

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-212

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: June 4, 2008

To: NDA 22-212

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-212 Durezol (difluprednate ophthalmic emulsion) 0.05%.

I have assessed the ONDQA review of NDA 22-212, and all approvability issues appear to be resolved. There are three outstanding items that the company has committed to resolving-improving the ~~_____~~

Since these items are minor and a resolution should be coming soon, ONDQA is recommending approval. I concur with the approval recommendation from a CMC perspective.

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/s/

Elaine Morefield
6/4/2008 12:53:07 PM
CHEMIST

NDA 22-212

Durezol (Difluprednate Ophthalmic Emulsion) 0.05%

Sirion Therapeutics, Inc.

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



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Chemistry Review Data Sheet

1. NDA 22-212
2. REVIEW #: 1
3. REVIEW DATE: 07-JAN-2008
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Amendment

Amendment

Amendment

Document Date

21-DEC-2007

18-MAR-2008

25-APR-2008

20-MAY-2008

21-May-2008

7. NAME & ADDRESS OF APPLICANT:

Name:

Sirion Therapeutics, Inc.

Address:

3110 Cherry Palm Drive

Suite 340

Tampa, FL 33619



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Christine Miller, PharmD
Senior VP of Drug Development

Telephone: 813 496 7325 ex 236

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Durezol
- b) Non-Proprietary Name (USAN): Difluprednate
- c) Code Name/# (ONDC only): ST-601
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Treatment of inflammation and pain following ocular surgery

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Ophthalmic

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:

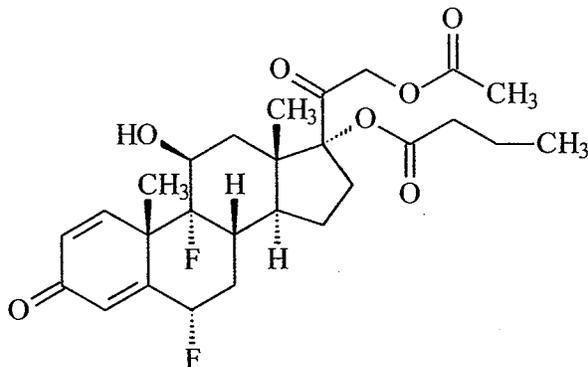


CHEMISTRY REVIEW



Chemistry Review Data Sheet

6 α ,9-Difluoro-11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate



Molecular Formula: $C_{27}H_{34}F_2O_7$
Molecular Weight: 508.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate	27-MAY-2008	Reviewed by G. Lunn
				1	Adequate	11-APR-2008	Reviewed by G. Lunn
				1	Adequate	11-APR-2008	Reviewed by G. Lunn
				1	Adequate	11-APR-2008	Reviewed by G. Lunn

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



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Chemistry Review Data Sheet

- 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	31-JAN-2008	By S. Adams
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Not required		
OPDRA	NA		
EA	Categorical exclusion requested. This is reasonable.		
Microbiology	Approvable	08-May-2008	By S. Langille

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 22-212

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. Although there are several outstanding issues the agreement of the sponsor to carry out the necessary studies is sufficient. 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 drug substance is covered by DMF _____ and a Letter of Authorization to refer to this DMF is supplied. This DMF, as amended, has been reviewed and found to be adequate. Some details are supplied in the NDA.

Difluprednate is $6\alpha,9\text{-difluoro-}11\beta,17,21\text{-trihydroxypregna-}1,4\text{-diene-}3,20\text{-dione } 21\text{-acetate } 17\text{-butyrate}$. It is a _____ with a melting point of _____ and a specific rotation of _____

A reasonable specification, including tests for appearance, identity, melting point _____

_____ The analytical methods are fully described. No validation details are supplied but the sponsor has agreed to carry out appropriate studies. The sponsor's commitment to carry out this work is sufficient and results need not be submitted prior to NDA approval.

Satisfactory Certificates of Analysis are provided for three batches of drug substance used to make drug product for clinical studies. Other details may be found in the DMF, see separate review.

The drug product is a sterile ophthalmic emulsion containing 0.05% difluprednate as the active component and 0.10% sorbic acid as a preservative. Inactive ingredients are glycerin, sodium



