CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

PATENT INFORMATION
PURSUANT TO 21 C.F.R. 314.53
FOR
NDA# 21-454

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Testim™ (Proposed for AA2500 gel)
- Active Ingredient: Testosterone
- Strength: 1%
- Dosage From: Topical Gel
- Approval Date: N/A

A. Patent Information

- U.S. Patent Number: 5,023,252

- Expiration Date: June 11, 2008

- Type of Patent:

1.	Drug Substance (Active Ingredient)	____Y	X_N
2.	Drug Product (Composition/Formulation)	X___Y	___N
3.	Method of Use	X___Y	___N

The compound that is the subject of this application consists of a topical hydro-alcoholic gel containing testosterone in a therapeutic amount, a pentadecalatone, alcohol and water. This compound is covered by claims of the above-referenced U.S. Patent Number, which claims define compositions, including a pentadecalatone, and methods for the administration of drugs using that composition.

- Name of Patent Owner: Bentley Pharmaceuticals Inc.

PATENT CERTIFICATION
PURSUANT TO 21 C.F.R. 314.53
FOR
NDA# 21-454

Auxilium A², Inc. ("Auxilium") hereby declares that United States Patent Number 5,023,252 covers the composition, formulation and/or method of use of Testim™ (proposed for AA2500 gel). This product is the subject of this application for which approval is being sought.

Auxilium hereby certifies that the above mentioned patent is owned by Bentley Pharmaceuticals Inc. ("Bentley") and that it has been granted a patent license by Bentley. Bentley consents to an immediate effective date upon approval of this application. (See Bentley Certification and Consent attached hereto.)

In the opinion and to the best knowledge of Auxilium there are no unexpired patents that claim the listed drug or any other drugs on which investigations that were relied upon in this application were conducted or that claim a use of the listed drug or such other drugs.

Auxilium A², Inc.
160 W. Germantown Pike
Suite D-5
Norristown, PA 19401

By: Geraldine A. Henwood
Geraldine A. Henwood
President & CEO

APPEARS THIS WAY
ON ORIGINAL

BENTLEY PHARMACEUTICALS, INC. CERTIFICATION AND CONSENT
RE: UNITED STATES PATENT NUMBER 5,023,252
FOR NDA# 21,454

Bentley Pharmaceuticals, Inc.("Bentley") is the owner of United States Patent Number 5,023,252 which covers the composition, formulation and/or method of use of TESTIM™ (proposed for AA2500 gel), the product that is the subject of NDA# 21,454 (the "Application").

Bentley has granted a license to Auxilium A², Inc. with respect to said patent pursuant to that certain License Agreement between the parties dated May 31, 2000. Bentley hereby consents to an immediate effective date upon approval of the Application.

Bentley Pharmaceuticals, Inc.

By: James R. Murphy
James R. Murphy
Chairman & CEO
December 4, 2001

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-454

Trade Name Testim 1% **Generic Name testosterone gel**

Applicant Name Auxilium Pharmaceuticals, Inc. **HFD- 580**

Approval Date October 31, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_x_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_x__/ NO /___/

If yes, NDA # 21-015 Drug Name Androgel

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-015

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__x_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x__/

If yes, explain:

APPEARS THIS WAY ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # AUX-TG-201-02

Investigation #2, Study # AUX-TG-207-01

Investigation #3, Study # AUX-TG-206-00

Investigation #4, Study # AUX-TG-209-00

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_x__/

Investigation #2 YES /___/ NO /_x__/

Investigation #3 YES /___/ NO /_x_/

Investigation #4 YES /___/ NO /_x_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: N/A

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x__/

Investigation #2 YES /___/ NO /_x_/

Investigation #3 YES /___/ NO /_x__/

Investigation #4 YES /___/ NO /_x__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on: N/A

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # AUX-TG-201-02

Investigation #_2_, Study # AUX-TG-207-01

Investigation #_3_, Study # AUX-TG-206.00

Investigation # 4, Study # AUX-TG-209-00

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or

sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1, #2, #3, #4

IND # 61307 YES /_x_/ NO /___/ Explain:

Investigation #2

IND # ___ YES /_ __/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /__x_/ Explain _____

Investigation #2

YES /___/ Explain _____	NO /_x__/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x__/

If yes, explain: _____

_____

_____

Eufrecina DeGuia
Preparer
Title: Regulatory Health Project Manager

10/31/02
Date

Daniel Shames M.D.
Division Director

Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD-580/Division File
HFD-580/EdeGuia, MKober
HFD-093/Mary Ann Holovac

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Daniel A. Shames
10/31/02 01:25:41 PM

