

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-048/22-223

CHEMISTRY REVIEW(S)



NDA 22-048 and 22-223

TRIESENCETM
(triamcinolone acetonide injectable suspension), 40 mg/mL

Alcon Research, Ltd.

Division of Pre-Marketing Assessment II, Branch IV
ONDQA

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE.....	11
P DRUG PRODUCT.....	39
A APPENDICES	99
R REGIONAL INFORMATION	99
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	100
A. Labeling & Package Insert	100
B. Environmental Assessment Or Claim Of Categorical Exclusion	102
III. List Of Deficiencies To Be Communicated.....	102

Chemistry Review Data Sheet

1. NDA 22-048 and 22-223
2. REVIEW # 1
3. REVIEW DATE: 29-Oct-2007
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	24-May-2007
BC	02-Jul-2007
IR	13-Sep-2007
BC	17-Sep-2007
IR	01-Oct-2007
BC	12-Oct-2007 (2)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	24-May-2007
BC	02-Jul-2007
BC	17-Sep-2007
BC	12-Oct-2007 (2)

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Name:	Alcon Research, Ltd.
Address:	6201 South Freeway Fort Worth, Texas 76134-2099
Representative:	Terry J. Dagnon Director, Regulatory Affairs
Telephone:	817-551-4325

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TRIESENCE
- b) Non-Proprietary Name (USAN): triamcinolone acetonide injectable suspension
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P (NDA 22-048) and S (NDA 22-223)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Suspension for injection

12. STRENGTH/POTENCY: 40 mg/mL

13. ROUTE OF ADMINISTRATION: Intravitreal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

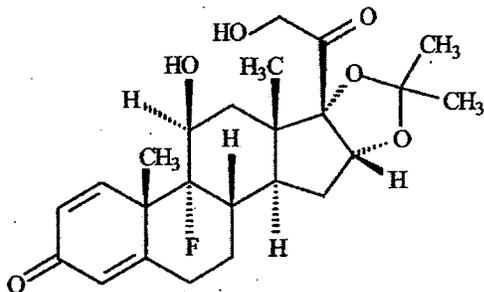
SPOTS product – Form Completed

Not a SPOTS product



Chemistry Review Data Sheet

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

9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone $C_{24}H_{31}FO_6$

MW = 434.50

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
_____	_____	_____	_____	1	Adequate	09-Oct-2007	
_____	_____	_____	_____	4	N/A	N/A	
_____	_____	_____	_____	4	N/A	N/A	

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03-Aug-2007	S. Ferguson (HFD-322)
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	Pending		
EA	N/A (request for a categorical exclusion)	N/A	
Microbiology	Acceptable	17-Sep-2007	John Metcalfe, Ph.D.

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The Chemistry Review for NDA 22-048

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval pending the labeling revisions (_____) and agreements on the drug product specification (pH acceptance criteria) and expiration dating.

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

N/A

II. Summary of Chemistry Assessments

The original NDA was submitted for a number of indications. It has been administratively split in order to create NDA 22-223 for review purposes and the following review priority classification was made.

NDA 22-048 - Priority (P) provides for the following indications: _____

_____ visualization during vitrectomy.

NDA 22-223 - Standard (S) provides for the following indications: sympathetic ophthalmia; temporal arteritis; uveitis; and ocular inflammatory conditions unresponsive to topical corticosteroids.

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

The proposed drug product, triamcinolone acetonide injectable suspension, is a single-dose, _____ sterilized, _____ aqueous ophthalmic suspension for intra-ocular use, containing 40 mg/mL of triamcinolone acetonide.

Alcon's triamcinolone acetonide injectable suspension has been developed as a product that is pharmaceutically and therapeutically equivalent to KENALOG-40 (approved via NDA 14-901) for the intended use. The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40. Alcon's proposed formulation of triamcinolone acetonide has reduced concentrations of the _____, polysorbate 80 (0.015% versus 0.04% of that in KENALOG-40), and the _____, carboxymethylcellulose (CMC) sodium (0.5% versus 0.75% of that in KENALOG-40), _____. The proposed Alcon's suspension has no preservative whereas KENALOG-40 contains benzyl alcohol.

CHEMISTRY REVIEW

Executive Summary Section

The preservative was removed since this ingredient is contraindicated for an intravitreal dosage form; therefore, the proposed drug product is a single-use product. The applicant stated that the resulting concentrations of the _____ CMC sodium and polysorbate 80, respectively, were selected to minimize patient exposure while ensuring a uniform dispersion of triamcinolone acetonide in the proposed formulation.

