CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

CHEMISTRY REVIEW(S)

Addendum to CMC review # 1 of NDA 21-454

From: **Rajiv Agarwal, Ph.D, Chemist**
To: **NDA # 21-454**
Date: **31-OCT-2002**
Subject: **Addition of amount of gel to be 5g in container/closure labels.**

The description of amount of gel per tube is not provided on the primary and secondary container/closure system and needs to be revised as follows. However this information was well described in inserts.

From: **Contains 50 mg testosterone per tube**
To: **Contains 50 mg testosterone per 5 g tube.**

A t-con was made on 31-OCT-2002 at 11:15 AM and requested the applicant to revise the container/closure labels as described above. Applicant is committing to revise the container labels as suggested by the Division According to the applicant, the requested changes will be implement during the next round of printing of labels ((see amendment dated 31-OCT-2002)).

Comment: Applicant's request to revise the container labels during the second round of printing is deemed acceptable and now NDA 21-454 may be approved from the chemistry point of view.

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

/s/

Rajiv Agarwal
10/31/02 01:38:09 PM
CHEMIST

Moo-Jhong Rhee
10/31/02 01:43:14 PM
CHEMIST
I concur

NDA 21-454

Testim 1%
Testosterone Gel

Auxilium Pharmaceuticals, Inc.

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-454

2. REVIEW #: 1

3. REVIEW DATE: 30-OCT-2002

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ON ORIGINAL

4. REVIEWER: Rajiv Agarwal, Ph.D

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	31-DEC-2001
Amendment	24-JAN-2002
Amendment	12-FEB-2002
Amendment	28-MAR-2002
Amendment	15-MAY-2002
Amendment	06-JUNE-2002
Amendment	07-JUL-2002
Amendment	30-JUL-2002
Amendment	29-AUG-2002
Amendment	05-SEP-2002
Amendment	24-OCT-2002
Amendment	28-OCT-2002
Amendment	29-OCT-2002
Amendment	29-OCT-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Auxilium Pharmaceuticals, Inc.

Address: 160 W. Germantown Pike, Suite D-5, Norristown, PA 19401

Representative: Ms. Diane P. Myers

Telephone: (610) 239-8850

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Testim 1%
b) Non-Proprietary Name (USAN): Testosterone gel
c) Code Name/# (ONDC only): AA2500
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

APPEARS THIS WAY ON ORIGINAL

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY:

Indicated for testosterone replacement therapy in adult males

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 50 mg per tube (5 g gel)

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

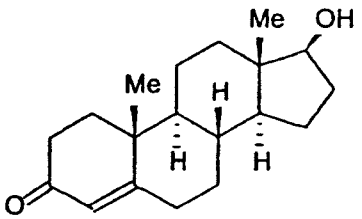
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

Chemical Name: Testosterone

Chemical Structure:



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Molecular weight: 288.42
Molecular formula: $C_{19}H_{28}O_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	/	Testosterone USP	3	Adequate	15-OCT-2002	Reviewed by Dr. Donna Christner for NDA —
—	II	/	Testosterone USP	1	Adequate	19-SEP-2002	Reviewed by Dr. Rajiv Agarwal
—	III	/ /	/	3	Adequate	• — 4-MAR-2002 • / 10-MAY-1995 • / 17-SEP-1999	• Adequate for NDA 17-765, Dr. J.S. Hathaway, HFD 540 • Adequate for ANDA 60-764, Ms. N. Sager HFD-643, no further updates. Adequate, for NDA 17-760, Dr. L.Rodriguez (HFD-550)

[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)

18. STATUS:

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ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	16-APR-2002	
DMETS	Acceptable	29-AUG-2002	Mr. Scott Dallas
Pharm/Tox	Acceptable	24-SEP-2002	Dr. K. Raheja
Biopharm	Acceptable	30-OCT-2002	Dr. D. Chatterjee
Methods Validation	The method validation package will be sent to and validated by FDA laboratories		
Microbiology	Acceptable	31-JUL-2002	Dr. David Hussong

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The Chemistry Review for NDA 21-454

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from the Chemistry, Manufacturing and Control point of view.

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

None

II. Summary of Chemistry Assessments

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

The drug product "Testim 1%" is a hydroalcoholic gel containing 1% (50 mg/5 g gel) of testosterone, a drug substance. Since the drug product contains a very high percentage of alcohol, oxacyclohexadecan-2-one is used to . The acceptance criterion of assay for the is in place and is also a part of release and stability specification. The utilized in the formulation of clinical and primary stability batches is manufactured by out the used in the to-be-marketed product will be manufactured by the shows insignificant amounts of impurities and is better than the manufactured at The use (quality) of manufactured at to-be-used in the future formulations is deemed adequate on the basis of the stability data provided on of the gel drug product.
In order to control the quality of the starting material, specifications of starting materials and results of acceptance testing of needs to be provided. This issue was communicated to the applicant and a satisfactory response was provided.

The drug product is packaged in a closed end, single use aluminum tube, which is deemed appropriate for packaging the gel drug product. Stability data on the drug product also supports the usage of aluminum tube in packaging the drug product.

The quality of the gel product is controlled by various tests: Description , pH, viscosity, testosterone ID, testosterone and oxacyclohexadecan-2-one assay, testosterone and oxacyclohexadecan-2-one related impurities, content uniformity (testosterone and oxacyclohexadecan-2-one) and in-vitro release. All the acceptance criteria are deemed satisfactory except for viscosity, and related impurities from

testosterone and oxacycohexadecan-2-one. The major issues identified in the application is a rather generous levels of impurities, therefore, needs to be revised to reflect the actual manufacturing capability and stability characteristics of the drug product.
Applicant has accepted the Division's recommendation and updated the specifications as suggested.

The system suitability of the analytical methods HPLC and GC was not adequate and, upon request, applicant has provided the information system suitability parameters (capacity factor, resolution and tailing factor) via an amendment. Provided information is deemed adequate.

Initially, the applicant did not provide information on the amount of gel used for — in in-vitro release study. In a t-con dated 22-OCT-2002, applicant states that — . is used to determine the in vitro release. Applicant is asked to modify the method to use — to avoid experimental error in measuring the alcoholic gel. Furthermore, an acceptance criterion of release rate at — is recommended to further control the quality of the product. Via an amendment dated 24-OCT-2002, applicant has provided the commitment to use — in the dissolution study and included the acceptance criteria at — in release specifications as proposed by the Division.