APPEARS THIS WAY
ON ORIGINAL

Auxilium A², Inc.
160 W. Germantown Pike
Suite D-5
Norristown, PA 19401
P 610-239-8850
F 610-239-8853

Debarment Certification

NDA 21-454

Auxilium A^2, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: Diane P. Ryers

Title: Director, Regulatory Affairs

Date: 21 December 2001

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-454 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: December 31, 2001 Action Date: October 31, 2002

HFD 580 Trade and generic names/dosage form: Testim™ 1% (testosterone gel)

Applicant: Auxilium Pharmaceuticals, Inc. Therapeutic Class: 3S

Indication(s) previously approved: testosterone replacement therapy

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _____

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☑ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

APPEARS THIS WAY ON ORIGINAL

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed or those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

f studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ɔction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Eufrecina deGuia
10/31/02 02:07:27 PM

APPEARS THIS WAY
ON ORIGINAL

Request for Waiver of Requirements for Pediatric Assessment for AA2500 Testim™

Background

Auxilium requests a full waiver from requirements to test AA2500 (Testim ™), a 1% testosterone gel formulation in a pediatric population. There are a number of reasons for this request. These reasons include:

- Testosterone has no therapeutic indication in neonates, infants and children;
- Testosterone would be unsafe to use in neonates, infants and children;
- There is an extremely small population of pediatric patients in need of testosterone therapy for primary hypogonadism;
- This formulation of testosterone offers no therapeutic benefit over currently available therapy, and
- The necessary studies required to establish dosage and safety recommendations for pediatric patients are not possible because of the small number of pediatric patients affected with conditions requiring testosterone therapy.

Rationale for Adult Use

AA2500 (Testim™) 1% testosterone gel has been submitted with a proposed indication for — The intent is for the supplement to provide exogenous testosterone in individuals who no longer produce adequate endogenous testosterone, and that application of drug occur on a daily basis.

Pediatric Role of Testosterone/ Rationale for Not Studying AA2500

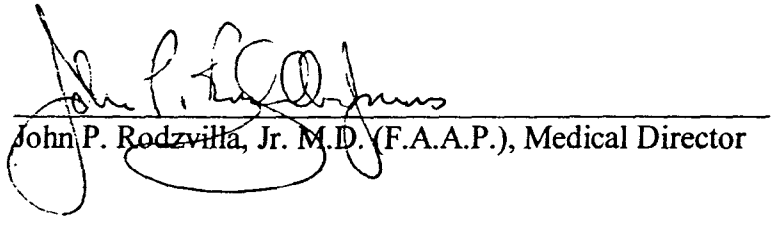
Testosterone is needed in utero to establish a male phenotype. After birth testosterone is dormant until the time of puberty at which time endogenous testosterone increases to produce the secondary male sex characteristics. Therefore, at the present time there is no therapeutic use for testosterone in the neonate, infant or child. Furthermore, the use of testosterone in these age groups would be unsafe. The administration of testosterone to the prepubertal child would initiate precocious puberty, a disease state. It would cause masculization of females and premature closure of epiphyses in both males and females resulting in extremely short stature. Therefore, there is no rationale for testing of Testim™ in neonates, infants or children.

development of and maintenance of the male secondary sex characteristics in males over twelve years of age. It would be used for the very small number of patients with primary hypogonadism. In this age group the pediatric recommended standard of care is the administration of a long acting depot testosterone preparation.[1,2] Since it is well known that there is minimal compliance at this age, the use of a daily-administered gel would offer a significant disadvantage to patients in this age group. Furthermore, the life style of most teenagers would contraindicate the use of a gel that could be transferred by contact in sports or otherwise to others providing a risk in this age group, particularly to females of childbearing age. The use of a transdermal gel in these individuals would offer no advantages over the currently available products and in fact the use of transdermal testosterone, which needs daily application, would offer disadvantages.

Furthermore, Auxilium requests a waiver from testing in this age group on the basis that the number of patients suffering from a condition that would need Testim™ therapy in this age group would be extremely small. The numbers would preclude proper testing in this age group and it would be practically impossible to gather a patient population to adequately study and gather data to provide recommendations for optimal dosage levels and safety.

For all of the aforementioned reasons the packet insert of Testim™ states that the product [redacted] This is to protect the pediatric population from the dangers of testosterone and to bar the use of the product in age groups in which it was not possible to adequately test dosage and safety and compliance impact.

