CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-669

CHEMISTRY REVIEW(S)

NDA 21-669

2% Chlorhexidine Gluconate, Cloth*
(*equivalent to 500mg per cloth)

Sage Products, Inc.

Milton J. Sloan, Ph.D.
Division of Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-669

2. REVIEW #: 3

3. REVIEW DATE: December 16, 2004; April 15, 2005

4. REVIEWER: Milton J. Sloan, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-August-2003
Amendment (BL)	31-March-2004
Amendment (BC)	15-June-2004
Amendment (BZ)	06-August-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AZ)	25-Oct-2004
Amendment (MS)	25-Feb-2005
Amendment (Fax)	22-March-2005
Amendment (MS)(Fax)	04-April-2005
Amendment (Fax)	07-April-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Sage Products, Inc.
Address:	3909 Three Oaks Road Cary Illinois 60013
Representative:	N/A
Telephone:	(815) 455-4700

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: 2% Chlorhexidine gluconate, Cloth
   b) Non-Proprietary Name (USAN): 2% Chlorhexidine gluconate, Cloth
   c) Code Name/# (ONDC only):N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3S
      - Submission Priority: Standard Review

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

10. PHARMACOL. CATEGORY: Antiseptic / Antimicrobial

11. DOSAGE FORM: Cloth

12. STRENGTH/POTENCY: 2% CHG w/w /(500 mg CHG per [redacted] cloth)

13. ROUTE OF ADMINISTRATION: Topical via [redacted] cloth

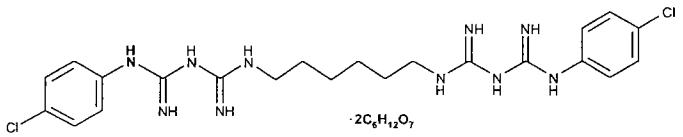
14. Rx/OTC DISPENSED: ___Rx __X_OTC

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:

N, N''-bis (4-chlorophenyl)-3,12-diimino-2, 4,11,13-tetraazatetradecanediimidamide



Molecular formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate		None
	II			3	Adequate		None
	III			6	Adequate		None

[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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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	64,143	
Minutes of Teleconference	64,143	CMC meeting to discuss pre-NDA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	12-May-2004	J.D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	Acceptable with Recommendations	Dec. 14, 2004	Guiragos Poochikian, PhD.
Methods Validation	N/A	N/A	N/A
DMETS	Acceptable pending Comments for LNC	May 13, 2004 (June 09,2004)	Charlie Hoppes, RPh. MPH
EA	Categorical exclusion claimed	N/A	N/A
Microbiology	N/A	N/A	N/A
OTC Labeling	Review with pending Comments in DFS	May 12, 2004	Michelle Jackson, Ph.D.

The Chemistry Review for NDA 21-669

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective. The concerns have been addressed that were listed in Section VIII (List of Comments and Deficiencies to Sponsor) of Review #2 and listed in the approvable (AE) letter. Complete review evaluations of the responses to the deficiencies are found at the beginning of the Chemistry Assessment section and in the Drug Product section of this review. The sections that were previously found inadequate are the subject of this review. The Specifications & Method for Drug Product Ingredients, Methods of Manufacturing and Packaging, Regulatory Specifications and Methods for Drug Product, Container/Closure System, and Drug Product Stability subsections, and Methods Validation, and Labeling sections are now adequate to support this NDA.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
The established name is [redacted] chlorhexidine gluconate solution (U.S.P.). Chlorhexidine Gluconate Solution is a colorless to pale yellow aqueous solution of [redacted] percent. Its chemical name is N,N"-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide. It is miscible with water, soluble in [redacted] with a pH: 5.5-7.0. The drug substance is the subject of a USP monograph and has been adequately characterized. Information pertaining to the manufacturing, process controls, specifications, analytical methods, container/closure system and stability has been filed by [redacted] and by [redacted]
Copies of letters of authorization (LOA's) permitting Sage to reference the DMF's are included in the NDA. The DMF's were found adequate to support this NDA.

Drug Product
Sage Products, Inc. has submitted this NDA for a new antiseptic drug product containing a 2% (w/w) chlorhexidine gluconate (CHG) solution for approval to market

in the U.S.. The finished drug product consists of a disposable cloth made of polyester [redacted] material containing a 2% chlorhexidine gluconate solution, wrapped in [redacted], and packaged in a [redacted] The formulated bulk solution is composed of purified water, propylene glycol, aloe vera, glycerin, dimethicone, igepal, polysorbate 20, fragrance, glucono-delta-lactone, and [redacted] CHG solution. The bulk drug product will not be separately marketed. The packaging configuration contains two disposable cloths impregnated with a 2% weight-by-weight chlorhexidine gluconate (CHG) solution equivalent to 500 mg chlorhexidine gluconate per cloth. A tear-open flexible plastic package is the proposed configuration rather than [redacted] previously proposed.

