

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75276

CHEMISTRY REVIEW(S)

FINAL APPROVAL PACKAGE SUMMARY FOR 75-276

ANDA: 75-276

FIRM: Altana Inc.

DRUG: Betamethasone Dipropionate

DOSAGE: Gel (Augmented)

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 1/28/03

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is satisfactory 6/23/98

METHODS VALIDATION: The method validation is satisfactory 3/9/01
(Drug product)

STABILITY:

LABELING REVIEW STATUS: Labeling is satisfactory 3/26/03

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing instruction for intended production of _____ kg. Also provided copies of the executed batch records, Batch #9753 _____ kg manufactured using _____ drug substance, batch #9754 _____ kg manufactured using _____ drug substance. The firm will be using both suppliers, same process and same equipment.

COMMENT: The application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D.

DATE: 4/28/03

SUPERVISOR: James M. Fan



4/29/03

4/28/03

JSI

APPROVAL PACKAGE SUMMARY FOR 75-276

ANDA: 75-276

FIRM: Altana Inc.

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CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 4/26/00

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is satisfactory 6/23/98

METHODS VALIDATION: The method validation is satisfactory 3/9/01
(Drug product)

STABILITY:

LABELING REVIEW STATUS: Labeling is satisfactory 4/24/00

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing instruction for intended production of kg. Also provided copies of the executed batch records, Batch #9753 kg manufactured using drug substance, batch #9754 kg manufactured using drug substance. The firm will be using both suppliers, same process and same equipment.

COMMENT: The application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D.

DATE: 5/1/01

SUPERVISOR: Paul Schwartz, Ph.D.

DATE: 5/1/01

ps 5/1/01

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

1 (ONE)

2. ANDA NUMBER

75-276

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
Attention: Viginia Carman
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS for ANDA SUBMISSION

The reference listed drug is Diprolene[®] manufactured by Schering Corporation. The applicant has certified that the list drug products referred to in the application are covered by two patents and no exclusivity provisions and the product will not be introduced prior to the expiry of the two patents.

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Betamethasone Dipropionate Gel

7. NONPROPRIETARY NAME

Betamethasone Dipropionate Gel

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

12/18/1997 Original submission
1/29/1998 Major amendment

10. PHARMACOLOGICAL CATEGORY

Glucocortic

11. HOW DISPENSED

Prescription (R)

12. RELATED DMF(s)

Product	Holder	DMF (type)	LOA letter
▶ Betamethasone Dipropionate USP		(II)	v1.1 (letter)
▶ Betamethasone Dipropionate USP		(II)	v1.4, p1276
▶ Coated aluminum tubes and caps		(III)	v1.5, p2057
▶ Coated aluminum tubes and caps		(III)	v1.5, p2061
▶ Coated aluminum tubes and caps		(III)	v1.5, p2062
▶ Polyethylene Resin		(III)	v1.5, p2069
▶ Polyethylene Resin		(III)	v1.5, p2068
▶ Polyethylene Resin		(III)	v1.5, p2066
▶ Tube liner		(III)	v1.5, p2064

13. DOSAGE FORM

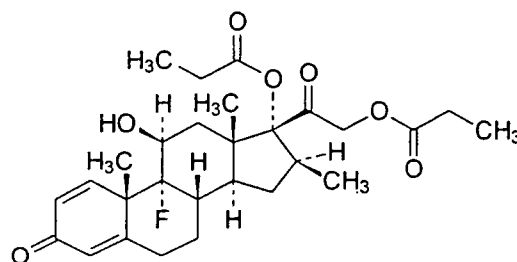
Gel

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

- ✓ Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11 β ,16 β)-. C₂₈H₃₇FO₇. 504.6. 5593-20-4.