Prepared by:



John P. Rodzvilla, Jr. M.D. (F.A.A.P.), Medical Director

REFERENCES

1. DiGeorge AM. Disorders of the Gonads. In: Behrman RE, Kliegman RM, Arvin AM, editors. Nelson Textbook of Pediatrics, 15th ed. Philadelphia, Saunders, 1996: 1628-34.
2. Griffin JE, Wilson JD. Disorders of the Testes. In: Braunwald, E, Fauci, AS et al, editors. Harrison's Principles of Internal Medicine, 15th ed. New York, McGraw-Hill, 2001: 2143-53.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 31, 2002

To: Diane Myers Director, Regulatory Affairs and Quality Assurance	**From:** Freshnie DeGuia Regulatory Project Manager
Company: Auxilium Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 610-239-8853	**Fax number:** (301) 827-4267
Phone number: 610-239-8850	**Phone number:** (301) 827-4260

Subject: NDA 21-454 Testim 1% (testosterone gel) APPROVAL LETTER

Total no. of pages including cover: 26

COMMENT: Please see attached approved Physician Insert and Patient Package Insert

Document to be mailed: (YES) NO

Note: Auxilium Pharmaceuticals confirmed receipt of AP letter. 10/31/02

APPEARS THIS WAY
ON ORIGINAL

NDA 21-454

Medical Team Leader's Memorandum: New NDA

TO: Daniel Shames, M.D., Division Director
Division of Reproductive and Urological Drug Products (HFD-580)

FROM: Mark S. Hirsch, M.D., Medical Team Leader,
Division of Reproductive and Urological Drug Products (HFD-580)

Date NDA submitted: December 31, 2001
Date NDA received: December 31, 2001
Date memo completed: October 30, 2002

Sponsor: Auxilium Pharmaceuticals, Inc
Drug name: Testim™ 1% (testosterone gel)
Strength: 50 mg and 100 mg testosterone
Indication: testosterone replacement therapy

APPEARS THIS WAY
ON ORIGINAL

Recommendation: The purpose of this memo is to provide the Division Director with my recommendation for action on this NDA. I recommend **approval** of the NDA.

Executive summary:
After carefully reviewing the primary reviews of the medical officer, clinical pharmacologist, toxicologist, chemist and statistician, as well as the proposed final draft labeling, I believe that Auxilium Pharmaceuticals has supplied sufficient information to support the safety and efficacy of Testim 1% for the desired indication.

Auxilium submitted results from one large, randomized, placebo and active-controlled, multi-center, Phase 3 trial and results from at least four additional Phase 1 and 2 clinical pharmacology trials.

Clinical
The primary review by the medical officer documents in detail the substance of these trials.

In brief, the single Phase 3 trial randomized over 400 patients to four parallel arms (50 mg Testim, 100 mg Testim, placebo gel, and transdermal patch). At Day 30, a full pharmacokinetic (pK) profile was drawn and an average serum testosterone concentration (Cavg) was calculated. Based on the Cavg, an individual patient on gel could be titrated up or down on Day 60. The controlled study treatment period continued for 90 days.

Efficacy
Results from this trial demonstrate that the majority of Testim patients (approximately 74%) had average serum T concentrations within the normal range on Day 90. When compared to placebo, both doses of Testim were clearly more effective in provided serum T concentrations within the normal range. When compared to patch (which was not titrated to maximal labeled doses), Testim also performed quite well. Efficacy was confirmed by both hormonal parameters (total testosterone, free testosterone, and dihydrotestosterone) and by clinical parameters (sexual function questionnaire, body composition by DEXA scan, mood questionnaire, and bone mineral density). Results from the clinical parameters lend support to the hormonal assessments.

Safety
For *safety*, the Phase 3 results were notable for the low incidences of any adverse event report. The only event terms of note include a very low incidence of application site reaction (approximately 3-4%), gynecomastia (1%), mood swings (15), increased hematocrit or hemoglobin (1-2%), and changes in blood pressure (15). There were few discontinuations due to adverse events and only two (mood swings and hypertension) were considered even possibly related to drug. There were no serious adverse events attributed to drug.

The open-label safety extension of this trial, in which at least 140 patients have received at least 6 months of Testim indicate no additional safety concerns. In sum, the use of Testim by hypogonadal men appears safe. I believe that the proposed labeling actually enhances safe use by encouraging monitoring of serum T levels, hematocrit, and serum cholesterol, by assessing geriatric patients for the presence of prostate cancer and BPH symptoms prior to use, and by giving important advise about the potential for transfer.

