CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-051

CHEMISTRY REVIEW(S)

Veramyst
(fluticasone furoate)
Nasal Spray
27.5 mcg/spray

NDA 22-051

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Glaxo Group Limited
d/b/a GlaxoSmithKline
One Franklin Plaza, P.O. Box 7929
Philadelphia, PA 19101

Indication: treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older

Presentation: Each 50 microliter spray of the **Veramyst** suspension delivers 27.5 mcg of micronized fluticasone furoate.

Each presentation (trade and physician sample) consists of an amber glass bottle, fitted with a manual metered pump spray unit. The bottle and pump are integrated into an off-white plastic device with a view window, dark blue side-actuated lever, and dark blue detachable cap covering the applicator tip. Each bottle provides 120 doses and has a net fill weight of 10.0 grams. The 120 dose presentation, with a net fill weight of 10.0 grams, is commercially available. Additionally, a [redacted].

EER Status: **Pending**

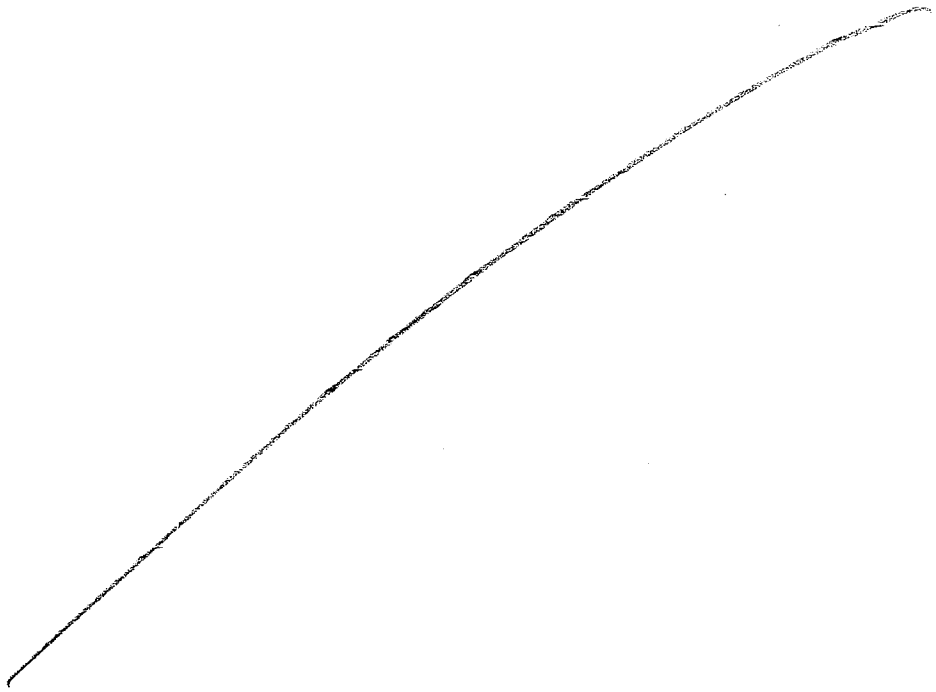
Consults:

Biometrics:	Acceptable 27-MAR-2007
Pharm/Tox:	Acceptable for impurities 26-MAR-2007
EA:	Categorical exclusion granted under 21 CFR §25.31 (b).
DMETS:	Acceptable 7-MAR-2007
Microbiology:	Acceptable 25-OCT-2006
Methods Validation:	Method validation package is provided. Samples will be requested for method validation study to be conducted by FDA laboratories.

Original Submission: 28-JUN-2006

Drug Substance

Fluticasone furoate, a corticosteroid, has the chemical name 6α,9α-Difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester. It is a white solid with a molecular weight of 538.58 g/mol and the molecular formula of $C_{27}H_{29}F_3O_6S$. The molecule possesses [redacted] configuration) and displays a [redacted].



Conclusion: Drug substance is acceptable.