**16. RECORDS AND REPORTS**

None

17. COMMENTS

The following sections are not satisfactory:

- 22. Synthesis
- 23. Raw material
- 25. Manufacturing and processing
- 26. Container/closure system
- 28. Laboratory controls
- 29. Stability
- 32. Labeling

The following sections are pending:

31. Samples and results

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable. A NA major letter will issue.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya, Ph.D./June 26, 1998

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Chem. Review #1

JUL 20 1998

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-276

APPLICANT: Altana Inc.

DRUG PRODUCT: Betamethasone Dipropionate Gel, 0.05%

The deficiencies presented below represent Major deficiencies.

A. Deficiencies:

1. Please provide the particle size testing method for the drug substance of Betamethasone Dipropionate USP.
2. Please establish an individual impurity limit for the drug substance of Betamethasone Dipropionate USP.
3. Please clarify whether every batch of the drug substance and the inactive ingredients was tested in-house or not. If they are not, please provide a brief procedures for qualifying vendors.
4. Please provide schedules and the tests for retesting of the drug substance and inactive ingredients.
5. Please revise the manufacturing instructions for kg to kg batch size to incorporate the changes at steps used in the three executed batches.
6. Since the polyethylene resins used to manufacture the caps for the 15 g tubes are only described as high in the standard tube specifications, please provide the name of manufacturer/supplier and the part number/code.
7. Please provide the tube specifications and drawing of the 15 g tube, manufactured by
8. Please provide a container/closure testing commitment which should include the protocol and schedule for initial release testing and retesting.
9. Please provide the sampling procedure for in-process testing and include a limit of relative standard deviation (RSD) in the assay specifications of the in-process controls since the assay tests included multiple samples at different positions

10. Please reduce the Betamethasone Dipropionate assay upper limit in the in-process controls, finished products, and stability specifications from % of label claim to %, which is based on % overage in the formulation and % maximum allowable error in the assay method.
11. Specification of homogeneity is defined as all assays for Betamethasone Dipropionate fall within % of the mean in the finished product specifications. However, it is not clear how the mean is defined. Based on the stability data you provided, the mean is not calculated from the assays at top, middle, and bottom of tube. Please clarify.
12. Please provide a justification, such as comparison between your product and the innovator product, for the high limits of degradation products in the finished product and stability specifications.
13. The limits of degradation products in the certificates of analysis for the finished products, batch 9753, 9754, and A095, were different from the proposed specifications for finished product on pages 2416 and 2417. Please clarify.
14. In the Betamethasone Dipropionate assay method NMT % difference between the area obtained for the final injection of the standard and the mean of the areas obtained for the first five injections of the standard is inconsistent with the conclusions of sample solution stability in the method validation. Please justify.
15. Please add a note in the sample preparation section of the Betamethasone Dipropionate assay method to indicate that a sample solution should be analyzed within 24 hours since a sample preparation is stable for 24 hours as the method validation reported.
16. Two testing alert reports in the application reported that the assay results of the batch 9753 and A095 are out of the upper limit of assay specification without any assignable lab causes found. It is against the principle of GMP to repeat the test and average the results to pass a specification if the initial tests and results were found to be valid. Please comment.

17. Since significant upward trends for the degradants were observed in the accelerated and long-term stability data of all three batches, please note that complete long-term stability data are required to approve your proposed expiration date.
 18. The DMF is currently inadequate. The DMF holder, has been notified.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:
1. The agency's district office will request samples of the finished dosage form for the methods validation at the appropriate time. Please submit samples promptly when requested.

Sincerely yours,

/S/

7/17/98

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 2
2. ANDA # 75-276
3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The reference listed drug Diprolene manufactured by Schering Corporation. The applicant has certified that the listed drug products referred to in the application are covered by two patents and no exclusivity provisions and the product will not be introduced to the market prior to the expiry of the two patents.