Specifically regarding the potential for transfer, the sponsor conducted two trials trials (-206 and –209). These trials confirmed the expected potential for transfer when partners rub vigorously and for fifteen minutes against the applications sites in men. This transfer was markedly reduced at the abdomen site when a shirt covered the application site and was effectively prevented at the arm and shoulder site when a shirt was worn. The review team paid particular attention to the detailed results of these two trials. In addition, the sponsor provided results from a hand-washing trial that demonstrated that thorough washing of the hands with plain bar soap and water was effective in removing Testim from the skin. Based on all these results, the Division and sponsor were successful in drawing up product labeling that was considered optimal for safe use of the product.

In related matters, review of *financial disclosure* materials indicated compliance with all regulations. No clinical site inspections were conducted as per current guidelines of the Division of Scientific Investigation (*DSI*). Request for waiver for *pediatric* requirements was granted based upon the Division's judgement that actual testosterone "replacement" is rarely indicated in children and that use of transdermal testosterone gel for a novel pediatric indication (e.g. to induce puberty) should be conducted under an IND in the appropriate Division.

In terms of the review disciplines other than medical, there were no outstanding issues, as follows:

Clinical pharmacology and Biopharmaceutics
The clinical pharmacology team found the application "acceptable". They assisted in labeling discussions and agreed to final draft labeling. They point out that an intermediate dosage strength is not yet available, but that such a dose is not absolutely necessary for approval.

Pharmacology/toxicology
The toxicologist recommended "approval". Of note, the excipient, pentanedecalactone was also considered safe based on the preclinical information submitted in the NDA.

Biometrics
The biometrics consultant concluded that the study "demonstrates efficacy of Testim as testosterone replacement therapy". There were some minor concerns regarding [redacted]. These were all resolved through successful and cordial negotiation with the sponsor.

Chemistry
The chemistry team also agreed that the product "may be approved". The issues of note included approval of a —→ expiry and final acceptance by the sponsor of both a [redacted] acceptance criterion for the dissolution specification and the exact dissolution method. The maunfacturing sites were found acceptable by Office of Compliance. The microbioloist's recommendation was to approve.

Division of Drug Marketing, Advertising and Communications
Comments provided by Division of Drug Marketing, Advertising, and Communications (DDMAC) regarding the proposed package insert were acknowledged and all issues were resolved through effective labeling negotiations.

Office of Drug Safety
Division of Surveillance, Research, and Communication Support
Comments from the Division of Surveillance, Research, and Communication Support (*DSRCS*) of the Office of Drug Safety (ODS) regarding the proposed patient package insert (PPI) were acknowledged. Most of the recommendations from ODS were instituted, though not all. Time did not allow for full re-formatting of the PPI although the substance and spirit of the document was not affected. In addition, the ODS recommendation to state that ' [redacted] was not instituted. The PPI was amended, however, to inform patients that they should not give their Testim to anyone else and should keep it in a safe location.

Division of Medication Errors and Technical Support
Comments from the Division of Medication Errors and Technical Support (*DMETS*) of ODS were also acknowledged. DMETS had no objection to the tradename, Testim. In addition, container and carton labeling comments made by DMETS were acknowledged and were instituted as deemed appropriate by the clinical review team and the chemists.

Summary statement:
My review of the primary reviews and of the entire contents of the action package reveals no outstanding issues. Approval is recommended.

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/s/

Mark S. Hirsch
10/31/02 11:20:28 AM
MEDICAL OFFICER

Daniel A. Shames
10/31/02 12:26:57 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 30, 2002

APPLICATION NUMBER: NDA 21-454, Testim 1% (testosterone gel)

BETWEEN:

Name: Terri Sebree, Senior Vice President, Development
Romeo Bachand, M.D., Ph.D., Director, Regulatory Affairs and Quality Assurance
Ted Smith, Senior, Vice President, Development
Diane Myers, Director, Regulatory Affairs and Quality Assurance
Phone: 610-239-8850
Representing: Auxilium Pharmaceuticals

AND

Name: Eufrecina DeGuia, Regulatory Health Project Manager
Mark Hirsch, M.D., Medical Team Leader
Daniel Davis, M.D., Medical Reviewer
Ameeta Parekh, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics
Dhruba Chatterjee, Ph.D., Biopharmaceutics Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Further discussions of FDA's labeling comments.

Dr. Hirsch acknowledged receipt of the sponsor's response to the second round of labeling comments from the Division. He also noted that the process is going well and that both the Division and the sponsor have focused on few issues that still require resolution and will be discussed today:

1. [redacted]. Dr. Hirsch, however, agreed that the sponsor's Phase 3 trial is a good study for testosterone replacement but not compelling enough for [redacted]

2. [redacted]
The Division does not agree to the proposed addition of this statement to the Clinical Pharmacology, Pharmacokinetics Section, under [redacted]

•

FDA's position not to include the above statement is acceptable to the sponsor.