The drug substance is testosterone, USP, and is manufactured — for this formulation by — The Chemistry, Manufacturing and Control information of the drug substance is located in two DMFs — , DMF — and — , DMF — , and deemed adequate to support the NDA. — Applicant was asked to have — in-process tests to demonstrate that — . Relevant information to show that the testosterone — and assay values by HPLC indicates that drug substance is —

Sponsor is requesting a — of shelf life. Based on the available real time stability studies on primary batches, — , of expiry date can be granted. Applicant provided — of additional data on the primary stability batches via an amendment.

Applicant is requesting a 21 months of expiry date, **21 months of expiry date can be granted.**

The final recommendation from the Office of Compliance for all the manufacturing and testing sites is ACCEPTABLE (**see Appendix-1**).

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

Indicated for

C. Basis for Approvability or Not-Approval Recommendation

- Applicant has satisfactorily resolved the outstanding issues delineated in the Information Request Letter dated 12-AUG-2002.
- The final recommendation from the Office of Compliance for all the manufacturing and testing sites is ACCEPTABLE.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Rajiv Agarwal, Ph.D
Moo-Jhong Rhee, Ph.D
Eufrecina De-Guia

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/s/

Rajiv Agarwal
10/30/02 01:52:12 PM
CHEMIST

Moo-Jhong Rhee
10/30/02 02:19:18 PM
CHEMIST
I concur

6 Page(s) Withheld

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21454/000**
Priority: **3S**
Org Code: **580**
Stamp: **31-DEC-2001** Regulatory Due: **31-OCT-2002**
Action Goal:
District Goal: **01-SEP-2002**
Applicant: **AUXILIUM A2 INC**
160 WEST GERMANTOWN PIKE STE
NORRISTOWN, PA 19401
Brand Name: **TESTIN 1% (TESTOSTERONE 1% GEL)**
Established Name:
Generic Name: **TESTOSTERONE 1% GEL**
Dosage Form: **GEL (GEL)**
Strength: **50 MG**

FDA Contacts: **L. STEPHENS (HFD-410) 301-827-3279 , Project Manager**
R. AGARWAL , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-SEP-2002 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 16-APR-2002 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:
AUXILIUM A2 INC
160 W GERMANTOWN PIKE, SUITE I
NORRISTOWN, PA 19401
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-SEP-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date: **22-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-454
Review number: 1
Serial number/date/type of submission: 000/12-31-2001/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Auxilium A^2, Inc. Norristown, PA
Manufacturer for drug substance: ———————————
Manufacturer and commercial packager of AA2500 ———
Reviewer name:Krishan L. raheja, D.V.M., Ph.D.
Division name: Division of Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: 9-19-2002

Drug: Testosterone

Trade name: Testim 1% (testosterone gel)
Generic name (list alphabetically): Testosterone 1%gel
Code name: AA2500
Chemical name: 17-Beta hydroxyandrost-4-en-3-one
CAS registry number: 58-22-0
Mole file number:-
Molecular formula/molecular weight: $C_{19}H_{28}O_2$/288.42
Structure:

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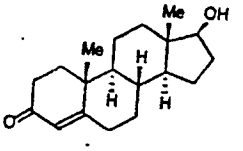

Excipient: Oxacyclohexadecan-2-one (a lactone)

Trade name: —

Chemical and common names: angelica lactone, cyclopentadecanolid, cyclopentadecanolide, exaltex, 15-hydroxypentadecanoic acid, w-lactone, w-pentadecalactone, pentadecanolide, pentalide and thibetolide.

CAS registry No.: 106-02-5
Mole file number:
Molecular formula/molecular weight: $C_{15}H_{28}O_2$/240.39
Structure:

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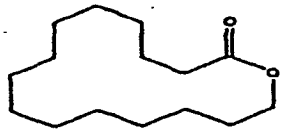

Relevant INDs/NDAs/DMFs: IND 61,307

Drug class: Androgen

Indication: Testim is indicated for testosterone replacement therapy in adult males —.

Clinical formulation: Testim is a clear to translucent topical gel containing 1% testosterone as the active pharmacological ingredient in a single phase solution. The gel has an alcoholic/musk odor. Testim is designed to provide consistent transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin. The composition of dosage form (per 5 g tube) is shown in table 1 below:

Table 1

Component	Amount (g)	% w/w	Function	Reference to standard
Active: testosterone (micronized)	0.05	1.00	Active ingredient	USP
Inactives				
Oxacyclohexadecan-2-one				Validated GC assay; Internal standard
Carbopol				NF
				NF
Propylene glycol				USP
Glycerin				USP
Polyethylene glycol				NF
Alcohol				USP
Tromethamine				USP
Purified water				USP
Total	5.000	100%		

Testim is supplied in unit-dose tubes in cartons of 30 and each tube contains 50 mg testosterone in 5 g of gel

Oxacyclohexadecan-2-one is a non-compendial compound.

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Route of administration: Transdermal, applied on shoulders and/or upper arms

Proposed use: testosterone replacement therapy

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Testosterone is the primary androgen secreted by the testes and is responsible for the development, maturation, and persistence of normal male characteristics.
Dihydrotestosterone is the primary active metabolite and is produced by steroid 5-a-reductase located in non-genital skin, liver, and the urogenital tract of the male and in genital skin of both sexes.
Pharmacology of testosterone is well known.
Testim is recommended to be applied once daily on dry skin of shoulders and/or upper arm at doses of 50-100 mg to achieve proper serum testosterone levels.
In sponsor's Phase III program, it was reported that AA2500 normalized testosterone and dihydrotestosterone levels and resulted in improvement of testosterone deficiency symptoms.

Oxacyclohexdecan-2-one, an excipient is a non-compandial compound that has not been approved previously in any pharmaceutical product. It belongs to a class of substances called lactones.

Safety evaluation: Therapeutically testosterone replacement therapy has been used over many years in a variety of different pharmaceutical preparations. There is extensive published pre-clinical and human experience literature with testosterone to support its safety for the intended use. Sponsor has also conducted 2 local tolerance studies to demonstrate Testim's dermal safety.