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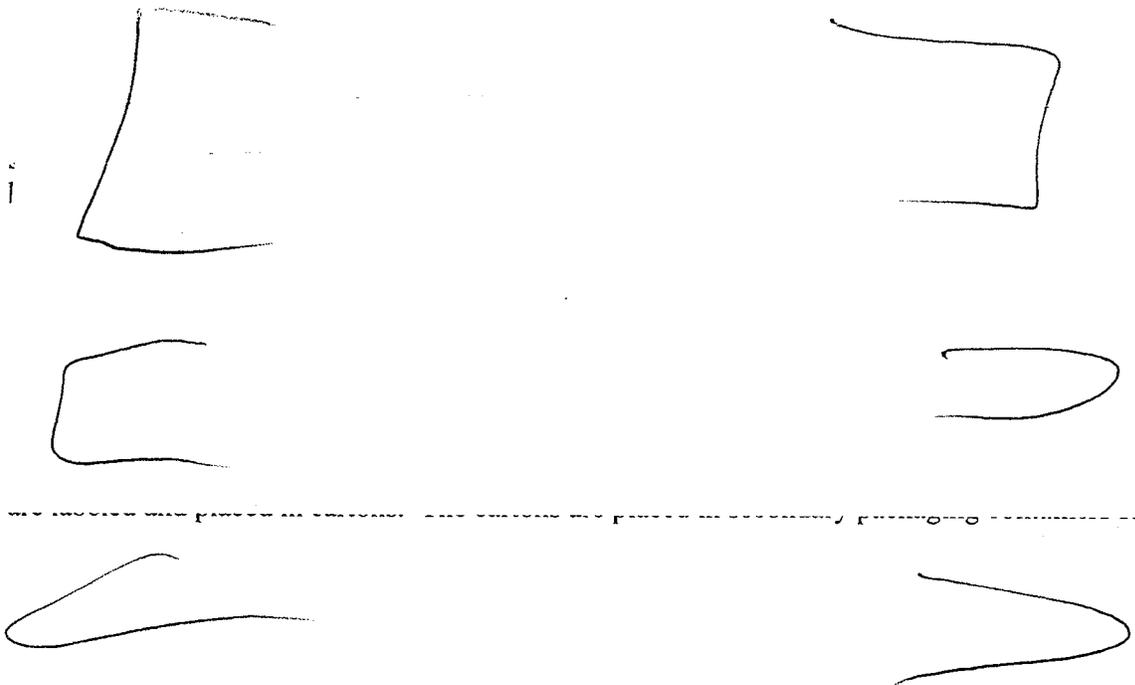
Executive Summary Section

acetate, boric acid, castor oil, polysorbate 80, sodium edetate, sodium hydroxide, and water for injection. The excipients are all of compendial quality.

The product was originally developed by Senju Pharmaceuticals in Japan and a number of product development reports are supplied. Phase 2 and 3 trials were carried out using product manufactured by Senju in Japan. Phase 3 trials were also carried out using product manufactured by _____ the proposed commercial manufacturer. The same formulation was used for all clinical trials. The product is isotonic to slightly hypertonic to tears. The tonicity is governed mostly by _____ during the drug development process. The product is preserved with 0.10% sorbic acid. This has not changed during the drug development process. The stability of the emulsion is governed by _____. In this case the emulsion appears to be stable _____.

Drug product manufacturing, packaging, and labeling will be carried out by _____. Drug substance testing and drug product release and stability testing will be carried out by _____. An Establishment Evaluation Request was made via EES and an Overall Recommendation of Acceptable has been made.

The manufacturing process is described in detail. Briefly, difluprednate is _____





CHEMISTRY REVIEW



Executive Summary Section

A reasonable specification that includes tests for appearance, identity, assay, impurities,

is provided.

The analytical procedures are fully described. Validation was originally carried out by the original developer of this product, Senju. However, only very limited validation has been carried out by the sponsor. The sponsor has agreed to revalidate the methods, as appropriate, in the laboratory in which the methods will be used. The sponsor's commitment to carry out this work is sufficient and results need not be submitted prior to NDA approval.

Satisfactory batch analyses are provided for four batches packaged in the 5 mL container and three batches packed in the container.

A satisfactory justification of the drug product specification is provided. The specified impurities are DF17C (6 α ,9-difluoroprednisolone 17-carboxylate), DFB (6 α ,9-difluoroprednisolone 17-butyrate), DF21B (6 α ,9-difluoroprednisolone 21-butyrate),

Following ICH Q3B(R) DF17C, DFB, and DF21B should be toxicologically qualified. Following a discussion with the PharmTox reviewer DF17C, DFB, and DF21B are acceptably qualified because they are metabolites and are also negative in two genotoxic tests. do not need to be toxicologically qualified because they are below the ICH Q3B qualification threshold for this product. Studies to justify the specifications for are continuing. The sponsor's commitment to carry out these studies is sufficient and final results need not be submitted prior to NDA approval.

The container-closure system is an opaque white 5 mL bottle embossed with lot number and expiration date. The bottle is formed and filled in a

The materials of the container-closure systems are covered by DMFs and Letters of Authorization are provided. For product launch an oval bottle will be used. All other components are identical and only the shape of the bottle is different. In addition, a 2.5 mL fill is planned as well as the 5 mL fill.

Satisfactory stability data obtained for the 5 mL bottles stored at 25°C/40% RH (9 months for 4 batches), 30°C/65% RH (6 months for 3 batches) and 40°C/≤ 25% RH (6 months for 3 batches) are presented. In addition 24 months of satisfactory data for the Senju product stored at 25°C/40% RH for 24 months are presented (6 batches). There are no out of specification results. The main trends that are observed are

Photostability testing was also carried out and



Executive Summary Section

_____ was observed with freeze/thaw testing. The proposed expiration dating period of 24 months is acceptable.

The stability data support the storage statement of "Store at 25°C (77°F); _____
_____ Protect from freezing." The following statement will be added to the storage statement "Protect from light. When not in use keep the bottles in the protective carton and the unused vials in the protective foil pouch."