3. Potential effect of showering on Testim.
   Auxilium accepted FDA's recommending labeling in the **Dosage and Administration Section.**

(Please see appended electronic signature page)
Mark Hirsch, M.D.
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

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/s/

Eufrecina deGuia
10/31/02 12:11:19 PM
CSO

Please sign off for Dr. Hirsch.

Daniel A. Shames
10/31/02 12:50:34 PM
MEDICAL OFFICER

Meeting Minutes

Date: October 29, 2002 **Time**: 9:00 – 9:30PM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim 1% (testosterone gel)

Indication: testosterone replacemen

Sponsor: Auxilium Pharmaceuticals, Inc

Type of Meeting: Information request

Meeting Chair: Moo-Jhong Rhee, Ph.D

Meeting Recorder: Rajiv Agarwal, Ph.D

FDA Attendees:

Rajiv Agarwal, Ph.D, CMC reviewer
Moo-Jhong Rhee, Ph.D, Chemistry Team Leader

Auxilium attendee:

Ms. Diane Myers
(610-292-2004)

Meeting Objectives:

- To discuss the 21 months of expiry date. Applicant is requesting a ——— of expiry date.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult males

Discussion: *Originally, applicant submitted — (at long term storage conditions) and — (at accelerated storage conditions) of the stability data on the drug product. Long term stability data was further updated via two amendments dated 07-JUL-2002 and 29-AUG-2002 with a total of 21 months of stability characteristics of the drug product packaged in aluminum tube. Based on the analysis of the stability data of the degradation products, it is deemed that 21 months of the expiry date will be appropriate.*

The User Fee goal date is October 31, 2002.

Decisions Reached:

- Applicant has accepted the proposed expiry date (21 months) of the drug product packaged in aluminum tube and is committing to update the NDA with the amendment by 29-OCT-2002.

(Please see attached electronic signature page)

Signature, minutes preparer

Concurrence, Chair

cc:
NDA Arch:
HFD-580/Division File

APPEARS THIS WAY
ON ORIGINAL

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/s/

Rajiv Agarwal
10/30/02 12:27:34 PM
CHEMIST

Moo-Jhong Rhee
10/30/02 02:14:03 PM
CHEMIST
I concur

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 28, 2002

APPLICATION NUMBER: NDA 21-454, Testim 1% (testosterone gel)

BETWEEN:

Name: Terri Sebree, Senior Vice President, Development
Romeo Bachand, M.D., Ph.D., Director, Regulatory Affairs and Quality Assurance
Ted Smith, Senior, Vice President, Development
Diane Myers, Director, Regulatory Affairs and Quality Assurance
Phone: 610-239-8850
Representing: Auxilium Pharmaceuticals

AND

Name: Eufrecina DeGuia, Regulatory Health Project Manager
Mark Hirsch, M.D., Medical Team Leader
Daniel Davis, M.D., Medical Reviewer
Ameeta Parekh, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics
Dhruba Chatterjee, Ph.D., Biopharmaceutics Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Information Request
Dr. Hirsch acknowledged receipt of the Washing Data faxed to the Division on October 26, 2002. The following issues were clarified:

1. Positive Control: The control was a swab of hands to which Testim had been applied and not washed off.

2. Drug remained on both hands for at least 2-3 minutes prior to washing.

3. Washing was performed with regular bar soap for approximately 2-3 minutes.

4. No blood levels were obtained.

5. The swab itself was a dry, porous swab standardized for this purpose.

Dr. Hirsch acknowledged the data and agreed that it was now possible to draft a package insert that allowed safe use of the product. Dr. Hirsch also committed to sending the Division's proposed labeling to sponsor today.

(Please see appended electronic signature page)
Mark Hirsch, M.D.
Medical Team Leader

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/s/

Eufrecina deGuia
10/30/02 04:55:25 PM
CSO

Mark S. Hirsch
10/31/02 11:15:28 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECONFERENCE MINUTES

Date:	October 25, 2002
Time:	10:30 - 11:00 PM
Location:	5600 Fishers Lane - Rockville, MD 20857 Room 17B-433
NDA:	21-454
Drug:	Testim (testosterone 1% gel)
Type of Teleconference:	Information Request
External participant:	Auxilium
Internal participant lead:	Mark Hirsch
External participant lead:	Diane Myers
Meeting Recorder:	Margie Kober

FDA Participants:
Mark Hirsch, M.D., Clinical Team Leader, Division of Reproductive and Urologic Drug Products(DRUDP, HFD-580)
Daniel Davis, M.D., Medical Officer, DRUDP
Ameeta Parekh, Ph.D., Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP
Dhruba J. Chatterjee, Ph.D., Biopharmaceutics Reviewer, OCPB @ DRUDP
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP

External Participants:
Diane Myers
Romeo Bhashan
Ted Smith
Terri Sebree

Meeting Objective:
To discuss issues raised during the review of Testim and discussed with sponsor on October 22, 2002.