Drug Product

Veramyst Nasal Spray is a metered-dose, manual-pump spray assembly containing ar , aqueous suspension of micronized fluticasone furoate that delivers 27.5 mcg per actuation. The drug product is a white aqueous suspension contained in an amber glass bottle and is available as 120 /bottle (commercial pack) and

The drug product contains mg of micronized fluticasone furoate, mg of anhydrous dextrose USP (, mg of microcrystalline cellulose NF with (w/w) carboxymethylcellulose sodium NF), mg of polysorbate 80 NF , mg of % solution of benzalkonium chloride NF ( ), 0.15 mg edetate disodium USP and about mg of purified water USP per 1 g of suspension, adjusted to pH to with NF. The fill weight is 10.0 g for the commercial pack and .

The proposed release specifications include description, identity by

Adequate stability data were provided to support the requested expiration dating period of 24 months for both presentations of drug product, stored upright with cap in place, at room temperature of 25°C (77°F) with excursions permitted between 15° and 30 °C (59° and 86°C). Drug product should NOT be stored in the refrigerator or freezer.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided. Samples of the drug substance and drug product will be requested for the method validation study to be conducted in the FDA laboratories.

Overall Conclusion:

From a CMC perspective, the application is recommended for A**pproval.**

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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

/s/

Blair Fraser
4/5/2007 06:10:54 AM
CHEMIST

NDA 22-051

Veramyst (fluticasone furoate) Nasal Spray (suspension), 27.5 µg/spray

Glaxo Group Limited d/b/a GlaxoSmithKline

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division I

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-051

2. REVIEW #: 2

3. REVIEW DATE: 28-Mar-2007

4. REVIEWER: Eugenia M. Nashed

5. PREVIOUS DOCUMENTS (CMC Review #1) :

Submission(s) Reviewed	Document Date	Stamp Date	Assigned Date
Original NDA	28-Jun-2006	29-Jun-2006	13-Jul-2006 (NDA accessible on 13-Jul-2006)
Amendment BZ	05-Oct-2006	05-Oct-2006	05-Oct-2006
Amendment BZ	20-Oct-2006	20-Oct-2006	20-Oct-2006

6. SUBMISSION(S) BEING REVIEWED (CMC Review #2) :

Submission(s) Reviewed	Document Date	Stamp Date	Assigned Date
Amendment BC	26-Jan-2007		
Amendment BC	31-Jan-2007		
Amendment BC	15-Mar-2007		
Amendment BC	26-Mar-2007		
Amendment BC	27-Mar-2007		

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

Address: One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101

Representative: Munir Abdullah, Director, U.S. Regulatory Affairs

Telephone: (919) 483-9318 Fax: (919) 315-0033

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Veramyst
b) Non-Proprietary Name (USAN): Fluticasone Furoate (r-INN, USAN, JAN)
c) Code Name/# (ONDC only): GW685698X
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Corticosteroid for treatment of the symptoms of seasonal and perennial allergic rhinitis (SAR and PAR) in adults and children aged 2 years and older

11. DOSAGE FORM: Nasal Spray Suspension

12. STRENGTH/POTENCY: 27.5 µg/spray; Daily dose: 55 or 110 µg once daily

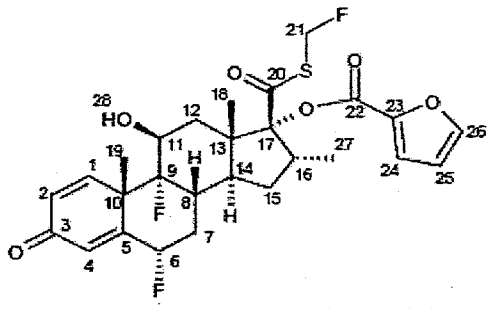
13. ROUTE OF ADMINISTRATION: Intranasal

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:



Molecular Formula: $C_{27}H_{29}F_3O_6S$ Molecular Weight: 538.58 g/mol

6α,9α-Difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	3			1	Adequate	11-AUG-2006 Craig Bertha	
	3			1	Adequate	07-AUG-2006 Craig Bertha	
	3			1	Adequate	08-AUG-2006 Craig Bertha	
	3			1	Adequate	09-AUG-2006 Craig Bertha	
	3			3	Adequate	19-DEC-2003	Reviewed for use in nasal spray drug product
	3				Adequate	11-AUG-2006 Craig Bertha	

[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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
INDs 48,647 70,297	GSK	Fluticasone Furoate Nasal Spray Inhalation Powder	Pending		Referenced for this NDA.