Oxacyclohexadecan-2-one has been used previously for fragrance and emollient properties at very low concentrations i.e., around 0.1%. It is reported that its average maximum daily exposure from use as a topical fragrance is 14 mg. Oxacyclohexadecan-2-one is also approved under 21CFR172.515 as a direct food additive in alcoholic and nonalcoholic beverages, baked goods, frozen dairy products, gelatin puddings and soft candy. The estimated human daily intake in these foods is reported to be a maximum of 9.81 mg. It was stated that the most recently published per capita intake is reported as 0.9 ug/kg/day.
Based on an estimated 70 kg male using AA2500, dermal exposure on a mg/kg basis with proposed gel formulation is about [redacted] assuming use of maximum dose of two 5 g tubes of AA2500 (testosterone 100 mg containing oxacyclohexadecan-2-one [redacted]

Oxacyclohexadecan-2-one was initially granted GRAS status by FEMA in 1965 and this status was reaffirmed in 1977 and again in 1998. NTP carcinogenicity studies with y-butyrolactone and 3,4-dihydrocoumarin i.e., compounds structurally related to oxacyclohexdecan-2-one, suggested minimal carcinogenic potential at high doses.

Pentadecalactone (oxacyclohexadecan-2-one), a non-compendial compound has not been approved in any pharmaceutical preparation. While it has been used at low concentrations as fragrance and emollient, in the Testim gel formulation it is proposed to be used at a high concentration. Since no information was available regarding pentadecalactone's genotoxicity and reproductive toxicity, sponsor was asked to conduct a battery of mutagenicity assays and a male fertility study to demonstrate this excipient's safety.

Safety issues relevant to clinical use: none

Other clinically relevant issues: none

Conclusions: The safety of testosterone is well established. The excipient, pentadecalactone, is considered safe based on being negative in a battery of genotoxicity assays, having no structural alerts and carcinogenicity studies conducted with other lactones at very high doses via the oral route had marginal effects.

Communication review:
Labeling review: Standard testosterone label

RECOMMENDATIONS: Based on extensive clinical experience with testosterone, pre-clinical studies conducted by the sponsor and review of the published literature, Pharmacology recommends approval of Testim 1% (testosterone gel) for testosterone replacement therapy in adult males

Internal comments: none

External recommendations (to sponsor): none

Draft letter content for sponsor (if not same as above):

NDA issues: none

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Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc:
Original NDA 21-454
HFD-580
HFD-580/A.Jordan/K.Raheja/D.Davis
N21454.000/9-19-2002

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

Studies reviewed within this submission: Battery of genotoxicity studies and segment 1 male reproductive toxicity study.

Studies not reviewed within this submission: No other pre-clinical studies were conducted.

Introduction and drug history: As given under Overall Summary and Evaluation

TABLE OF CONTENTS

PHARMACOLOGY:

Pharmacology of testosterone is well established

Regarding the excipient, oxacyclohexadecan-2-one, citing published literature (JPET 151:305-318, 1955) it was reported that Na^+ and K^+ transport in red blood cells could be completely inhibited with pI50 of 2 x 10^{-2}M i.e., 20 mM. Plasma concentration with therapeutic dose even if it is totally absorbed will be about 0.30 mM, suggesting adequate safety margin.

SAFETY PHARMACOLOGY:

There is an extensive published literature to establish the safety of testosterone, the active ingredient of the proposed formulation. However, since no information was available in the Material Safety Data Sheet for oxacyclohexadecan-2-one and none was provided from the published literature about the genotoxic potential of this excipient, sponsor conducted ICH recommended battery of genotoxicity assays. These assays demonstrated that oxacyclohexadecan-2-one was not genotoxic under the experimental conditions used.

PHARMACOKINETICS/TOXICOKINETICS:

The PK/TK of testosterone is well established. No PK/TK data was submitted for the excipient, oxacyclohexadecan-2-one.

TOXICOLOGY:

Extensive information is available about the safe clinical use of testosterone in hormone replacement therapy.

Toxicology of oxacyclohexdecan-2-one:

Acute toxicity: Citing published literature, LD_{50} was reported to be 5 g/kg when administered dermally to rabbits or orally to rats. In mice LD_{50} following oral dosing was reported to be 2820 and 2950 mg/kg for males and females, respectively. Clinical signs of lethargy, dyspnea, and salivation were noted with doses of 1600 mg/kg and above.

Subchronic toxicity: An oral 13-week toxicity was conducted by the and reviewed by FEMA Expert Panel and WHO for review of GRAS substances. In this study 2 treatment groups having 23 rat/s were used. One group served as control while the other group received a dose of 17.1 mg/kg/day for 13 weeks.

No significant treatment effect was seen on body weight and food consumption. No changes were reported in hematologic and biochemical parameters during the sixth and the 13th weeks, with the exception of significant increases in alkaline phosphatase levels at 13 weeks of treatment in both males and females, which were within the range of historical values. There were no changes in urine analysis. Compared to controls, liver and kidney weights were significantly increased in both treated males and females but were considered within the historical controls. It was stated that there were no gross or histopathological changes indicating any compound-related differences between the control and treated animals.

Note: This study was reported in 1971 and basis of dose selection was not provided. No T/K information was provided.

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				

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Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

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GENETIC TOXICOLOGY:
It was stated that IARC supplement 7 concluded that testosterone did not induce sperm abnormalities or micronuclei in mice treated in vivo. Also it was not mutagenic to bacteria. In a study by Lasne et al (Carcinogenesis 11:541-547, 1990) it was reported that testosterone possesses a weak transforming effect in Syrian Hamster embryo (SHE) cells. This study did not confirm the transformation since the cells were not inoculated in animals.
Since no information was available in published literature on the mutagenicity of oxacyclohexadecan-2-one, sponsor conducted the ICH recommended battery of genotoxicity assays, the results of which are presented below:

Study title: In vivo mouse micronucleus assay with — (oxacyclohexadecan-2-one)

Key findings: Oxacyclohexadecan-2-one was negative in this assay

Study no: — 22572-0-455OECD
Study type (if not reflected in title):
Volume #, and page #: 11 of 84, page 002
Conducting laboratory and location: —
Date of study initiation: 6-12-2001
GLP compliance: yes
QA reports: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: Lot # G/20154020, serial No. AL093606, not labeled, purity not given

Formulation/vehicle: solution/corn oil

Methods:

Strains/species/cell line: mice — CD-1 (ICR) BR

Dose selection criteria:

Basis of dose selection: MTD based on toxic signs, death or depression of the ratio of polychromatic erythrocytes (PCE_s) to normochromatic erythrocytes (NCE_s).