The vehicle for the Alcon formulation contains additional salts (potassium chloride, calcium chloride, magnesium chloride, sodium acetate and sodium citrate) as compared to those of KENALOG-40. These additional salts are at the _____ as Alcon's BSS® (NDA 20-742), which is frequently used by the ophthalmic medical community in conjunction with KENALOG-40. BSS® also contains sodium chloride; however, the concentration of sodium chloride is _____ triamcinolone acetonide injection compared with BSS® to ensure that the tonicity of the product is within the physiological range.

The specification for the Alcon's proposed drug product contains all the tests required by the USP monograph for triamcinolone acetonide injectable suspension and includes additional attributes such as _____. In addition, the specification for the drug product includes the particle size measurement and drug release assay. The particle size distribution appears relatively narrow and consistent among the batches, and does not appear changing during the stability studies. Therefore, the drug release assay is conducted only as a release test. The proposed drug product meets the acceptance criteria described in the USP monograph for triamcinolone acetonide injectable suspension with the exception of the pH value (i.e. the proposed pH range for the Alcon's drug product is 6.0 to _____ versus 5.0 to 7.5 specified in the USP monograph). The acceptance criteria for the drug product pH are currently under discussion with the applicant.

The manufacturing process of the drug product consists of _____ major steps: _____

_____ Triamcinolone acetonide injectable suspension is packaged in a Type 1 glass vial with a rubber stopper and an _____ seal. Each labeled vial is sealed in a polycarbonate blister with _____ backing material, which provides tamper evidence. The glass vials are sterilized by _____
_____ The drug product in the final package is _____ sterilized _____

The active ingredient of the proposed drug product, triamcinolone acetonide, a glucocorticosteroid, is a well characterized and known USP drug substance. The triamcinolone acetonide drug substance appears as a white to cream-colored, crystalline powder, which is practically insoluble in water. Triamcinolone acetonide has _____ carbons and the specific _____ is part of the drug substance control.

Triamcinolone acetonide drug substance used in the proposed Alcon's product meets the requirements of the USP monograph for triamcinolone acetonide. The chromatographic purity test includes acceptance criteria for individual, specified and unspecified impurities. Additional drug substance controls include particle size distribution and bacterial endotoxins tests. Triamcinolone acetonide drug substance used in the proposed triamcinolone acetonide injectable suspension is manufactured as _____. Triamcinolone acetonide is a hygroscopic material. A retest period of _____ is proposed for triamcinolone acetonide



Executive Summary Section

drug substance. Triamcinolone acetonide will be packaged in well-closed containers (_____) and stored under the USP storage conditions of “dry place” at _____

For the majority of the chemistry, manufacturing, and controls (CMC) information for the triamcinolone acetonide drug substance, the reference is made to the DMF Type _____ held by _____. The DMF had been reviewed before with reference to other products. A recent DMF amendment was reviewed in support of the current NDA and it was found acceptable.

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

For the treatment of ophthalmic conditions the initial recommended dose of TRIESENCE™ is 4 mg (100 µL of 40 mg/mL suspension) administered intravitreally with subsequent dosage of 4 mg (100 µL of 40 mg/mL suspension) as needed over the course of treatment.

For the visualization during vitrectomy, the recommended dose of TRIESENCE™ is _____ suspension) administered intravitreally.

The primary container/closure system for the drug product consists of a glass vial with a rubber stopper and _____ seal. The _____ vial is made of Type I flint _____ glass with a _____ gray stopper and a _____ seal. Each labeled vial will be sealed in a polycarbonate blister with _____ backing material, which provides tamper evidence.

The storage conditions statement recommends the following storage: “store at _____ 25°C” and the additional restrictions such as “Do Not Freeze” and “Protect from Light”. The expiration dating for the product proposed by the applicant is 18 months (currently under consideration).

C. Basis for Approvability or Not-Approval Recommendation

The original application and subsequent amendments contain adequate information regarding the quality of the drug substance and the drug product. During the review several minor issues, including the following were resolved.