NDAs 19-389 20-121 20-626 20-983 21-077	GSK		Approved		On the market. Referenced for this NDA.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	Statistical evaluation of the proposed alternative PTIT method for spray weight, SCU and droplet size distribution	Aug 30, 2006	Completed Mar 21, 2007 and Mar 27, 2007	The proposed PTIT acceptance criteria for spray weight, spray content uniformity, and droplet size distribution were discussed with Meiyu Shen, Yi Tsong, Craig Bertha, Alan Schroeder, Prasad Peri and Rik Lostritto, during CMC/Stat meeting on Feb 22, 2007. Responses from GSK submitted on Mar 26, and Mar 27, 2007, are acceptable.
EES	GMP Inspections	Aug 2, 2006	Pending	EER pending: 4 establishments AC, last inspection for the sterility testing site (UK) is scheduled for Apr 23-24, 2007.
Pharm/Tox	Qualification of impurities in drug substance & drug product	Aug 30, 2006	Completed Mar 26, 2007	The PharmTox team found the data supporting qualification of [redacted] impurities [redacted] to be Acceptable.
Biopharm				
DMETS	Labeling/name		Completed Mar 7, 2007	No objection to name Veramyst.
Methods Validation				Will be initiated, as needed, upon completion of the review
DDMAC	Labeling		Completed Mar 21, 2007	
EA	None			Exception requested - acceptable
Microbiology	[redacted] effectiveness	Aug 29, 2006	Completed Oct 25, 2006	Adequate; Review by Bryan Riley, Ph.D.

The Chemistry Review for NDA 22-051

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC recommendation: Approval, pending acceptable GMP status (EER pending).

- Comments resulting from CMC Review #1 were forwarded to the applicant in IR letters dated Dec 6, and Dec 20, 2006. Additional comments concerning the PTIT methods were forwarded from the Stat team on Jan 16, 2007. The responses provided by the applicant are subject of this review (CMC Review #2). IR letters resulting from this review, dated Mar 9, and Mar 22, 2007, were forwarded to the applicant. Three teleconferences (Mar 22, Mar 26 and Mar 27, 2007) were held with the applicant to address recent changes to the drug substance synthesis and design changes to the device and assembly process, introduced very late in the review process (see Agreements below). Also, the proposed PTIT methods and regulatory agreements were discussed in details. All issues were adequately addressed by the applicant in submissions dated Jan 26, Jan 31, Mar 15, Mar 26, and Mar 27, 2007.

- The EER for this NDA is still pending. AC status is currently available for four establishments, inspection was performed at one testing site and no report is available yet, and the last inspection is scheduled (Apr 23-24, 2007) for one testing site in UK. An acceptable GMP status is needed for all manufacturing and testing facilities before the approval.

- 24 months expiry period for the drug product and ——— retest period for the drug substance have been requested, and are supported by the submitted data (Process —)evice —— . However, changes implemented to the drug substance manufacturing process (Process — now, and Process — the future) and device modifications (Devic — ntroduced late in the review cycle, necessitated agreement for submission additional release and stability data – see Agreements below, and Draft CMC Comments for the Action Letter, at the end of this review.

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

Phase 4 Commitments

None, regarding the CMC portion of the application.

Agreements

1. Agreement to carry on drug substance stability studies and submit comparative data to support recent synthetic changes ( ) and confirm the retest period for the drug substance manufactured with a fully representative commercial process. Updated reports on the mass imbalance, formation of " ", and re-evaluation of the current acceptance criteria for drug substance and drug product impurities will be submitted, as specified in the amendment dated Mar 26, 2007.

2. Agreement to submit release and stability data on six drug product batches (three for each presentation, 120 spray manufactured with the fully representative commercial process, to support recent device and assembly process changes, and to confirm 24 month expiry period for the drug product manufactured with the fully representative commercial process. Comparative analyses of the dose performance parameters for commercial, stability and clinical batches will be provided, as specified in the amendment dated Mar 26, 2007.