Range finding studies: Doses of 500, 1000 or 2000 mg/kg were administered orally to 3 mice/sex. Daily observations of toxic signs and/or mortality data were used to estimate the MTD

Test agent stability: not given

Metabolic activation system: NA

Controls:

Vehicle: corn oil

Negative controls: corn oil

Positive controls: cyclophosphamide in sterile deionized water

Comments: since no differences in toxicity were observed between the sexes in the dose range-finding study, only males were used.

Exposure conditions:

Incubation and sampling times: as given in table below

Doses used in definitive study: since no deaths occurred in the dose range-finding study, doses of 500,1000 and 2000 mg/kg were used.

Study design: as shown in a table 2 below:

Table 2

Treatment	Stock conc. (mg/ml)	Harvest timepoint 24 hours	48 hours
500 mg/kg	50	6	-
1000 mg/kg	100	6	-
2000 mg/kg	200	6	6
vehicle control corn oil	0	6	6
positive control cyclophosphamide	8	6	-

— in corn oil was administered by the oral route. The dosing volume was 10 ml/kg

Analysis:

No. of replicates: At the harvest timepoints, the animals were euthanized by CO_2 inhalation. The tibias were removed for marrow extraction from 5 surviving animals from each of the treatment and control groups.

Counting method: bone marrow was spread on slides and air-dried. The slides were fixed in methanol, stained by Giemsa and protected by mounted coverslips. The slides were scored for micronuclei and PCE/NCE cell ratio. The micronucleus frequency was determined by analyzing the number of micronucleated PCE_s from at least 2000 PCE_s per animal . The PCE:NCE ratio was determined by scoring the number of PCE and NCE observed scoring at least the first 500 erythrocytes/animal.

Criteria for positive results: detection of a significant increase in micronucleated PCE_s for at least one dose level, and a statistically significant dose-related response.

Summary of individual study findings: No signs of clinical toxicity were observed in any of the treated animals. The micronucleus data and historical control data is shown in table below:

Table 3

Treatment	Dose	Harvest time	% micronucleted PCE_s mean of 2000/animal +/-S.E.	Ratio PCE:NCE Mean +/- S.E.
Vehicle control	Corn oil	24 hr 48 hr	0.03 +/-0.02 0.09 +/- 0.03	0.56 +/- 0.04 0.75 +/- 0.06
Positive control	CP 80 mg/kg	24 hr	1.72 +/- 0.18*	0.64 +/- 0.06
Test article	500 mg/kg 1000 mg/kg 2000 mg/kg	24 hr 24 hr 24 hr 48 hr	0.05 +/- 0.02 0.09 +/- 0.02 0.03 +/- 0.02 0.04 +/- 0.01	0.76 +/- 0.07 0.52 +/- 0.06 0.82 +/- 0.02 0.55 +/- 0.02**
Historical control data				
Pooled vehicle conrols		24 hr minimum maximum average N 48 hours minimum maximum average N	 / 0.058 +/- 0.005 229 / 0.053 +/-0.005 210	 / 0.658 +/-0.021 229 / 0.611 +/- 0.018 210
Positive controls	CP 80 mg/kg	24 hr minimum maximum average N	 / 2.70+/-0.069 197	 / 0.620 +/- 0.023 197

Results showed that cytotoxicity to the bone marrow expressed as statistically significant decrease in PCE/NCE ratio was observed at the 2000 mg/kg dose level at the 48 hour harvest timepoint. A statistically significant increase in micronucleated PCE_s was not observed at any dose level or harvest timepoint. The positive control induced statistically significant increases in miconucleated PCE_s when compared to vehicle controls.

Study validity: valid

Study outcome: — was evaluated as negative

Study title: Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay with a confirmatory assay for oxacyclohexadecan-2one

Key findings: The test compound was negative in this assay

Study no: — study No.: 22572-0-409OECD
Study type (if not reflected in title):
Volume #, and page #: volume 11 of 84, page 11-020
Conducting laboratory and location: —
Date of study initiation: 6-13-2001
GLP compliance: yes

QA reports: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: Lot 119417.0009,not labeled, purity not given
Formulation/vehicle: solution/DMSO

Methods:

Strains/species/cell line: Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli $WP2_{uvr}A$

Dose selection criteria:

Basis of dose selection: Based on cytotoxicity of [redacted] to the test system as a decrease in the number of revertant colonies per plate and/or thinning or disappearance of the bacterial background lawn.

Range finding studies: Dose range-finding studies were performed using strain TA100 and $WP2_{uvr}A$ in the presence and absence of S9. Ten doses of test compound up to 5000 ug/plate were used for cytotoxicity (one plate per dose).

Test agent stability: not given

Metabolic activation system: S9 mix

Controls:

Vehicle: DMSO

Negative controls: DMSO

Positive controls: benzo(a)pyrene, 2-aminoanthracen, 2-nitrofluorene, sodium azide and ICR-191.

Comments:

Exposure conditions:

Incubation and sampling times: 52+/-4 hours at 37 C.

Doses used in definitive study: 33.3, 100, 333, 1000, 3330 and 5000 ug/plate in all 5 tester strains with S9 and in strain $WP2_{uvr}A$ without S9. Doses of 1, 3.33, 10, 33.3, 66.7 and 100 ug/plate in all four Salmonella tester strains without S9.

Study design: Due to absence of toxicity in the Salmonella strains in the absence eof S9, [redacted] was reevaluated in all 4 strains at doses of 10.0, 33.3, 100, 333, 1000, 3330 and 5000 ug/plate without S9 in experiment 22572-D1.

Analysis:

No. of replicates: 3 plates/dose

Counting method: The condition of the background lawn was evaluated macroscopically and microscopically using dissecting microscope for indications of cytotoxicity and test article precipitate. Evidence of cytotoxicity was scored relative to the vehicle control plate and was recorded along with the revertant counts for all plates at that dose level. Revertant colonies were counted using automated colony counter.