The acceptance criteria for the drug substance were revised to include: each specified identified impurity, each specified unidentified impurity, any unspecified impurity (with an acceptance criterion of NMT _____), and total impurities. The data of the dose uniformity studies were provided indicating that a 0.1 mL dose of the drug product consistently delivers about 4 mg of triamcinolone acetonide (average of ten vials 3.785 mg). The loss on drying testing for triamcinolone acetonide drug substance to be conducted prior to weighing the material in the manufacturing process of the drug product was recommended by the Agency. The grade of sodium carboxymethylcellulose to be used in the proposed formulation was specified as a _____. To confirm the absence of the foreign material in the proposed drug product, the USP <788> Particulate Matter in Injections test (microscopic particle count test, partial count procedure) was conducted for two batches stored at the 25°C for 44 weeks by dissolving triamcinolone acetonide and excipients using appropriate solvents and filtering through a nylon filter. The results of this test conformed to the acceptance criteria for small-volume injections specified in <788>. As the current drug product is a suspension, the foreign particulate matter testing will not be part of the routine drug product control.

CHEMISTRY REVIEW

Executive Summary Section

The stability data submitted in the original NDA application and subsequent amendments (including the October 12, 2007 amendment) include 39 weeks of stability results at 25°C/40% RH and 30°C/65%, and 26 weeks of data at 40°C/25% RH for three commercial size batches of triamcinolone acetonide injectable suspension packaged in the proposed commercial container/closure system. In addition, the stability information provided in the application for this product includes the statistical analysis conducted on the three stability batches of the drug product. The proposed by the applicant expiration dating of 18 months is currently under discussion within the Agency.

Triamcinolone acetonide drug substance is manufactured by — . Upon approval, triamcinolone acetonide injectable suspension will be manufactured and marketed by Alcon, Inc. An overall compliance recommendation was made by the Office of Compliance on August 3, 2007 with an acceptable cGMP status for all facilities involved in the manufacture, packaging, and testing of the drug substance and the drug product. In addition, the product quality microbiology review recommended approval of this NDA from the microbiology viewpoint (review dated September 17, 2007).

III. Administrative

A. Reviewer's Signature

DFS

B. Endorsement Block

Chemist/DMatecka/Date: Same date as draft review

ChemistryTeamLeader/NSchmuff/Date

ProjectManagerName/Date

C. CC Block

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X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Dorota Matecka
10/30/2007 07:51:02 PM
CHEMIST

Norman Schmuff
10/31/2007 06:29:02 AM
CHEMIST

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Addendum to CMC Review # 1 of NDA 22-048 and 22-223

TRIESENCE™
(triamcinolone acetonide injectable suspension), 40 mg/mL

Alcon Research, Ltd.

This addendum includes a review of the amendment dated November 8, 2007 and labeling recommendations. From the chemistry, manufacturing and controls standpoint, the recommendation for this NDA continues to be approval (as formerly stated in review dated October 29, 2007).

A. Amendment dated November 8, 2007

This amendment provides a response to the following comments forwarded to the applicant via e-mail dated November 2, 2007:

- 1. We acknowledged your response to Question 2 in the amendment dated October 12, 2007. Please confirm that the LOD testing is actually conducted on triamcinolone acetonide drug substance prior to weighing it in the manufacturing process (Compounding Module) of the drug product.*
- 2. Please revised the proposed pH acceptance criteria from _____ to 6.0 – 7.5 in the drug product, triamcinolone acetonide injectable suspension, specification.*

In response to the first comment, via the applicant stated that _____

Comment:

The response from the applicant does not confirm what seemed to be suggested in their previous statements regarding this issue (i.e., that LOD testing is actually conducted on triamcinolone acetonide drug substance: _____)

_____ However, since the applicant seems to follow the storage recommendations from the manufacturer for this drug substance by storing it “under the USP conditions of well-closed containers in a dry place” then the proposed _____ retest period (including LOD) should be adequate.

In response to the second comment, the applicant agreed to tighten the originally proposed pH acceptance criteria from _____ to 6.0 – 7.5 in the drug product specification. The revised specification for the drug product reflecting this change was provided in the amendment (see attachment below).

Comments:

The revised acceptance criteria, as stated above, are acceptable and also conform now to the USP recommended pH acceptance criteria for triamcinolone acetonide injectable suspension (5.0-7.5; see review # 1 for discussion of this issue).

The proposed expiration dating of 18 months for the drug product (with the revised acceptance criteria for pH) is also found acceptable.

B. Labeling issues

Several editorial revisions were made in several sections of the product labeling. In addition, the following additional recommendations were suggested:

1. []
2. The labeling should clearly indicate that this is a single dose product (single use vial).
3. []
4. []

The above labeling revisions were forwarded to the medical officer reviewing this NDA (Dr. Martin Nevitt) by e-mail dated November 6, 2007.

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

/s/

Dorota Matecka
11/27/2007 03:36:04 PM
CHEMIST

Norman Schmuff
11/28/2007 08:08:38 PM
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