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

Sage Products has developed a product that will utilize [redacted] cloth technology to deliver a 2% chlorhexidine gluconate antiseptic solution to the skin of patients. The product's intended use is for preparation of skin prior to surgery and to have continued antimicrobial activity up to 6 hours after application. The product consist of a prepackaged set of two [redacted] disposable cloths containing a no-rinse surfactant solution containing CHG as the active ingredient. Each cloth will be used to cleanse the appropriate areas of skin prior to a surgical procedure. The disposable cloths are intended for single use and measure approximately 8" x 8". The product is intended to be sold over-the-counter to healthcare professionals. The current recommended nomenclature for finished drug product is: 2% Chlorhexidine gluconate, Cloth *(*equivalent to 500 mg chlorhexidine gluconate per cloth).

C. Basis for Approvability or Not-Approval Recommendation

Initial review of this NDA submission was completed on June 9, 2004. Three major deficiencies and several inconsistencies were identified and needed to be addressed before a recommendation of approval could be concluded. Sage Products, Inc. responded to the list of comments and deficiencies on June 15, 2004. Their response did not adequately address the deficiencies. An approvable (AE) letter was issued to Sage with a complete list of CMC deficiencies and comments. Sage submitted a request for clarification of these deficiencies and comments. The questions were addressed in writing and a teleconference was held on July 26, 2005 to discuss what was needed (Attachment 1 of Review). Three months later Sage re-submitted NDA #21-669. Sage responses are the subject of this review. A face-to-face meeting (2/7/05) with Sage was requested and held during review of this resubmission to discuss pending issues in the NDA. Subsequent teleconferences and faxes resulted in acceptable amendments to the NDA in which Sage requested as recommended, that the FDA consider only the 2-pack product configuration used in the clinical studies for the NDA approval. As a result, most of the deficiencies and inconsistencies were eliminated and no longer a concern or issue with this NDA.

The manufacturing sites have all been found acceptable with the Office of Compliance. The applicant has satisfactorily demonstrated via the CMC data submitted in the application adequate controls that will assure for this new formulation the identity, strength, quality and purity of the product throughout the shelf life. We unequivocally recommend approval for the 2-pack finished drug product used in the clinical studies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Milton J. Sloan, Ph. D., Chem Reviewer — Date: Feb 21, 2005, April 18, 2005

James D. Vidra, Ph. D., Chem TeamLeader — Date: April 18, 2005

C. CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Kim/MO
HFD-520/Sloan/CHM
HFD-520/Vidra/CHMTL
HFD-830/Schmuff/ActingDivDir
HFD-520/Ellis/PCL
HFD-520/Coderre/MIC
HFD-520/Valappil/STT
HFD-520/Bonapace/BPH
HFD-560/Jackson/OTC

49 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 1

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

/s/

Milton Sloan
4/21/05 12:11:57 PM
CHEMIST

Jim Vidra
4/21/05 12:21:11 PM
CHEMIST

CHEMISTRY REVIEW

#2

NDA 21-669

2% CHG Pre-Op Prep
Chlohexidine Gluconate
Antiseptic Washcloths

Sage Products, Inc.

Milton J. Sloan, Ph.D.
Division of Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-669

2. REVIEW #:2

3. REVIEW DATE: June 16, 2004

4. REVIEWER: Milton J. Sloan, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-August-2003
Amendment (BL)	31-March-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BC)	16-June-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Sage Products, Inc.
Address:	3909 Three Oaks Road Cary Illinois 60013
Representative:	N/A
Telephone:	(815) 455-4700

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: 2% CHG Pre-OP
   b) Non-Proprietary Name (USAN): Chlorhexidine Gluconate
   c) Code Name/# (ONDC only):N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3S
      - Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiseptic / Antimicrobial

11. DOSAGE FORM: Liquid on cloth

12. STRENGTH/POTENCY: 2% CHG w/w

13. ROUTE OF ADMINISTRATION: Topical via [redacted] cloth

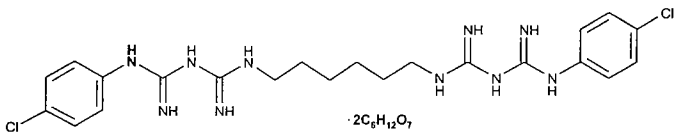
14. Rx/OTC DISPENSED: ___Rx __X_OTC

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:

N, N''-bis (4-chlorophenyl)-3,12-diimino-2, 4,11,13-tetraazatetradecanediimidamide



Molecular formula: $C_{22}H_{30}Cl_2N_{10}•2C_6H_{12}O_7$

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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	II			3	Adequate		None
	III			6	Adequate		None

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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:

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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	12-May-2004	J.D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
DMETS	See review with pending Comments in DFS	May 13, 2004	Charlie Hoppes, RPh. MPH
EA	Categorical exclusion claimed	N/A	N/A
Microbiology	N/A	N/A	N/A
OTC Labeling	Review with pending Comments in DFS	May 12, 2004	Michelle Jackson, Ph.D.

The Chemistry Review for NDA 21-669

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended as approvable (AE) from the Chemistry, Manufacturing, and Controls perspective. Pending deficiencies still remain in the Drug Product (II) section of this review that are found in the Specifications & Method for Drug Product Ingredients, Methods of Manufacturing and Packaging, Regulatory Specifications and Methods for Drug Product, Container/Closure System, and Drug Product Stability subsections. Pending deficiencies are also found in the Methods Validation, and Labeling sections. These concerns are listed in Section VIII (List of Comments and Deficiencies to Sponsor) and should be communicated to the sponsor.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
The established name is [redacted], chlorhexidine gluconate solution (U.S.P.). Chlorhexidine Gluconate Solution is a colorless to pale yellow aqueous solution of [redacted] percent. Its chemical name is N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide. It is miscible with water, soluble in [redacted] with a pH: 5.5-7.0. The drug substance is the subject of USP monograph and has been adequately characterized. Information pertaining to the manufacturing, process controls, specifications, analytical methods, container/closure system and stability has been filed by [redacted] and by [redacted] Copies of letters of authorization (LOA's) permitting Sage to reference the DMF's are included in the NDA.

Drug Product
Sage Products, Inc. has submitted this NDA for a new antiseptic drug product containing a 2% (w/w) chlorhexidine gluconate (CHG) solution approval to market in the U.S. The finished drug product, 2% CHG Pre-Op Prep, is formulated with CHG a topical antiseptic/antimicrobial. The 2% CHG Pre-Op Prep consists of a disposable cloth moistened with a 2% chlorhexidine gluconate solution, wrapped in and packaged

in [redacted] The solution is added to the cloth to create the final product, 2% CHG Pre-Op Prep solution, polyester [redacted] cloth material, [redacted] and the label. The formulated bulk solution is composed of purified water, propylene glycol, aloe vera, glycerin, dimethicone, igepal, polysorbate 20, fragrance, glucono delta lactone, and [redacted] CHG solution. The bulk drug product will not be marketed. Each packaging configuration contains a 2% weight-by-weight chlorhexidine gluconate (CHG) solution. [redacted] CHG solution. The second is a tear-open flexible plastic package containing two disposable cloths impregnated with the same solution.

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

Sage Products has developed a product that will utilize [redacted] cloth technology to deliver a 2% chlorhexidine gluconate antiseptic solution to the skin of patients. The product's [redacted] is for preparation of skin prior to surgery [redacted]. The products consist of a prepackaged set of [redacted] two [redacted] disposable cloths impregnated with a no-rinse surfactant solution containing CHG as the active ingredient. Each cloth will be used to cleanse the appropriate areas of skin prior to a surgical procedure. The disposable cloths are intended for single use and measure approximately 8" x 8". The product is intended to be sold over-the-counter to healthcare professionals.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing sites have all been found acceptable with the Office of Compliance. However, the applicant has not satisfactorily demonstrated via the CMC data submitted in the application adequate controls that will assure for this new formulation the identity, strength, quality and purity of the product throughout the shelf life. A list of comments were communicated to the applicant and discussed in a recent teleconference. The applicant has submitted an amendment to the NDA in response to the comments and the discussions follow below.

There are several deficiencies that cannot be completed within the PDUFA time frame. In particular, the applicant reports the issue of content uniformity between the cloths will take some analysis and possibly some further testing [redacted] Sage requests now that the FDA considers only the 2-pack product configuration for the NDA first-cycle approval.