The agreements were necessitated by changes implemented to the drug substance manufacturing process (in the future), device modifications (Device) and assembly process changes, introduced very late in the review cycle (Jan 26, 2007). Refer to page 75 of this review, and Draft CMC Comments for the Action Letter, at the end of this review.

Risk Management Steps

Regulatory Agreements Proposed by the Applicant.

Regulatory Relief based on QbD approach.
The applicant has submitted proposals

In response, revised Table 1, Regulatory Approach for PAT and PTIT (refer to page 83 of this review) was submitted on Mar 26, 2007, and it is acceptable.

Regulatory Approach based on PAT methodology.
The applicant proposed to control the critical step of the drug substance synthesis ( ) by the method instead of the analysis. The comparative data and method validation were submitted, reviewed and found adequate (refer to CMC review #1, and revised Table 1, Regulatory Approach for PAT and PTIT, on page 83 of this review).

Regulatory Approach based on PTIT methodology.
The applicant proposed alternate acceptance criteria, based on the PTIT approach, for three dose performance attributes for this drug product: Spray weight, Spray content uniformity, and Droplet size distribution. The proposed methodology was consulted to the Biometrics Division for statistical evaluation, in comparison to the acceptable Zero Tolerance (ZT) methods for these attributes. The findings of the Stat team (Meiyu Shen and Yi Tsong) have been discussed in details during the join CMC-Stat meeting (Feb 22, 2007) with senior reviewers of Branch 2, and Rik Lostritto, Division Director of DMPA III, and ONDQ liaison for PTIT policy. It was concluded that the testing for droplet size distribution should be limited to the proposed ZT acceptance criteria since the Agency needs to evaluate the applicability of the PTIT approach to the droplet size distribution testing. The proposed PTIT approach for Spray weight and Spray content uniformity was found acceptable, providing that applicant will adopt acceptance criteria revisions proposed by the CMC-Stat team. The PTIT acceptance criteria were negotiated with the applicant during teleconferences on Mar 22, and Mar 27, 2007, and final, agreed-on Specifications were submitted on Mar 27, 2007. Refer to pages 37 and 95 of this review.

Regulatory Approach based on or Drug Substance and Drug Product.

Since the applicant demonstrated good knowledge and control of the process within the proposed ranges of parameters, the request for future process changes within those parameter ranges are adequately supported. The relevant comments have been forwarded to the Applicant in letter dated Mar 22, 2007, and discussed during teleconference on Mar 22, 2007. The revised versions of Table 2 (Drug Substance Manufacture), and Table 3 (Drug Product Manufacture) were submitted on Mar 26, 2007, and are acceptable. Refer to page 84 of this review.

II. Summary of Chemistry Assessments

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

The drug substance, fluticasone furoate is a new ester form of fluticasone. Fluticasone propionate has been approved as the drug substance in Flonase® and also in the recently approved generic version, Fluticasone Propionate Nasal Spray (Roxane Labs).
The applicant has developed an aqueous nasal spray suspension of fluticasone furoate delivered *via* novel side-actuated device as a once-daily treatment for the symptoms of allergic rhinitis. The initial IND was submitted on Oct 30, 2003, EOP2 meeting was held on Jul 19, 2004, and p-NDA CMC meeting on Jan 20, 2006.

Drug Substance

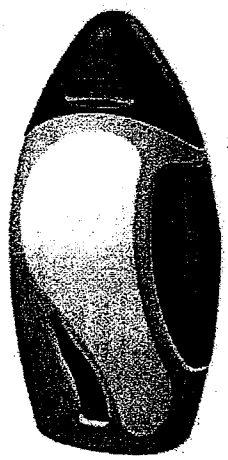
The drug substance, fluticasone furoate (GW685698X), is a white solid and possesses ——— The specific

The drug substance is practically insoluble in water (———, and has no —— or ———. It is slightly soluble in ———, ———, and ——— Non-micronised and micronised fluticasone furoate are non-hygroscopic and typically

The drug substance is manufactured by Glaxo Wellcome in Jurong, Singapore, and micronised in the United Kingdom.