- | | |
|-------------------------------|---|
| 5. <u>SUPPLEMENT(s)</u> | 6. <u>PROPRIETARY NAME</u> |
| Original 12/18/97 | N/A |
| 7. <u>NONPROPRIETARY NAME</u> | 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> |

Betamethasone Dipropionate

9. AMENDMENTS AND OTHER DATES:

1/29/98 Major amendment
1/15/99 Major amendment
11/15/99 Major amendment

- | | |
|-------------------------------------|----------------------|
| 10. <u>PHARMACOLOGICAL CATEGORY</u> | 11. <u>Rx or OTC</u> |
|-------------------------------------|----------------------|

Glucocortic

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

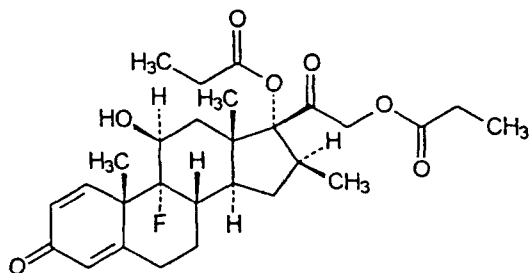
- | | |
|------------------------|--------------------|
| 13. <u>DOSAGE FORM</u> | 14. <u>POTENCY</u> |
|------------------------|--------------------|

Gel

0.05%

15. CHEMICAL NAME AND STRUCTURE

Betamethasone Dipropionate. Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11 β ,16 β)-.C₂₈H₃₇FO₇. 504.6. 5593-20-4. Glucocorticoid.



16. RECORDS AND REPORTS

17. COMMENTS

DMF is deficient.

the firm will be asked to provide the number of samples and where samples are taken from.

The firm will be asked to explain the difference between specification No. and specification on the stability report regarding the degradation products.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER:

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

4/24/00

Supervisor: Paul Schwartz, Ph.D.

4/27/00

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Chem. Review #2

JUN 2 1990

38. Chemistry Comments to be Provided to the Applicant.

ANDA: 75-276

APPLICANT: Altana Inc.

DRUG PRODUCT: Betamethasone Dipropionate Gel, 0.05%

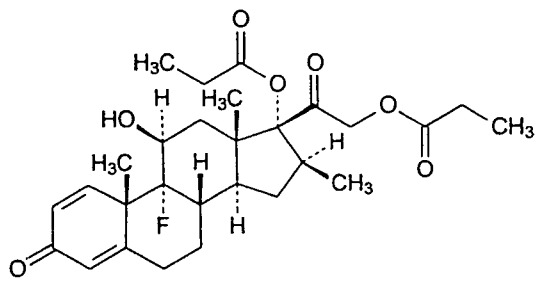
The deficiencies presented below represent MINOR deficiencies.

1. DMF 7389 remains deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the new DMF deficiencies have been addressed.
2. Please explain the difference between the specifications on Specification No. _____ and the specifications on the stability reports regarding the degradation products.
3. Please provide the number of samples and where samples are taken from for your in process, _____ test.
4. Please provide the stability data (assay and degradation) of the RLD at expiry to justify your proposed limits.

Sincerely yours,

/S/

R. Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research



16. RECORDS AND REPORTS

17. COMMENTS

The DMF is deficient. The DMF holder has been notified. Please do not respond until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

12/11/00

Supervisor: Paul Schwartz, Ph.D.

12/11/00

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Chem Review #3

DEC 26 1984

38. Chemistry Comments to be Provided to the Applicant.

ANDA: 75-276 APPLICANT: Altana Inc.

DRUG PRODUCT: Betamethasone Dipropionate Gel, 0.05% (Augmented)

The deficiencies presented below represent MINOR deficiencies.

The DMF is deficient. The DMF holder has been notified.
Please do not respond until you have been notified by the
DMF holder that the DMF deficiencies have been addressed.

Sincerely yours,

/S/

fr Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO.4

2. ANDA # 75-276

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The reference listed drug Diprolene manufactured by Schering Corporation. The applicant has certified that the listed drug product referred to in the application are covered by two patents and no exclusivity provisions and the product will not be introduced to the market prior to the expiry of the two patents (12/18/01).