The integrity of manufacturing controls to ensure content uniformity is developed. The claim by the applicant that each cloth contains [redacted] is not supported in the data submitted in the NDA. The content uniformity and the amount of CHG on each cloth has not been demonstrated in the manufacturing or analytical controls. Moreover, the

applicant has not developed an analytical method to assess this quantity. The content uniformity is of concern in each finished drug product configuration.

The stability data for the 2-pack configuration manufactured at Sage has not been used been in pivotal efficacy studies (Phase III). Sage has no "primary stability" or "clinical batch". Thus, there is no direct connection between the clinical studies and the results in the stability studies. The only stability study of a lot or batch that has been used in clinical trials is the bulk solution lot #206-2022-08 [redacted] used in the Pre-Op Skin Prep Studies [redacted] This bulk solution was used in the manufactured finish drug product lots NPM-011(2)-STBL-1B and NPM-011(6)-STBL-1B with [redacted] components. The lot contained the [redacted] 2-pack that failed to meet the percent concentration (accelerated) and microbial limits (accelerated and long term) acceptance criteria at the 5th month. Sage report that this finished drug product configuration [redacted] 2-pack) would not be marketed because of poor stability performance. A discussion or assessment on the difference or lack of product performance was not offered in the NDA. The stability data indicates a failure due to contamination (accelerated and long term) after [redacted] for both Sage and [redacted] finished drug product. Consequently, the stability data for the 2-pack manufactured with Sage's components and raw material is the only stability data offered to support this application. The 2-pack data on the finished drug product of Sage represents a distinct version of the finished product and is inadequate to support the NDA. The Sage 2-pack has no direct link to any of the clinical studies. Sage has not assessed the impact of this change (Sage's 2-pack configuration versus [redacted] 2-pack) on the quality of the clinical trial finished drug product.

The applicant has provided a stability update for the only Sage 2-pack and is now proposing one-year expiration based on the updated stability data. [redacted] stability data was provided at the time of submission for each finished drug product configuration. The update of stability was requested in addition to changes in the format of the data. The applicant has provided additional data ([redacted]) to support the proposed one year expiration period. A trend that can be observed is in the percent weight loss. With the proposed value of nmt [redacted] the drug product fails at [redacted] and reaches [redacted] at 12 months.

At the time of submission, the applicant had not identified and developed adequate controls for [redacted] significant impurities. The identities of these impurities have still not been submitted however, Sage has determined that they are process related impurities. Test method [redacted] was submitted to monitor these impurities. Sage still has not identified the [redacted] impurities in the finished drug product but have proposed acceptance criteria and to monitor at release and stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Milton J. Sloan, Ph. D., Chem Reviewer — Date: June 21, 2004
James D. Vidra, Ph. D., Chem TeamLeader — Date

C. CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Kim/MO
HFD-520/Sloan/CHM
HFD-520/Vidra/CHMTL
HFD-830/Lin/ActingDivDir
HFD-520/Ellis/PCL
HFD-520/Coderre/MIC
HFD-520/Valappil/STT
HFD-520/Bonapace/BPH
HFD-560/Jackson/IDS

27 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 2

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

/s/

Milton Sloan
6/25/04 12:21:23 PM
CHEMIST
A list of Deficiencies and Comments to the Sponsor are included in review.

Jim Vidra
6/25/04 12:38:11 PM
CHEMIST

#1

NDA 21-669

2% CHG Pre-Op Prep
Chlohexidine Gluconate
Antiseptic Washcloths

Sage Products, Inc.

Milton J. Sloan, Ph.D.
Division of Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-669

2. REVIEW #:1

3. REVIEW DATE: January 31, 2004

4. REVIEWER: Milton J. Sloan, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-August-2003
Amendment (BL	31-March-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Sage Products, Inc.
Address:	3909 Three Oaks Road Cary Illinois 60013
Representative:	N/A
Telephone:	(815) 455-4700

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: 2% CHG Pre-OP
b) Non-Proprietary Name (USAN): Chlorhexidine Gluconate
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiseptic / Antimicrobial

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 2% CHG w/w

13. ROUTE OF ADMINISTRATION: Topical via [redacted] cloth

14. Rx/OTC DISPENSED: ___Rx __X_OTC

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

___X___Not a SPOTS product

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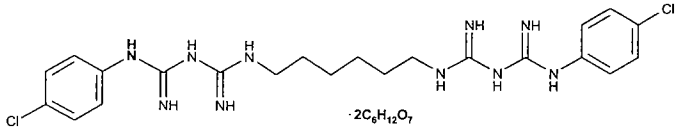
N, N''-bis (4-chlorophenyl)-3,12-diimino-2, 4,11,13-tetraazatetradecanediimidamide