APPEARS THIS WAY
ON ORIGINAL

Discussion Points:
The Division accepts the sponsor's re-analysis of the data from studies 206 and 209 and agrees that clothing prevents transfer of Testim.

The Division still does not accept that washing completely removes Testim from the skin surface. The data from study 207 does not answer this question in full. The data from equipment cleaning also does not answer this question. Submission of additional data is invited.

Action Items:
Auxilium will provide additional data regarding drug residual on skin after washing.
Auxilium will provide laboratory normal values for testosterone levels in pre-menopausal women.
A teleconference will take place on Monday, October 28, 2002, to discuss additional data.

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/s/

Margaret Kober
10/31/02 11:17:09 AM
CSO
Chief, Project Management Staff

Mark S. Hirsch
10/31/02 11:23:29 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 25, 2002

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Eufrecina DeGuia, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Testim™ 1% (testosterone gel), NDA 21-454

The patient labeling which follows represents the revised risk communication materials DSRCS Review of Patient Labeling for Testim™ 1% (testosterone gel), NDA 21-454, and has been reviewed by our office and by DDMAC. We have simplified wording, made it consistent with the PI, removed promotional language and other unnecessary information, and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions.

APPEARS THIS WAY
ON ORIGINAL

4 Draft Labeling Page(s) Withheld

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/s/

Jeanine Best
10/25/02 10:54:38 AM
CSO

Anne Trontell
10/25/02 01:10:57 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 24, 2002

APPLICATION NUMBER: NDA 21-454, Testim 1% (testosterone gel)

BETWEEN:

Name:	Terri Sebree, Senior Vice President, Development Romeo Bachand, M.D., Ph.D., Director, Regulatory Affairs and Quality Assurance Ted Smith, Senior, Vice President, Development Diane Myers, Regulatory Affairs and Quality Assurance
Phone:	610-239-8850
Representing:	Auxilium Pharmaceuticals

AND

Name:	Eufrecina DeGuia, Regulatory Health Project Manager Mark Hirsch, M.D., Medical Team Leader Dhruba Chatterjee, Ph.D., Biopharmaceutics Reviewer Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Deficiencies and Information Request

In an effort to finalize reviews of the NDA, teleconferences were held today and the following issues were discussed:

1. Inadequate information:
   - The Division believes that there is inadequate information to physicians and patients relevant to gel transfer.
   - The Division is concerned that a shirt may not completely block transfer.
   - The Division is concerned that there is not sufficient evidence to conclude that washing effectively removes Testim.
   - The Division acknowledged the sponsor's position that a shirt blocks transfer and was agreeable to review re-analysis of data that the sponsor believes is critical.
2. Handwashing issue:
   - The sponsor was asked to provide an argument in writing that regular handwashing washes off Testim. The sponsor was also encouraged to look at in-vitro data, if any. Auxilium strongly believes that washing off application sites is effective in removing testosterone.
3. Casual contact:
   - The sponsor believes that shirt blocks transfer. The sponsor noted that their Studies 206 and 209 results showed blockage of transfer when drug is administered to the shoulder and a shirt is worn. The sponsor committed to submit re-analysis of these data studies results to support this contention.

(Please see appended electronic signature page)
Mark Hirsch, M.D.
Medical Team Leader

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/s/

Eufrecina deGuia
10/30/02 09:35:02 AM
CSO

Mark S. Hirsch
10/30/02 01:53:56 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 22, 2002

APPLICATION NUMBER: NDA 21-454, Testim 1% (testosterone gel)

BETWEEN:

Name:	Terri Sebree, Senior Vice President, Development Romeo Bachand, M.D., Ph.D., Director, Regulatory Affairs and Quality Assurance Ted Smith, Senior, Vice President, Development Diane Myers, Director, Regulatory Affairs and Quality Assurance Roland Cathrall, M.D.
Phone:	610-239-8850
Representing:	Auxilium Pharmaceuticals

AND

Name:	Eufrecina DeGuia, Regulatory Health Project Manager Mark Hirsch, M.D., Medical Team Leader Daniel Davis, M.D., Medical Reviewer Moo Jhong Rhee, Ph.D., Chemistry Team Leader Rajiv Agarwal, Ph.D. Chemistry Reviewer Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Information Request
The following issues were discussed:

CMC

1. Implementation of Dissolution Test:
   - The sponsor agreed with the dissolution specifications (addition of — timepoint with an acceptance criterion) proposed by the Division and the drug product specifications for in-vitro release testing will be revised accordingly.
   - In addition to the revision to the specification, the in-vitro test method will be revised to specify that — of the drug product is to be used — in the testing apparatus.
   - Measures taken to — t during the test will be described.
   - The sponsor committed to provide the information on how to carry out the whole experiment and an amendment would be submitted by the end of the week.