Criteria for positive results: For test article to be considered positive, it had to produce at least 2-fold increase in the mean revertants per plate of at least one of tester strains TA98, TA100 and $WP2_{uvr}A$ over the mean revertants per plate of the appropriate vehicle control. This increase in the mean number of revertants per plate had to be accompanied by a dose- response to increasing concentrations of the test article. For strains TA1535 and TA 1537 the increase should be at least 3-fold.

Summary: At 100 mg/ml DMSO, which was the most concentrated solution prepared, — formed a transparent, colorless solution and it remained a solution at all succeeding lower dilutions.
Cytotoxicity evidenced by reduction in the number of revertants and thinning of background lawn was observed at dose of >3330 ug/plate in the presence of S9 and at doses >66.7 ug/plate in the absence of S9. Also ——— was incompletely soluble at doses of >3330 ug/plate with or without S9, but normal growth was observed in all tester strains at all doses evaluated.
Revertant frequencies for all doses, in all tester strains with or without S9, approximated or were less than control values.

Study validity: study is considered valid
Study outcome: — was not mutagenic under the conditions of the assay conducted.

Study title: L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay with a confirmatory assay with —

Key findings: — was negative in the L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay

Study no: — study No. 22572-0-431 ICH
Study type (if not reflected in title):
Volume #, and page #: 11 of 84, page 11-050
Conducting laboratory and location: —
Date of study initiation: 6-12-2001
GLP compliance: yes
QA reports: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: G/20154020
Formulation/vehicle: solution/DMSO

Methods:

Strains/species/cell line: L5178Y cell line heterozygous at the TK locus
Dose selection criteria:
Basis of dose selection: dose range finding cytotoxicity study with treatment period of 4 hours with and without S9 activation and in non-activation assay with a treatment period of approximately 24 hours.
Range finding studies: Ten treatments were used in each case that ranged from 1.97 to 1000 ug/ml.
Test agent stability: not given
Metabolic activation system: S9
Controls:
Vehicle: DMSO
Negative controls: DMSO
Positive controls: methyl methanesulfonate as direct acting mutagen and methylcholanthrene, which requires activation by S9 to become mutagnic.

Comments: ——— concentrations were chosen to cover a toxicity range of 10% to 20% survival (relative total growth) to no apparent effect on growth compared to the vehicle control. Doses selected included nontoxic to highly toxic treatment conditions.

Exposure conditions:

Incubation and sampling times: 4 hours in the absence and presence of S9 activation system and 24 hours in the non-activation system.

Doses used in definitive study: Doses used for the mutation assay were based on results of the cytotoxicity assays. These were as follows:

In the absence of S9 activation with 4 hour treatment period, ——— was noncytotoxic to weakly cytotoxic from 1.97 to 31.3 ug/ml and excessively cytotoxic from 62.5 to 1000 ug/ml. In the presence of S9 activation, test article induced no cytotoxicity from 1.97 to 31.3 ug/ml, moderate cytotoxicity at 62.5 ug/ml and excessive cytotoxicity at 125 ug/ml and higher concentrations.

In the non-activation system using 24 hour treatment period, test article had no cytotoxicity from 1.97 ug to 15.7 ug/ml and excessive cytotoxicity at and above 31.3 ug/ml

Study design: In the initial mutation assay in the absence of metabolic activation, 8 treatments ranging from 5 to 45 ug/ml and in the presence of S9 metabolic activation doses from 10 to 80 ug/ml were analyzed for mutation and cytotoxicity.

In the confirmatory nonactivation mutation assay with 24 hour treatment period, 7 doses ranging from 5 to 35 ug/ml were analyzed.

The mutant frequency was calculated as the ratio of the total number of mutant colonies found to the total number of cells seeded, adjusted by the absolute selection coloning efficiency.

Analysis:

No. of replicates: triplicate

Counting method: After 13-days in the incubator, the colonies were counted with the ——— Colony Counter. Colony sizing was performed on all cultures

Criteria for positive results: The test article was considered positive if dose-dependent increases of 2-fold or greater in mutant frequency were obtained over the concurrent background mutant frequency i.e., vehicle controls.

Summary: None of the analyzed treatment induced a mutant frequency that exceeded the minimum criteria of 142.7 x 10^{-6}. ——— was therefore evaluated negative in the L5178Y mouse lymphoma assay under nonactivaiton and activation conditions. Mutant colonies from all the cultures showed the expected distribution and mutant colonies from the positive controls showed both small and large colonies.

Study validity: assay is considered valid

Study outcome: ——— was negative under the experimental conditions used.

Genetic toxicology summary: ——— was negative in the Salmonella-Escherichia coli/mammalian reverse mutation assay, L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay and in the Mouse in vivo micronucleus assay

Genetic toxicology conclusions: ——— was negative in the ICH recommended battery of genotoxicity assays.

LABELING RECOMMENDATIONS:

CARCINOGENICITY:

Citing published literature it was reported that in mice, subcutaneous testosterone implant induced cervical-uterine tumors, which metastasized in some cases. Also in some strains of mice testosterone injection increased their susceptibility to hepatoma. Testosterone is also reported to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. After a review of the available clinical data following testosterone administration in humans and despite the evidence from the animal studies reviewed, the working group preparing the 1987 IACR Monograph supplement 7 on sex hormones concluded that for humans, the overall evidence for carcinogenicity following testosterone administration is limited.

Although no carcinogenicity studies have been conducted with oxacyclohexadecan-2-one, carcinogenicity studies with 2 structurally related compounds i.e., y-butyrolactone and 3,4-dihydrocoumarin were conducted by the NTP in 1992-93. Results of these studies have been reported by Adams et al in Food and Chemical Toxicology 36:249-278, 1998 and are summarized below.