Molecular formula: $C_{22}H_{30}Cl_2N_{10}•2C_6H_{12}O_7$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II			3	Adequate		None
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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)

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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Minutes of Teleconference	64,143	CMC meeting to discuss pre-NDA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable		
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
OPDRA			
EA	Categorical exclusion claimed	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-669

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended as approvable (AE) from the Chemistry, Manufacturing, and Controls perspective. Some pending deficiencies remain in the Drug Product (II) section of this review that are found in the Specifications & Method for Drug Product Ingredients, Methods of Manufacturing and Packaging, Regulatory Specifications and Methods for Drug Product, Container/Closure System, Microbiology, and Drug Product Stability subsections. Pending deficiencies are also found in the Environmental Assessment, Methods Validation, and Labeling sections. These concerns are listed in Section VIII (List of Comments and Deficiencies to Sponsor) and have been communicated to the sponsor.

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

The applicant may be requested to commit to performing stability studies of the proposed marketed finished drug product using revised analytical methods.

II. Summary of Chemistry Assessments

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

Drug Substance
The established name is [redacted] chlorhexidine gluconate solution (U.S.P.). Chlorhexidine Gluconate Solution is a colorless to pale yellow aqueous solution of [redacted] percent. Its chemical name is N,N"-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide. It is miscible with water, soluble in [redacted] with a pH: 5.5-7.0. The drug substance is the subject of USP monograph and has been adequately characterized. Information pertaining to the manufacturing, process controls, specifications, analytical methods, container/closure system and stability has been filed by [redacted] and by [redacted] Copies of letters of authorization (LOA's) permitting Sage to reference the DMF's are included in the NDA.

Drug Product
Sage Products, Inc., has submitted this NDA for a new antiseptic drug product containing a 2% (w/w) chlorhexidine gluconate (CHG) solution approval to market in the U.S. The finished drug product, 2% CHG Pre-Op Prep, is formulated with CHG, a

topical antiseptic/antimicrobial. The 2% CHG Pre-Op Prep consists of a disposable cloth moistened with a 2% chlorhexidine gluconate solution, wrapped in [redacted] and packaged in [redacted]. The solution is added to the cloth to create the final product, 2% CHG Pre-Op Prep solution, a polyester [redacted] cloth material, packages with a [redacted], as a carrier support system, a [redacted] and the label. The formulated bulk solution is composed of purified water, propylene glycol, aloe vera, glycerin, dimethicone, igepal, polysorbate 20, fragrance, glucono delta lactone, and [redacted], CHG solution. The bulk drug product will not be marketed. Sage intends to market [redacted] packaging configurations. Each packaging configuration contains a 2% weight-by-weight chlorhexidine gluconate (CHG) solution. [redacted] The second is a tear-open flexible plastic package containing two disposable cloths impregnated with the same solution.

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

Sage Products has developed a product that will utilize [redacted] cloth technology to deliver a 2% chlorhexidine gluconate antiseptic solution to the skin of patients. The product's intended use is for preparation of skin prior to surgery and to have continued antimicrobial activity up to 6 hours after application. The products consist of a prepackaged set of either two [redacted] disposable cloths impregnated with a no-rinse surfactant solution containing CHG as the active ingredient. Each cloth will be used to cleanse the appropriate areas of skin prior to a surgical procedure. The disposable cloths are intended for single use and measure approximately 8" x 8". The product is intended to be sold over-the-counter to healthcare professionals.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing sites have all been found acceptable with the Office of Compliance. However, the applicant has not satisfactorily demonstrated via the CMC data submitted in the application adequate controls that will assure for this new formulation the identity, strength, quality and purity of the product throughout the [redacted] shelf life.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Milton J. Sloan, Ph. D., Chem Reviewer — Date: June 09, 2004
James D. Vidra, Ph. D., Chem TeamLeader — Date

C. CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Kim/MO
HFD-520/Sloan/CHM
HFD-520/Vidra/CHMTL
HFD-830/Lin/ActingDivDir
HFD-520/Ellis/PCL
HFD-520/Coderre/MIC
HFD-520/Valappil/STT
HFD-520/Bonapace/BPH
HFD-560/Jackson/IDS
HFD-560/Frazier/PM

43 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 3

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/s/

Milton Sloan
6/21/04 07:34:13 PM
CHEMIST
List of comments were sent to applicant and discussed via teleconference.

Jim Vidra
6/22/04 09:34:41 AM
CHEMIST