Drug Product

The drug product, Veramyst (fluticasone furoate) Nasal Spray, consists of a white suspension contained in an amber glass bottle, fitted with a metering (50 µL) spray pump. The bottle and pump are incorporated in an off white plastic device with a view window and dark blue side-actuated lever and dark blue detachable cap covering the applicator tip.



Each spray of the suspension delivers 27.5 µg of micronised fluticasone furoate as an ex-device dose. The fill weight of 10.0 g delivers at the minimum 120 sprays after priming (commercial pack), and the fill weight of

The drug product contains — mg of fluticasone furoate, — mg of anhydrous dextrose (————), — mg of microcrystalline cellulose with ———— carboxymethylcellulose sodium (————, — mg of polysorbate 80 (————, — mg of —% solution of benzalkonium chloride (———— mg edetate disodium (————and ———mg of purified water per ———— .. It has a pH between —and—.

Manufacture, packaging and testing are carried by Glaxo (Glaxo Wellcome) at Barnard Castle in the United Kingdom. In addition, stability testing may be carried by GSK at Ware, UK, and the stability testing for antimicrobial effectiveness testing is performed at the ———— ————, and the ————————————

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

The drug product, Veramyst (fluticasone furoate) Nasal Spray suspension, 27.5 mg, is intended for use as a nasal spray for the symptoms of allergic rhinitis (SAR and PAR). The proposed dosage is up to 110 µg given as 2 sprays in each nostril once-daily, for adults and children 2 years and older.

The drug product is recommended for storage in the upright position with the cap in place between 15° and 30 °C (59° and 86°C). It should NOT be stored in the refrigerator or freezer. 24 months expiry period for the drug product and ———retest period for the drug substance have been requested, and are supported by the submitted data.

C. Basis for Approvability or Not-Approval Recommendation

CMC recommendation: Approval, pending acceptable GMP status (EER pending, last inspection scheduled for Apr 23-24, 2007).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

84 Page(s) Withheld

✓ § 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/

Eugenia Nashed
3/28/2007 04:02:32 PM
CHEMIST

Blair Fraser
4/4/2007 05:08:26 AM
CHEMIST

NDA 22-051

Fluticasone Furoate Nasal Spray (suspension), 27.5 µg/spray

Glaxo Group Limited d/b/a GlaxoSmithKline

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division I

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-051

2. REVIEW #: 1

3. REVIEW DATE: 20-Dec-2006

4. REVIEWER: Eugenia M. Nashed

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Stamp Date	Assigned Date
Original NDA	28-Jun-2006	29-Jun-2006	13-Jul-2006 (NDA accessible on 13-Jul-2006)
Amendment BZ	05-Oct-2006	05-Oct-2006	05-Oct-2006
Amendment BZ	20-Oct-2006	20-Oct-2006	20-Oct-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Group Limited d/b/a GlaxoSmithKline

Address: One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101

Representative: Munir Abdullah, Director, U.S. Regulatory Affairs

Telephone: (919) 483-9318 Fax: (919) 315-0033

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None at this time
b) Non-Proprietary Name (USAN): Fluticasone Furoate (r-INN, USAN, JAN)
c) Code Name/# (ONDC only): GW685698X
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

PHARMACOL. CATEGORY: Corticosteroid for treatment of the symptoms of seasonal and perennial allergic rhinitis in adults and children aged 2 years and older

11. DOSAGE FORM: Nasal Spray Suspension

12. STRENGTH/POTENCY: 27.5 µg/spray

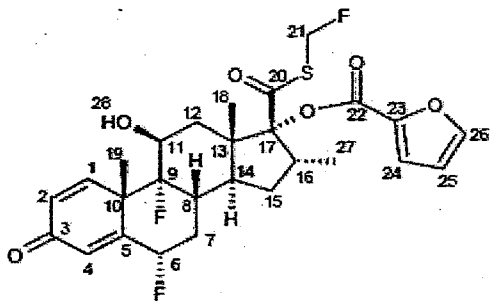
13. ROUTE OF ADMINISTRATION: Intranasal

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:



Molecular Formula: $C_{27}H_{29}F_3O_6S$ Molecular Weight: 538.58 g/mol

6α,9α-Difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]	[redacted]	1	Adequate	11-AUG-2006	
[redacted]	3	[redacted]	[redacted]	1	Adequate	07-AUG-2006	
[redacted]	3	[redacted]	[redacted]	1	Adequate	08-AUG-2006	
[redacted]	3	[redacted]	[redacted]	1	Adequate	09-AUG-2006	
[redacted]	3	[redacted]	[redacted]	3	Adequate	19-DEC-2003	Reviewed for use in nasal spray drug product
[redacted]	3	[redacted]	[redacted]	1	Adequate	11-AUG-2006	

[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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
INDs 48,647 70,297	GSK	Fluticasone Furoate Nasal Spray [redacted] Inhalation Powder	Pending		Referenced for this NDA.
NDAs 19-389 20-121 20-626 20-983 21-077	GSK		Approved		On the market. Referenced for this NDA.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EES	GMP Inspections	Aug 2, 2006	Pending	3 establishments AC, 3 inspections for drug substance manufacturing and stability and sterility testing sites (UK) are pending
Pharm/Tox			Pending	Qualification of impurities in drug substance & dp
Biopharm				
DMETS			Pending	
Methods Validation				Will be initiated, as needed, upon completion of the review
DDMAC	Labeling		Pending	
EA	None			Exception requested
Microbiology	[redacted] ffectiveness	Aug 29, 2006	Completed Oct 25, 2006	Adequate; Review by Bryan Riley, Ph.D.

The Chemistry Review for NDA 22-051

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable (AE) from a CMC perspective.

- Comments forwarded to the applicant in IR letter dated Dec 6, and Dec 20, 2006, need to be adequately addressed prior to the approval of the application.
- The EER for this NDA is currently pending. AC status is currently available for four establishments, and inspection is assigned for two sites in UK. An acceptable GMP status will be needed for all manufacturing and testing facilities before the approval.

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

The applicant has submitted a summary of the "Regulatory Agreement" proposed for future post-approval changes in the section 3.2.R.4 (not present in the Table of Contents, and included in the Regional Information, after the Executed Batch Records and Statisticians Package). Since the validation of the manufacturing process is not completed yet and the regulatory pathway for a review and approval of such agreement is not completed yet, the applicant will be reminded to follow the existing regulations and guidance until the complete set of data supporting the requested "regulatory relief" is submitted, reviewed and approved.

II. Summary of Chemistry Assessments

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

The drug substance, fluticasone furoate is a new ester form of fluticasone. Fluticasone propionate has been approved as the drug substance in Flonase® and also in the recently approved generic version, Fluticasone Propionate Nasal Spray (Roxane Labs).
The applicant has developed an aqueous nasal spray suspension of fluticasone furoate delivered *via* novel side-actuated device as a once-daily treatment for the symptoms of allergic rhinitis. The initial IND was submitted on Oct 30, 2003, EOP2 meeting was held on Jul 19, 2004, and p-NDA CMC meeting on Jan 20, 2006.

Drug substance

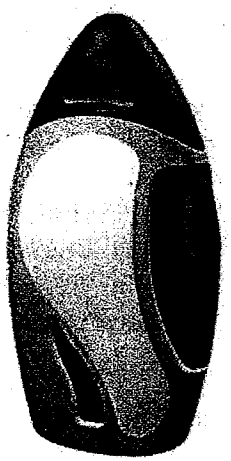
The drug substance, fluticasone furoate (GW685698X), is a white solid and possesses [redacted] The specific

The drug substance is practically insoluble in water ( ) and has no or centers. It is slightly soluble in),) and). Non-micronised and micronised fluticasone furoate are non-hygroscopic and typically

The drug substance is manufactured by Glaxo Wellcome in Jurong, Singapore, and micronised in the United Kingdom.

Drug Product

The drug product consists of a white suspension contained in an amber glass bottle, fitted with a metering (50 µL) spray pump. The bottle and pump are incorporated in an off white plastic device with a view window and dark blue side-actuated lever and dark blue detachable cap covering the applicator tip.