In study with y-butyrolactone (4-hydroxybutanoic acid lactone) oral doses of 0, 112 and 225 mg/kg/day were used in F344 male rats and 0, 225 and 450 mg/kg/day in female rats, given 5 days a week for 2 years. For both sexes of $B6C3F_1$ mice doses of 0, 262 and 525 were used. Decreased body weight was reported in high dose group of female rats and all of the drug-treated mice. The increased mortality in high dose male mice was attributed to fighting on emergence from drug sedation. There was no difference in survival between control and treated female mice. Male mice exhibited a statistically significant increase in the incidence of adrenal medulla hyperplasia in the low dose group only and an increased incidence of benign and malignant pheochromocytoma, which was not statistically significant (p=0.092) and also occurred only in the low dose group.

Summary of neoplastic and non-neoplastic effects in $B6C3F_1$ male mice is given in table below:

Table 4

Lesion	Dose groups		
	0 mg/kg/day	262 mg/kg/day	525 mg/kg/day
Pheochromocytoma Incidence/total number mice %	2/48 4.2% (p=0.472	6/50 12% (p=0.092)	1/50 2.0% (p=0.592)
Pheochromocytoma Incidence/total number mice Surviving >582 days %	2/43 4.7%	6/36 17%	1/24 4.2%
Adrenal medulla hyperplasia Incidence/total number mice %	2/48 4.2% (p=0.071)	9/50 18% (p=0.011)	4/50 8.0% (p=0.191)
Adrenal medulla hyperplasia Incidence/total number mice Surviving >582 days %	2/43 4.7%	9/36 25%	4/24 17%

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Historical incidence of pheochromocytoma for 2-year NTP corn oil gavage studies with vehicle control groups (mean +/- SD) was 18/582 (3.1 +/- 1.8%), with a range 0-6%.

The NTP report concluded the following:

"Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenicity of y-butyrolacatone in male F344 rats given 112 or 225 mg/kg or in female rats given 225 or 450 mg/kg in corn oil. There was equivocal evidence of carcinogenic activity of y-butyrolactone in male $B6C3F_1$ mice based on marginally increased incidences of adrenal medulla pheochromocytomas and hyperplasia in the low dose group. The sensitivity of the study in male mice to detect a carcinogenic effect was reduced by the low survival of the high dose group associated with fighting. There was no evidence of carcinogenic activity of y-butyrolactone in female $B6C3F_1$ mice receiving 262 or 525 mg/kg in corn oil".

The authors of this publication, concluded that the results of the NTP bioassay are not relevant to the safety evaluation of low levels of intake of y-butyrolactone from use as a flavor ingredient in humans.

Carcinogenicity study with 3,4-dihydrocoumarin was conducted by NTP in 1993 using F344/N rats and $B6C3F_1$ mice of both sexes. Animals were dosed orally 5 days/week with doses of 0, 150, 300 or 600 mg/kg to rats and 0, 200, 400 or 800 mg/kg to mice. There was a dose-related decreased survival in males. As shown in table below, decreased survival was attributed to a progressive degenerative nephropathy leading to renal failure.

Table 5

Pathology	Control	150 mg/kg	300 mg/kg	600 mg/kg
Male rats				
nephropathy	50/50	47/48	47/47	47/50
renal tubule hyperplasia	0/50	5/48*	6/47*	8/50**
renal tubule adenoma	1/50	1/48	3/47	6/50*
Female rats				
nephropathy	20/50	20/49	37/49**	31/49**
renal tubule hyperplasia	0/50	0/49	0/49	2/49
renal tubule adenoma	1/50	1/49	1/49	0/49
	Control	200 mg/kg	400 mg/kg	800 mg/kg
Male mice				
Nephropathy	45/50	46/51	45/51	43/49
renal tubule hyperplasia	0/50	1/51	3/51	1/49
renal tubule adenoma	0/50	0/51	2/51	1/49
renal tubule adenoma or carcinoma	0/50	1/51	2/51	2/49

- Significantly different ($p<0.05$) from control group. Significantly different ($p<0.01$) from control group. NTP historical control incidence for renal tubular adenoma was reported to be 8/1019.

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Renal transitional cell carcinomas were reported in 2 male rats (died on days 444 and 528) in the 600-mg/kg-dose level.

Also statistically significant increased serum levels of ALT, alkaline phosphatase, sorbitol dehydrogenase or y- glutamyl transferase in male rats at 300 and 600 mg/kg was reported at the 15 month evaluation. Increased alkaline phosphatase and y-glutamyl transferase were reported in female rats at 600 mg/kg. Although ALT was 4 times higher compared to controls at 600 mg/kg dose, no histopathology was reported.

NTP report concluded the following:

"Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenicity of 3,4-dihydrocoumarin in male F344 rats based on the increased incidence of renal adenomas and focal hyperplasia. The transitional cell carcinomas in two 600 mg/kg males may also have been chemical related. There was no evidence of carcinogenic activity of 3,4-dihydrocoumarin in female F344 rats receiving 150, 300 or 600 mg/kg. There was no evidence of carcinogenic activity of 3, 4-dihydrocoumarin in male mice receiving 200, 400 or 800 mg/kg".

Comment: The concentration of oxacylohexadecan-2-one when used as — is very low i.e., 0.1 – 0.15%, whereas the concentration in the proposed testosterone gel formulation is very high i.e., — The carcinogenicity studies with both y-butyrolactone and 3,4-dihydrocoumarin were conducted using oral route of administration whereas the Testim gel is to be applied dermally. As such results of oral studies may not be applicable to dermal studies without knowledge of dermal absorption and systemic exposure.
The observation of increased kidney weight in the 13-week oral toxicity in rats with oxacyclohexadec-2 one at a very low dose of 17 mg/kg/day suggests that pathological renal findings of hyperplasia and adenoma might be expected with high doses in a carcinogencity study.

Reproductive toxicology:

No reproductive toxicity studies are required for testosterone. However, since the — Material Safety Data Sheet for oxacyclohexadecan-2-one indicated that it could adversely affect male fertility, segment 1 male reproductive toxicity was conducted. Results of this study are described below.

Study title: Pentadecalactone: Effects on male fertility in rats

Key study findings: Under the conditions of this study, it was concluded that 1000 mg/kg/day was the NOAEL for effects on male fertility

Study no.: — project No. 493066
Volume #, and page #: 11 of 84, page 11-083
Conducting laboratory and location: —
Date of study initiation: 8-1-2001
GLP compliance: yes
QA reports: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: Lot No.AB13199, not radiolabeled, purity not given
Formulation/vehicle: solution/canola oil

Methods:

Species/strain: rat/ — CD (SD)GS BR
Doses employed: 0, 200, 500 and 1000 mg/kg/day for males only for 4 weeks prior to mating with untreated females, then throughout mating and continued for at least 9 weeks of dosing prior to necropsy.