5. SUPPLEMENT(s)

Original 12/18/97

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Betamethasone Dipropionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

9. AMENDMENTS AND OTHER DATES:

1/29/98 Major amendment
1/15/99 Major amendment
11/15/99 Major amendment
11/3/00 Minor amendment
12/5/00 Telephone amendment
2/21/01 Minor amendment
4/20/01 Telephone amendment
4/25/01 Telephone amendment
4/26/01 Telephone amendment
4/30/01 Telephone amendment

10. PHARMACOLOGICAL CATEGORY

Glucocortic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

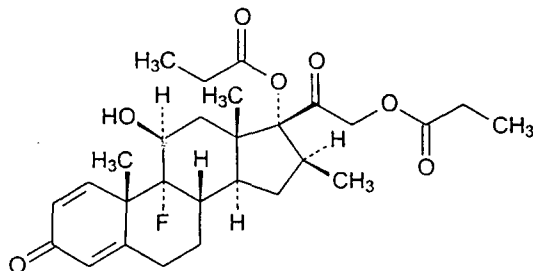
Gel (Augmented)

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Betamethasone Dipropionate. Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11 β ,16 β)-.C₂₈H₃₇FO₇. 504.6. 5593-20-4. Glucocorticoid.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

4/27/01

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 75-276
Dup
Division File
Field copy

Endorsements:

HFD-627/NNashed/ *NN 5/2/01*
HFD-627/PSchwartz/5/1/01 *PS 5/3/01*

F/T by: DJ 5/2/01

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Chem. Review #4

1. CHEMISTRY REVIEW NO 5

2. ANDA # 75-276

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The reference listed drug Diprolene manufactured by Schering Corporation. The applicant has certified that the listed drug product referred to in the application are covered by patent 4489070 expires May 13, 2003 and no exclusivity provisions.

The firm certifies that it will not introduce the product, subject of this application, to the market prior to the expiry of the above referenced patent.

5. SUPPLEMENT(s)

Original 12/18/97

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Betamethasone Dipropionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

9. AMENDMENTS AND OTHER DATES:

1/29/98 Major amendment
1/15/99 Major amendment
11/15/99 Major amendment
11/3/00 Minor amendment
12/5/00 Telephone amendment
2/21/01 Minor amendment
4/20/01 Telephone amendment
4/25/01 Telephone amendment
4/26/01 Telephone amendment
4/30/01 Telephone amendment
9/17/01 Telephone amendment
2/19/02 Telephone amendment
10/7/02 Telephone amendment
2/14/03 Telephone amendment
2/28/03 Telephone amendment
3/7/03 Minor amendment

10. PHARMACOLOGICAL CATEGORY

Glucocorticoid

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

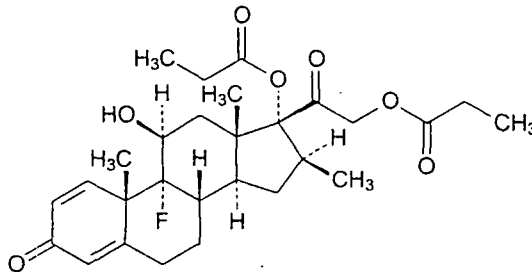
Gel (Augmented)

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Betamethasone Dipropionate. Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11 β ,16 β)-. C₂₈H₃₇FO₇. 504.6. 5593-20-4. Glucocorticoid.



16. RECORDS AND REPORTS

17. COMMENTS

The firm requests final approval. No changes to the chemistry, manufacturing and controls have been made since the tentative approval on February 28, 2003.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable (Final approval).

19. REVIEWER:

/S/

Nashed E. Nashed, Ph.D.

DATE COMPLETED:

4/28/03
4/28/03

Supervisor: James M. Fan

[Signature] *4/29/03*

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Chem. Review #5