Each spray of the suspension delivers 27.5 µg of micronised fluticasone furoate as an ex-device dose. The fill weight of 10.0 g delivers at the minimum 120 sprays after priming (commercial pack), and the fill weight of

The drug product contains mg of fluticasone furoate, mg of anhydrous dextrose), mg of microcrystalline cellulose with carboxymethylcellulose sodium , mg of polysorbate 80 (, mg of % solution of benzalkonium chloride), mg edetate disodium , and mg of purified water per It has a pH between nd

Manufacture, packaging and testing are carried by Glaxo (Glaxo Wellcome) at Barnard Castle in the United Kingdom. In addition, stability testing may be carried by GSK at Ware, UK, and the stability testing for antimicrobial effectiveness testing is performed at the , and the

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

The drug product, Fluticasone furoate Nasal Spray suspension, 27.5 mg, is intended for use as a nasal spray for the symptoms of allergic rhinitis (SAR and PAR). The proposed dosage is up to 110 µg given as 2 sprays in each nostril once-daily, for adults and children 2 years and older.

The drug product is recommended for storage in the upright position with the cap in place between 15° and 30 °C (59° and 86°C). It should not be stored in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

Based on the extensive information and data provided in this submission, the application is considered approvable, from a CMC perspective. The approval will be recommended when the applicant addresses adequately all deficiency comments outlined in IR letters dated Dec 6, and Dec 20, 2006. Also, an acceptable (AC) GMP status is required for all manufacturing and testing facilities supporting this application, before the approval. The EER for this NDA is currently pending. As of Dec 20, 2006, an AC status is available for 4 establishments, and two contract drug product testing facilities in UK have inspections scheduled.

See below, a summary of the more important CMC deficiencies remaining to be addressed by the applicant.

- **Clarification of the requested "regulatory relief".**

The applicant included a plethora of requests for "regulatory relief" based on the PAT, PTIT and QbD approaches. The information are scattered throughout the application and some of them are summarized in the Regional Information section m2.3.R of the application, after Executed Batch Records and the Statistical package, as a "Regulatory Agreement", section m2.3.R.4. The applicant needs to provide a concise tabular list of the requested regulatory relief in the QOS section of the application. Also, the applicant will be reminded to follow the existing regulations and guidance until the complete set of data supporting the requested "regulatory relief" is submitted, reviewed and approved upon the completion of the regulatory pathway development for a review and approval of such agreement.

- **Inadequate Controls for Drug Substance.**

The drug substance specifications need to be revised to include adequate controls for the composition/solvates and crystal form of drug substance. Also, the mass imbalance for the drug substance content and impurities have to be corrected, and specifications for impurities need to be revised accordingly. Acceptance criteria for several individual impurities exceed the ICH qualification threshold and evaluation by the PharmTox team is pending.

- **Inadequate Controls for Drug Product.**

The drug product specifications lack controls for the particle size distribution of drug substance within the drug product suspension. This parameter was listed as critical by the applicant. Also, target values for the drug product performance parameters (spray content uniformity, spray weight, droplet size distribution, etc) are missing from the specifications table. A consult to the Stat team to evaluate the alternative PTIT approach for the dose performance parameters is pending.

- **Revision of the requested expiry period or submission of additional data.**

24 months expiry period for the product and ——— retest period for the drug substance were requested. Only – month label-storage conditions stability data were submitted for drug substance manufactured with different manufacturing process (———) and drug product (amendment dated Oct 5, 2006) manufactured from that drug substance. The drug substance stability batches were manufactured in Oct 2004 and product stability batches were manufactured in Nov and Dec 2004, so additional stability data should be available and should be provided to support the requested expiry. Also, bridging data for current manufacturing process ——— should be submitted for comparison. Stability Protocols need to be corrected and resubmitted.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

103 Page(s) Withheld

✓ § 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/

Eugenia Nashed
12/20/2006 12:20:03 PM
CHEMIST

Blair Fraser
12/20/2006 12:37:30 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 22-051
Applicant: Glaxo Group Limited (Glaxo Smith Kline), Philadelphia, PA.
Stamp Date: 29-Jun-2006
PDUFA Date: 29-Apr-2007
Proposed Proprietary Name: Fluticasone Furoate Nasal Spray (FFNS for the rest of this IQA)
Established Name: Fluticasone Furoate
Dosage form and strength: Nasal Spray, suspension (27.5 mcg/ spray).
Route of Administration: Nasal
Indications: Once daily treatment for the relief of the symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and above.