Route of administration: oral gavage

Study design: as shown in table below:

Table 6

Group #	Treatment (mg/kg/day)	Animal numbers	
		Males	Females
1	Control 0	24	24
2	Low dose 200	24	24
3	Mid dose 500	24	24
4	High dose 1000	24	24

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Number/sex/group: as shown in table above

Parameters and endpoints evaluated: sperm evaluation and fertility index.

Results:

Mortality: no treatment-related mortality

Clinical signs: dose and time related salivation. All in high dose group (first noted on day 5 of dosing). 14 animals in mid dose group (first noted during week 2 of dosing) and 2 animals at low dose (first noted during week 7 of dosing). Salivation was noted mostly immediately after dosing and in some cases up to 1-hour post-dosing.

Body weight: no affected by treatment

Food consumption: not affected by treatment

Toxicokinetics: not conducted

***For fertility studies*:**

In-life observations: Mating performance and fertility indices were not affected by treatment. All males except one in control group and 2 in mid dose group mated during the first 5 days with the first mate. The one in the control group and one in the mid dose group mated with the second female. The fertility index (number siring a litter/number paired) was 100, 100, 96 and 100 % for the control and 3 treated groups, respectively.

The pregnancy performance was not affected as shown in table below:

Table 7

	Group/dose level (mg/kg/day)			
	1 (0)	2 (200)	3 (500)	4 (1000)
Number pregnant	24	24	23	24
Mean corpora lutea	13.3	13.8	13.7	12.6
Mean implants	12.6	13.5	12.8	12.3
Mean live implants	11.9	13.1	12.0	11.8
Mean dead implants	0.7	0.4	0.8	0.5
Mean early embryonic deaths	0.7	0.4	0.7	0.5
Mean late embryonic deaths	0	0	0.1	0

Females were killed on day 14-16 of gestation.

Terminal and necroscopic evaluations:

The weight of the testes, epididymides, prostates and seminal vesicles were not affected by treatment.

Epididymal sperm evaluation: Sperm count expressed based on counts/g cauda or counts/cauda was not affected. The motility (%) was 76, 80, 80 and 79 for the control and 3 treated groups, respectively. Progressive motility % and straight-line velocity were similar for all groups.

Labeling recommendations:

SPECIAL TOXICOLOGY STUDIES:

The dermal irritation of the final formulation of the new testosterone gel, as proposed for marketing, was evaluated in rabbits using a semi-occlusive dressing. The experimental set up as shown in table below:

Table 8

Animal #	Site	Treatment	Amount Applied (ml)	Region of dorsal trunk
1-3	Test Control	AA2500 Nil	0.5 0	Upper Lower

The gel formulation was applied to clipped skin, with each animal serving its own control. Following treatment, the sites were covered with semi-occlusive tape and elastic bandages wrapped around the torso. After 4 hours contact period, the patch was removed and the skin wiped with water. All sites were then examined for evidence of irritation 1, 24, 48 and 72 hours after patch removal. Observations were extended to Day 14 in order to evaluate the reversibility of reactions and the study was terminated.

Results: Skin irritation scores are given in tale below:

Table 9

Test site

Animal #	B.W Kg	Time after removal or Day of study/reaction score															
		Erythema								odema							
		1 h	24 h	48 h	72 h	D7	D9	D11	D14	1 h	24 h	48 h	72 h	D7	D9	D11	D14
1	3.01	2	2	2	1	1	0	0	0	0	0	0	0	0	0	-	-
2	2.96	2	2	2	1	1	1	1	1	0	0	0	0	0	0	0	0
3	3.00	2	3	2	1	1	0	0	0	0	0	0	0	0	0	-	-
Control site																	
1		0	0	0	0	0	0	-	-	0	0	0	0	0	0	-	-
2		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3		0	0	0	0	0	0	-	-	0	0	0	0	0	0	-	-

- = no observation at this timepoint

Scoring system was graded 0-4 for both erythema and edema. For erythema scores of 0, 1, 2, 3 and 4 represented no erythema, very slight (barely perceptible), well defined, moderate to severe and severe (beet red to slight eschar formation) erythema, respectively. For edema 0, 1, 2, 3 and 4 scores represented no edema, very slight edema (barely perceptible), slight edema (edges of area well defined by definite raising), moderate edema (raised approx. 1 mm), and severe edema (raised more than 1 mm and extending beyond the area of exposure), respectively.

Results demonstrated that reactions only occurred at sites treated with AA2500. After patch removal, well defined to moderate erythema was noted in all 3 animals up to 48 h, slight erythema from 72 h to Day 7 in 2 animals and up to Day 14 in the third. Dry flaky skin was noted in all animals from Day 3 to Day 14. No edema was noted in any animal at any observation timepoint. Under these experimental conditions, AA2500 was considered irritating to rabbit skin.

Since testosterone gel formulation will be applied without an occlusive covering in clinical practice, irritation study in rabbits was repeated without the use of gauze covering.
Experimental design was similar to that given above.
In this study, very slight erythema was noted in one animal only 5 hours after gel administration. Very slight to well defined erythema was noted up to 28 hours after gel administration in one animal and up to 76 h in a second animal. Very slight edema was noted in all animals 5 h after gel application, which was not noted in study with occlusive covering. Dry flaky skin was noted at treated site in only one animal from Day 8 to Day 15.
Although sponsor considered gel non-irritating to rabbit skin under the conditions of the study, edema was seen in this study and not when site was covered.

Summary: Although skin irritation was greater and lasted longer when occlusive covering was used, edema was seen only when site of gel application was not occluded.
Conclusions: Testim gel had very little irritation potential.