Clinical

Dr. Hirsch noted that the reviews are now being finalized, however, the following issues came up during review of the labeling:

1. **Transfer Issue:**
   - The Division expressed concern that the drug can be potentially transferred to pregnant women, or women with childbearing potential or to a child after casual , clothed contact with a male patient after application of Testim.
   - The Division's hypothesis is that the drug appears to permeate through clothing since there is an evidence of transfer in all four groups in Studies 206 and 209 even when male patients wore shirts.
   - The sponsor believes that Testim absolutely does not permeate clothing. They hypothesize that it could be due to the vigorousness of the rubbing and that their data shows that shirt wearing is an effective deterrent to transfer.
   - The sponsor proposed to submit more detailed analysis of data from Studies 206 and 209 to substantiate their argument. The Division agreed to receive the re-analysis.
   - Dr. Hirsch asked the sponsor what recommendation should be given to patient if direct contact with a partner is anticipated.
   - The sponsor believes that — would be completely effective and should be recommended. The Division asked for support for this contention.

2. **Washing Issue:**
   - The sponsor believes that washing or showering significantly reduces testosterone levels.

3. **Additional Comments:**
   - Auxilium claims that they have no reports from patients or investigators of masculinization of patient's partner in terms of the occurrence of acne, hirsutism, deepening of voice, etc. despite many couples with over one year of use.

(Please see appended electronic signature page)

Mark Hirsch, M.D.
Medical Team Leader

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/s/

Eufrecina deGuia
10/31/02 12:08:46 PM
CSO

Please sign off for Dr. Hirsch.

Daniel A. Shames
10/31/02 12:30:59 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: October 21, 2002 **Time**: 2:00 – 2:30PM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim 1% (testosterone gel)

Indication: testosterone replacement

Sponsor: Auxilium Pharmaceuticals, Inc

Type of Meeting: Information request

Meeting Chair: Moo-Jhong Rhee, Ph.D

Meeting Recorder: Rajiv Agarwal, Ph.D

FDA Attendees:

APPEARS THIS WAY
ON ORIGINAL

Rajiv Agarwal, Ph.D, CMC reviewer
Moo-Jhong Rhee, Ph.D, Chemistry Team Leader

Auxilium attendee:

Ms. Diane Myers
(610-292-2004)

Meeting Objectives:

- To discuss the addition of an acceptance criterion in in-vitro release specifications at point.
- To understand the methodology of sample preparation in the in-vitro release testing.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult males

Discussion: *Applicant did not provide information on the amount of gel used for in in-vitro release study. If applicant did not use a , then applicant will be asked to modify the method to use l to avoid experimental error in measuring the alcoholic gel. Furthermore, an acceptance criterion of release rate at in addition to will be recommended to further control the quality of the product*

The User Fee goal date is October 31, 2002.

APPEARS THIS WAY
ON ORIGINAL

Decisions Reached:

- Applicant will call on October 22, 2002 to concur the proposed acceptance criterion of in vitro release at — time point.
- Applicant will inform the Division about the method of sample preparation in in-vitro testing of the gel drug product.

(Please see attached electronic signature page)

Signature, minutes preparer

Concurrence, Chair

cc:
NDA Arch:
HFD-580/Division File

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ON ORIGINAL

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/s/

Rajiv Agarwal
10/24/02 02:03:54 PM
CHEMIST

Moo-Jhong Rhee
10/24/02 02:16:33 PM
CHEMIST
I concur

Meeting Minutes

Date: October 15, 2002 **Time**: 1:00 – 2:00 PM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim 1% (testosterone gel)

Indication: testosterone replacement —

Sponsor: Auxilium A^2

Type of Meeting: Status Meeting (9.5-month)

Meeting Chair: Dr. Mark Hirsch

APPEARS THIS WAY
ON ORIGINAL

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Moo Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Mike Welch, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Krishan Raheja, D.V.M. – Pharmacology Reviewer, DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the review of this pending application.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult males —

The User Fee goal date is October 31, 2002.