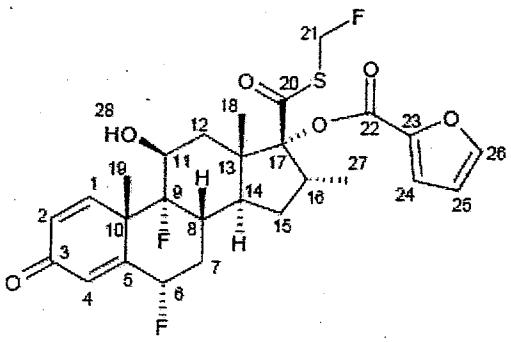
PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review team recommendation: Primary reviewer: Eugenia Nashed, Ph.D. Assistance with DMF Review: Craig M Bertha Ph.D. Possible consult to Mfg. Science Group upon discussion with Branch Chief-Dr. Blair Fraser)

Time goals:
Initial Quality Assessment in DFS: by 15-Aug-2006 (NDA accessible on 13-July-2006)
Chemistry filing memo in DFS: by 22-Aug-2006
Filing decision "Day 45": 22-Aug-2006 (tentative; to be set by Clinical Division)
Filing review issues "Day 74": 11-Sept-2006 (tentative; to be set by Clinical Division)
Chemistry Review (DR/IR) letter: by 29-Nov-2006
Mid-cycle meeting "Month 5": 28-Nov-2006 (tentative; to be set by Clinical Division)
Final Chemistry Review "Month 8" in DFS: by 28-Feb-2007
PDUFA: 29-Apr-2007

Related Documents
Pre-NDA CMC Meeting. (Art Shaw was the reviewer). See meeting minutes.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
INDs: 48,647; 70,297
NDAs: 19-389: 20-121: 20-626: 20-983: 21-077
DMFs:



Molecular Formula: C27H29F3O6S Molecular weight : 538.58

CONSULTS/ CMC RELATED REVIEWS	COMMENT
ClinPharm	To be determined by Primary Reviewer
CDRH	*Not Applicable*
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 8-Aug-2006
DMETS	*Labeling consult request will be sent as part of DPAP's request.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	*To be filed by the PM to Jim McVey.* Results of Antimicrobial Effectiveness Testing are included in m3.2.P.2 Pharmaceutical Development, Section 3 and Section 5.
Pharm/Tox	*PT Consult for Impurities, Leachables and Foreign particulates to be sent out.*
Biometrics	*Evaluation of PTIT approach for Spray Weight Uniformity, Spray Content Uniformity, and Droplet Size Distribution*

Summary:

- This is a standard (10 months) electronic NDA in CTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary for drug substance (44 pages) and for drug product (115 pages). This NDA is filed as a 505(b) application. Note that fluticasone propionate is already approved as the drug substance in Flonase® and the recently approved generic version Fluticasone Propionate Nasal Spray (Roxane Labs).
- Note that this drug development has a long history with several meetings with the Agency (EOP2 in 19-Jul-2004, Pre-NDA meeting 20-Jan-2006).

- [redacted]

Drug Substance

- Fluticasone Furoate is a white solid. See structure of the drug substance on page 1. It is

- [redacted]

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?		X	A graphical analysis of the updated stability data is needed.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?		X	Request these in the 74 day letter
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		In drug product QOS.
14	Is there a Methods Validation package?	X		3.2.r.2.-us-mvp.pdf
15	Is a separate microbiological section included?		X	Microbial limits have not been proposed. A micro consult needs to be submitted.

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

/s/

Prasad Peri
8/15/2006 02:34:00 PM
CHEMIST
ONDQA Initial Quality Assessment

Blair Fraser
8/15/2006 03:00:46 PM
CHEMIST