The sponsor claims a _____

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

Durezol (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. The recommended dose is one drop per eye four times daily for / days then twice daily for 7 days _____
_____ The ophthalmic emulsion is supplied in 5 mL white, opaque. _____ bottles with a removable cover and controlled drop tip and cap in containing 2.5 mL or 5 mL _____

The storage statement is "Store at 25°C (77°F); _____, _____ Protect from freezing. Protect from light. When not in use keep the bottles in the protective carton and the unused vials in the protective foil pouch." The expiration dating period is 24 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 ophthalmic emulsion are appropriate and the expiration dating period of 24 months when stored at 25°C is supported by adequate data. The 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}



CHEMISTRY REVIEW



Executive Summary Section

C. CC Block

Linda Ng, Ph.D.
Pharmaceutical Assessment Lead

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Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

George Lunn
5/27/2008 03:09:03 PM
CHEMIST

Norman Schmuff
5/28/2008 08:35:17 AM
CHEMIST

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Infective and Ophthalmology Products
NDA: 22,212
Applicant: Sirion Therapeutics, Inc
Letter Date: December 21, 2007
Stamp Date: December 26, 2007
PDUFA Date: June 26, 2008
Trademark: Durezol
Established Name: Difluprednate
Dosage Form: Ophthalmic emulsion 0.05%
Route of Administration: Eye drops
Indication: Treatment of inflammation and pain following ocular surgery

PAL: Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

This NDA, dated December 21, 2007, is a new molecular entity (NME) for priority review. The product is claimed to be a nano-emulsion product for the treatment of inflammation and pain following ocular surgery.

A microbiology consult was submitted by the OND PM, Jane Dean and Dr. Stephen Langille is the assigned microbiologist. Ms. Dean has submitted the trade name request to DMET on January 25, 2008 and the labeling consult to DDMAC on the same day. EES was submitted by the chemistry reviewer, Dr. George Lunn on January 9, 2008, and found approval by Compliance on January 31, 2008.

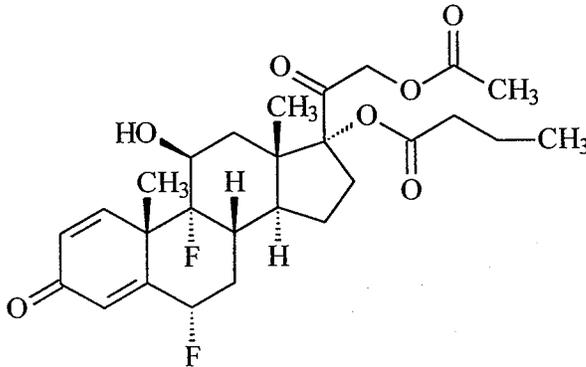
The drug substance, difluprednate is manufactured by _____ as described in type II DMF _____. The drug product is manufactured by _____ Release and stability testing is performed by _____

The claimed nano-emulsion has particles less than _____

The commercial container closure system consists of a _____ .5 mL fill in a 5 mL oval _____ bottle with white _____ tip and a white _____ screw cap and a protective snap-on white cap. _____

A expiry dating period of 24 months is requested.

Difluprednate with chemical name
6 α ,9-Difluoro-11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate
has a chemical structure:



Molecular Formula: $C_{27}H_{34}F_2O_7$
Molecular Weight: 508.55

Critical issues for review

- This is a new molecular entity. The DMF has not been evaluated. The potential toxicity of the impurities and level of residual solvents like _____ may need to be evaluated.
- The shape of the container will be _____ oval from stability to commercialization. Not clear if stability studies for the formulated product in the oval container closure system will be submitted to the NDA. _____

- Two fill sizes in the 5 mL bottle are proposed.

- The cap color should follow the AAO policy for the therapeutic area.

_____ Nonetheless, the medical officer should be consulted if the proposal is acceptable.

- A one-time droplet size study to include multiple tip batches should be submitted.

- A one-time leachable study through expiry with validated screening procedures should be included.
- Emulsion stability and particle size distribution, e.g., _____ in acceptance criteria of drug product specification be evaluated _____
_____ Bioavailability could be affected with too much variation of the particle sizes.
- Particulate matter is not normally included in suspension or emulsion because of interference. However, this product included the test. Not clear if the _____
- The level of total impurities for the drug product should be evaluated based on need and pre-clinical safety evaluation.
- Not clear how the tips and caps are sterilized. I _____
_____ should be evaluated to meet FR, vol 43 #122 of June 23, 1978. Information does not appear to be present.
- Two year expiry is requested. See comment earlier relating to container for commercialization

• **Comments for 74-Day Letter**

None recommended.

D. Review, Comments and Recommendation:

Acceptable for filing. No team review is recommended. A single reviewer can review this NDA due to the short review clock for this NDA. Dr. George Lunn has been assigned to review this NDA.

Linda Ng, Ph.D.
Pharmaceutical Assessment Lead

Date

Norman Schmuff, Ph.D.
Branch Chief

Date

3 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry- 2

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Linda Ng
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