	15-May-2009	M. Stock
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Not required		
OPDRA	NA		
EA	The sponsor requests a categorical exclusion. The request is accepted.	07-Oct-2008	G. Lunn
Microbiology	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-315

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

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)

The dexamethasone drug substance is covered by a DMF held by [redacted], and a Letter of Authorization to refer to this DMF is supplied. This DMF, as amended, has been reviewed and found to be Adequate. There have been no substantive changes since this review. An adequate drug substance specification that is tighter than the current USP specification is provided. The analytical methods are fully described. Satisfactory batch analyses are provided for 7 batches of drug substance. The retest date is [redacted] years when stored at controlled room temperature protected from light. This is based on [redacted] years of satisfactory stability data obtained at 25°C/60% RH. b(4)

The drug product is an intravitreal implant containing 0.35 or 0.7 mg dexamethasone. Dexamethasone is combined with biodegradable polymers and extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator. The rod-shaped implant is [redacted] mm in diameter and [redacted] in length. It is loaded into the needle of a single-use applicator that delivers the implant directly to the posterior segment of the eye. This implant is indicated for the treatment of adults with macular edema following branch retinal vein occlusion or central retinal vein occlusion. By weight the implant is [redacted] dexamethasone, [redacted], and [redacted]. b(4)

The polymers are similar. [redacted] Poly (D,L-lactide-co-glycolide), ([redacted] PLGA ester) is [redacted], with an ester group and [redacted], Poly (D,L-lactide-co-glycolide), ([redacted] PLGA acid) is [redacted] with an acid group. These polymers are used in absorbable sutures and are hydrolyzed in the body to lactic acid and glycolic acid. These polymers have b(4)

been used in approved US products. The polymers are manufactured by [redacted] under a DMF and a Letter of Authorization is provided. This DMF has been reviewed and the polymers have been found to be suitable for pharmaceutical purposes. Acceptable specifications for these polymers are provided in this NDA. Additionally the analytical methods are fully described and satisfactory batch analyses are provided.

The applicator is a consists of a 22-gauge thin-wall hypodermic needle with a plastic handle. To use the safety tab is removed and the needle is inserted into the eye. A button is pressed downwards and this causes a plunger to push the implant into the posterior chamber of the eye.

The drug product is manufactured by Allergan Pharmaceuticals, Ireland and [redacted] sterilization is carried out by [redacted]. The drug substance and sterilization facilities were found to be acceptable based on file review and the manufacturing facility was found to be acceptable based upon an inspection. On 5/15/09 an Overall Recommendation of Acceptable. Sterilization is by [redacted] The commercial batch size is [redacted] which produces [redacted] units for both strengths. The manufacturing process is clearly described in detail. b(4)

[redacted] b(4)

[redacted] The in-process controls are clearly explained and serve to adequately control this complex product. The plant and manufacturing process have been inspected by FDA and found to be acceptable.

Drug product specifications for appearance, identity, assay, impurities, insoluble particles, actuation force, drug release, sterility, endotoxins, and content uniformity are provided. As amended, these specifications are acceptable. The impurity specifications conform to ICH Q3B. The impurity [redacted] was qualified using an in vivo rabbit eye study. b(4)

The analytical methods are all fully described and have been validated. Drug release is [redacted] This method has been shown to be equivalent to measuring release at a more physiologically relevant 37°C. Measuring release at 37°C would require 21 days which is not practical. b(4)

Batch analyses are provided for 17 full scale batches of the 0.7 mg size and 12 full scale batches of the 0.35 mg size. These analyses are generally acceptable although for earlier there are a number of instances where the implant is not present or protrudes from the needle.

For each strength 24 months of stability data obtained at 25°C/60% RH, 12 months of data obtained at 30°C/65% RH, and 6 months of data obtained at 40°C/75% RH are provided for 3 full-scale batches (only 18 months at 25°C/60% RH for one of the 0.35 mg batches, however). One batch was also tested under freeze/thaw and low/high conditions. There are no obvious

trends and drug release appears to be smooth and consistent. For the most part there are no out of specification results although the [redacted] in some cases is of concern. The applicant explains that applicators with missing or protruding implants were from early lots. Since these batches were manufactured the manufacturing process has been refined. These early batches used an [redacted] to retain the implant. This has now been replaced by a sleeve and safety tab. Additionally the assembly process has been refined and a [redacted] is used to detect the implant in the needle. Following these improvements there have been no incidents of [redacted]. [redacted] are from the primary stability batches that were manually assembled. Since then the process has been automated and improved so as to reduce the incidence of [redacted]. Additionally, [redacted] are functionally equivalent to intact implants when tested in rabbits eyes. Shipping simulation tests showed that implants are not displaced by rough handling. Although there are some instances where the button is hard or impossible to depress these were in early batches. The design of the applicator has since been improved. Testing a batch of [redacted] applicators all were found to be functional.

b(4)

Statistical projections support an expiration dating period of 36 months which is acceptable.

The sponsor requests a categorical exclusion from the requirement to prepare an Environmental Assessment and the request is reasonable.

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

Posurdex (dexamethasone intravitreal implant) is an intravitreal implant that is indicated for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion. The recommended dose is one implant per eye.