Decisions Reached:

Clinical
- The Team Leader is approximately halfway through editing the primary review
- there is nothing noted so far that should preclude approval
- issues such as — will be removed from the label

Statistics
- review is completed and draft memo sent to the Medical Officer

- [redacted] for secondary endpoints should be reduced
- [redacted] should not be in the label

Chemistry

- review is completed pending confirmation of dissolution specifications from the Biopharm team, not yet in DFS
- **Description** and **How Supplied** sections of the package insert have been revised

Pharmacology and Toxicology

- review is done and it's been entered in DFS

Clinical Pharmacology and Biopharmaceutics

- Team Leader has just finished editing final review and it will be finalized after the OCPB briefing next week
- studies should be done for the release specifications
- there is no 75 mg dose to allow for intermediate dose titration
- the product looks efficacious, many patients will probably require 100 mg strength
- DHT results are acceptable
- references to [redacted] should be removed
- showering study provided important information
- the potential for transfer is significant

Action Items:

- Dr. Hirsch will finish review of the labeling revisions made by the team

(Please see attached electronic signature page)
Mark Hirsch, M.D.
Concurrence, Chair

cc:
NDA Arch:
HFD-580/Division File
HFD-580/
Concurrences:Chatterjee,Rhee,Welch,Agarwal, Hirsch102902

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/s/

Mark S. Hirsch
10/30/02 01:27:53 PM

APPEARS THIS WAY
ON ORIGINAL

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Meeting Minutes

Date: September 17, 2002 **Time**: 3:00 – 4:00 PM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim 1% (testosterone gel)

Indication: testosterone replacement

Sponsor: Auxilium A^2

Type of Meeting: Status Meeting (9-month)

Meeting Chair: Dr. Mark Hirsch

Meeting Recorder: Ms. Eufrecina DeGuia

APPEARS THIS WAY
ON ORIGINAL

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Moo Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Mike Welch, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Krishan Raheja, D.V>M. – Pharmacology Reviewer, DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the review of this pending application.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult males.

The User Fee goal date is October 31, 2002.

Decisions Reached:

Clinical
- draft review completed and given to the Medical Officer today
- the Medical Reviewer noted that there are no efficacy nor safety issues
- extensive revisions will be done to the label; decision will be made whether the Division allows
- Medical Officer acknowledged lack of an "intermediate" dosage strength
- Medical Officer states he has done extensive changes to label already but is not yet finished
- Financial Disclosure data reviewed and no notable findings

Statistics

- memo not yet written
- [redacted]

- [redacted]

Chemistry

- review is completed pending concurrence by the Team Leader
- the sponsor requested [redacted] of expiry date, but will be granted 21 months of expiry date
- microbiology consult is completed and it is satisfactory
- CMC deficiencies have been resolved
- Division of Medication Errors and Technical Support (DMETS) found the name tradename Testim 1% acceptable
- the adequacy of the in vitro release test method and acceptance criterion is pending with OCPB reviewer
- **Description** and **How Supplied** sections of the package insert have been revised
- all revisions to container/carton have been made by sponsor and are acceptable

Pharmacology and Toxicology

- review is completed pending Team Leader sign off
- the reviewer is still undecided whether [redacted] should be included in the label or whether [redacted] should be in the label
- [redacted]
- carcinogenicity testing was not done with lactone and is not considered necessary by the Pharmtox team

Clinical Pharmacology and Biopharmaceutics

- just began written review, although extensive review already done
- there are no significant issues
- spreadsheets of individual patients PK parameters were requested and data expected to arrive this week
- still need to review showering and transfer studies
- reviewer reiterated lack of intermediate dosage strength

Action Items:

- schedule one more meeting in the week of October 10, 2002

(Please see attached electronic signature page)
Mark Hirsch, M.D.
Concurrence, Chair

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/s/

Mark S. Hirsch
10/25/02 01:28:26 PM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: August 19, 2002 **Time**: 2:00 – 3:00 PM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim (testosterone) 1% gel

Indication: testosterone replacement

Sponsor: Auxilium A^2

Type of Meeting: Status Meeting (8-month)

Meeting Chair: Dr. Mark Hirsch

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Moo Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
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Meeting Objectives: To discuss the status of the review of this pending application.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult males

The User Fee goal date is October 31, 2002.

Decisions Reached:

Clinical

- the Medical Reviewer noted that Androderm was not titrated to maximum doses as per the label and this may account for low responder rates for Androderm
- the Medical Officer stated that he had completed the regulatory history and efficacy sections of the review
- there is not a lot of data submitted from the extension trials; only eight months data on some patients
- extensive revisions will be required to the label including deletions of