ADDENDUM TO REVIEW:
(if necessary)

APPENDIX/ATTACHMENTS: -

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

/s/

Krishan L. Raheja
9/24/02 01:37:15 PM
PHARMACOLOGIST

Alexander W. Jordan
9/25/02 08:47:43 AM
PHARMACOLOGIST

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

October 15, 2002

NDA 21-454

Drug: Testim™ 1% (Testosterone Gel)

Indication: Testosterone replacement therapy in adult males

Sponsor: Auxilium Pharmaceuticals

Stamp Date: Dec 31, 2001

Project Manager: Eufricina Deguia, HFD-580

Medical Reviewer: Dan Davis, MD, HFD-580

Statistical reviewer: Mike Welch, PhD, HFD-715

Overview of principal study

Testim 1% (testosterone gel) was evaluated for efficacy in a single, pivotal trial (AUX-TG-202.01R). This was a randomized, multi-center, multi-dose, active and placebo controlled 90-day study in over 400 adult males with morning testosterone levels below 300 ng/dL. The treatment objective was to normalize testosterone. The study was double-blind for doses of Testim and placebo but open label for the active control, a testosterone transdermal patch (Androderm, 5 mg daily). During the first 60 days, patients were randomized to Testim 50 mg, Testim 100 mg, placebo gel, or the testosterone transdermal patch (approximately 100 patients per group). At 60 days, patients receiving Testim were maintained at the same dose, or titrated up or down within their treatment group, based on testosterone concentration levels measured at Day 30.

The primary measure of efficacy is based on the 90 day responder rate in the (modified) intent to treat population. Responders were those whose C_{min} and C_{ave} serum testosterone levels were between 300 and 1,000 ng/dL at last exam. Sampling times for the PK profile for Days 30, 60 and 90 were at predose and 2, 4, 8, 12, and 24 hours post-dose. The responder rate in the combined Testim group was compared to the active control and placebo groups with intent of showing noninferiority and superiority, respectively. The observed rates and 95% confidence intervals for the differences between Testim and each control group rate are shown in the table below.

Primary Efficacy Results - Study AUX-TG-202.01R

	Testim (50 and 100 mg/d)	Transdermal patch	Placebo gel
Sample size (ITT*)	192	90	96
Responder rate (%) and 95% Conf Intervals	38.0 (31.1, 45.3)	5.6 (1.8, 12.5)	2.1 (0.2, 7.3)
95% CI of Difference (Testim – Control)		(23.4, 40.5)	(28.2, 43.3)
Based on Table 11.4.1.1.1.1 Confidence intervals computed by reviewer *Modified Intent-to-treat: Subjects with at least one post-baseline PK profile			

The sponsor's primary analysis was based on a modified intent to treat (MITT) population - those subjects with at least one PK profile obtained after randomization. Approximately 4% of the patients in the Testim MITT group did not complete the full 90 days of study and the PK values for these subjects were carried forward for computation of the responder rate. For the Androderm and placebo groups, 14% and 5%, respectively, of the subjects had values that were carried forward.

Responder analyses are also reported based on the per-protocol population and based on a responder definition using C_{ave} values only. These are secondary outcomes, and results are consistent with those based on the primary analysis.

Other secondary endpoints include change from baseline in C_{ave}, C_{min} and C_{max} at various time points; change from baseline in the body composition parameters; change from baseline in various sexual function parameters; change from baseline in mood parameters; and change from baseline in bone mineral density. These results, in general, showed numerical results favoring the Testim group.

Reviewer's comments

This study has presented results from a well-controlled, randomized, single study that demonstrates clear benefit of Testim to maintain testosterone levels as compared to the placebo and active controls. The endpoints, clinical effect size, statistical hypotheses, and analysis methods were adequate and prospectively defined for the purpose of showing efficacy of the Testim product.

. However, in view of the fact that testosterone replacement products have been approved based on a single, open label, non comparative trial, this study does exceed these past requirements.

. In conclusion, the sponsor has, from a statistical perspective, conducted a well-controlled single study that demonstrates efficacy of Testim as testosterone replacement therapy.

Labeling: It would be appropriate for the Clinical Studies section of the label to show that the primary responder analysis resulted in statistically significance differences in percent responders in favor of the Testim treatment group as compared to active and placebo controls.

Mike Welch, PhD
Team Leader, HFD-715

cc
HFD-580 Deguia, Davis, Hirsch
HFD-715 Nevius, Anello

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/s/

Mike Welch
10/17/02 12:49:58 PM
BIOMETRICS

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD-580

31 JUL 2002

NDA: **21-454/N-000/BC**

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Drug Product Name
Proprietary: Testim 1% Gel
Non-proprietary: Testosterone gel
Drug Product Classification: Topical anabolic steroid

Review Number: 1

Subject of this Review
Submission Date: 28 MAR-2002 (amendment)
Receipt Date: 29-MAR-2002
Consult Date: 02-MAY-2002
Date Assigned for Review: 06-MAY-2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): 31-DEC-2002 (not sent for microbiology review)
Date(s) of Previous Micro Review(s): (none)

Applicant/Sponsor
Name: Auxilim A2, Inc
Address: Not provided in consult
Representative: Not provided in consult
Telephone: Not provided in consult

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Name of Reviewer: David Hussong

Conclusion: APPROVE

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** Not a Supplement – New NDA

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Not provided in consult

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The product is a topical gel containing 1% (w/w) testosterone.

5. **METHOD(S) OF STERILIZATION:** Non-sterile

6. **PHARMACOLOGICAL CATEGORY:** Steroid

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The consult was requested for review of the microbial limits test methods, microbial limits acceptance criteria and the preservatives tests. Only a limited number of photocopied pages were provided. Cover letters and submission details (including labeling) were not provided. An amendment dated 28 MAR 2002 provides the product specification. Additional pages are dated 24 JAN 2002 and include preservatives test and microbial limits stability data. Microbial limits test methods were provided.

USP microbial limits are under revision with the intent of harmonizing with the European Pharmacopoeia.

filename: 21-454Rev1.doc

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - APPROVE

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product is manufactured as a topical gel for application to the skin and contains — alcohol by weight.

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/David Hussong/07/31/2002
Microbiology Supervisor/Peter Cooney

C. CC Block
cc:
Original NDA 21-454
HFD-580/Division File/NDA 21-454

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

/s/

David Hussong
8/1/02 09:36:38 AM
MICROBIOLOGIST

Peter Cooney
8/2/02 10:00:36 AM
MICROBIOLOGIST

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