The rod-shaped implant, which contains 0.7 mg or 0.35 mg dexamethasone, is contained inside a hypodermic needle that is part of a single-use applicator. In use the needle is advanced into the sclera and towards the center of the eye until the silicone sleeve is against the conjunctiva. The button on the applicator is pressed and this forces the implant out of the needle and into the eye. An audible click indicates that the button is fully depressed. The needle is withdrawn leaving the implant inside the eye. The implant contains biodegradable polymers that slowly degrade inside the eye releasing dexamethasone in a slow and controlled fashion. The applicator is supplied inside a foil pouch and the entire assembly is sterilized.

The storage statement is "Store at controlled room temperature 15° -30° C (59° - 86° F)." The expiration dating period is 36 months.

C. Basis for Approvability or Not-Approval Recommendation

The manufacture of the drug substance is described in a DMF that has been reviewed and found to be acceptable. The composition, manufacturing process, and specifications for the implant are appropriate and the expiration dating period of 36 months when stored at 15-30°C is supported

by adequate data. The applicator, container-closure system, and labeling are appropriate. All manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Norman R. Schmuff, Ph.D., Branch Chief {Signed Electronically in DFS}

C. CC Block

Linda Ng, Ph.D.
Pharmaceutical Assessment Lead

79 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

IV. EES Report

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22315/000	Action Goal:	
Stamp:	24-DEC-2008	District Goal:	25-AUG-2009
Regulatory Due:	24-JUN-2009	Brand Name:	POSURDEX
Applicant:	ALLERGAN 2525 DUPONT DR IRVINE, CA 92623	Estab. Name: Generic Name:	DEXAMETHASONE BIODEGRADABLE
Priority:	3P		INTRAVITREAL
Org Code:	520	Dosage Form: Strength:	(INJECTION) 0.35 AND 0.7 MG

Application Comment: THE CLINICAL DIVISION INFORMS US THAT THIS WILL BE A PRIORITY APPLICATION. HOWEVER THE CLOCK WILL NOT START UNTIL ALL THE CLINICAL DATA ARRIVES, PROBABLY IN DECEMBER 2008. (on 09-OCT-2008 by G. LUNN () 301-796-1701)

THE CLOCK STARTED FOR THIS PRIORITY NDA ON 12/24/08. THEREFORE THE GOAL DATE IS 6/24/09. (on 13-JAN-2009 by G. LUNN () 301-796-1701)

THIS COMMENT CLARIFIES THE NATURE OF THE DOSAGE FORM SINCE THE TERM "SMALL VOLUME PARENTERAL" IS NOT EXACT. THE DRUG SUBSTANCE IS COMBINED WITH BIODEGRADABLE POLYMERS AND EXTRUDED INTO A SMALL IMPLANT SUITABLE FOR DELIVERY INTO THE POSTERIOR SEGMENT OF THE EYE THROUGH A SPECIFICALLY DESIGNED APPLICATOR. THE ROD-SHAPED IMPLANT IS [redacted] IN DIAMETER AND [redacted] IN LENGTH. IT IS LOADED INTO THE NEEDLE OF A SINGLE-USE APPLICATOR THAT DELIVERS THE IMPLANT DIRECTLY TO THE POSTERIOR SEGMENT OF THE EYE. AFTER MANUFACTURE THE ENTIRE ASSEMBLY IS STERILIZED BY [redacted]

b(4)

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

(on 15-OCT-2008 by G. LUNN () 301-796-1701)

FDA Contacts:	R. RODRIGUEZ	(HFD-520)	301-796-0798	, Project Manager
	G. LUNN		301-796-1701	, Review Chemist
	L. NG		301-796-1426	, Team Leader

Overall Recommendation: ACCEPTABLE on 15-MAY-2009by M. STOCK (HFD-320)301-796-4753

Establishment: CFN 9616651 FEI 3002806285

ALLERGAN PHARMACEUTICALS IRELAND
CASTLEBAR ROAD
WESTPORT, CO. MAYO, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: SVT OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-OCT-2008				LUNNG
SUBMITTED TO DO	21-OCT-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	13-NOV-2008	GMP			ADAMSS
INSPECTION PERFORMED (see hard copy EIR or in TURBO Reports)	18-DEC-2008		18-DEC-2008		MMCCLAIN
DO RECOMMENDATION	15-MAY-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	15-MAY-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Establishment: CFN FEI b(4)

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

DMF No: AADA:

Responsibilities: b(4)

Profile: RSP OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-OCT-2008				LUNNG
SUBMITTED TO DO	21-OCT-2008	GMP			ADAMSS
DO RECOMMENDATION	11-JAN-2009			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	11-JAN-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN [redacted] FEI [redacted] b(4)

DMF No: [redacted] AADA:

Responsibilities: b(4)

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-OCT-2008				LUNNG
SUBMITTED TO DO	21-OCT-2008	GMP			ADAMSS
DO RECOMMENDATION	04-FEB-2009			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	04-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

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

/s/

George Lunn
5/27/2009 10:56:34 AM
CHEMIST

Rapti Madurawe
5/28/2009 10:08:50 AM
CHEMIST
Signed on behalf of Dr. Norman Schmuff, the secondary reviewer, who has approved this review for DFS placement.