CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-015

CHEMISTRY REVIEW(S)

FEB 2 5 2000

Summary of Chemistry Review of NDA 21-015

A. Drug Substance:

Testosterone is a primary androgenic hormone responsible for normal growth, development of the male sex organs, and maintenance of secondary sex characteristics. It is manufactured by ———— and the manufacturing facility is deemed **in compliance to cGMP.**

The quality of testosterone is **assured** by the tests such as appearance, identification, melting range, specific rotation, loss on drying, assay, and organic volatile impurities with specifications as delineated in the USP monograph. To further assure the quality, additional assay and impurity test———— are implemented.

B. Drug Product:

The drug product, **Androgel**, is a hydroalcoholic gel containing **1% of testosterone**. It also contains isopropyl myristate as an emollient and ethanol as absorption enhancer. The gel is manufactured and tested by **Laboratories Besins Iscovesco in compliance to cGMP.** ———— is also involved as an alternative testing laboratory and is also **in compliance to cGMP.**

The quality of gel is controlled by tests such as appearance, pH, viscosity, identification of ethanol and testosterone; assay of testosterone, isopropyl myristate, and ethanol; determination of related substances, and weight variation. All these tests and specifications are considered to be adequate.

The gel is packaged into a packet made of laminated aluminum foil with two available strengths, 2.5g and 5g per packet. The packaging process is being done **at** ———— and the facility is **in compliance to cGMP.**

Based on three primary stability data, **18-month of expiry date** is granted.

The tradename, **Androgel**, was accepted by OPDRA and the labeling as well as labels are considered to be adequate

C. Conclusion and Recommendation:

From Chemistry point of view, this NDA can be approved.

/S/ 2/25/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

FEB 2 5 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 21-015
CHEMISTRY REVIEW #: 3
DATE REVIEWED: 25-FEB-2000
REVIEWER: David Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-APR-1999	29-APR-1999	12-MAY-1999

NAME & ADDRESS OF SPONSOR:

Unimed Pharmaceuticals, Inc.
2151 E. Lake Cook Road
Suite 210
Buffalo Grove, IL 60089

DRUG PRODUCT NAME:

Proprietary:	Androgel™
Nonproprietary/Established/USAN:	Testosterone gel
Code Name/#:	T-gel
Chem.Type/Ther.Class:	3S

PARMACOLOGICAL CATEGORY/INDICATION: Androgen/Hormonal replacement therapy in males
DOSAGE FORM: Gel
STRENGTHS: 25, 50 mg (1% gel; 2.5 g/packet & 5.0 g/packet)
ROUTE OF ADMINISTRATION: Topical
DISPENSED: ___x___ Rx _____ OTC
SPECIAL PRODUCTS: ___ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

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

a. Androst-4-en-3-one, 17-hydroxy-,(17β)-
b. 17β-Hydroxyandrost-4-en-3-one

see Chemistry Review #1 for structure.

Molecular formula: $C_{19}H_{28}O_2$
Molecular weight: 288.43
CAS # 58-22-0

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND ——	Androgel (testosterone)	Unimed Pharmaceuticals	Active	N/A	N/A
DMF ——	Testosterone	——	Adequate	1/18/00	

RELATED DOCUMENTS:
none

PATENT STATUS:
none

CONSULTS:

The EER was sent to Compliance on September 23, 1999. The Office of Compliance issued an overall acceptable recommendation on February 25, 2000 (see Appendix A).

REMARKS/COMMENTS:

An overall acceptable recommendation has been issued for the EER.

CONCLUSIONS & RECOMMENDATIONS:
This NDA may be approved from a CMC point of view.

cc:
Orig. NDA #21-015
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

/S/ 2/25/00

David T. Lin, Ph.D.
Review Chemist

R/D Init by:
filename: nda21045.3 (doc) 2/25/00

/S/

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 21-015
CHEMISTRY REVIEW #: 2

DATE REVIEWED: 22-FEB-2000
REVIEWER: David Lin

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-APR-1999	29-APR-1999	12-MAY-1999
Amendment	21-JAN-2000	24-JAN-2000	25-JAN-2000
Amendment	11-FEB-2000	14-FEB-2000	15-FEB-2000
Amendment	15-FEB-2000	16-FEB-2000	16-FEB-2000
Amendment	18-FEB-2000	22-FEB-2000	22-FEB-2000

NAME & ADDRESS OF SPONSOR:

Unimed Pharmaceuticals, Inc.
2151 E. Lake Cook Road
Suite 210
Buffalo Grove, IL 60089

APPEARS THIS WAY
ON ORIGINAL

DRUG PRODUCT NAME:

Proprietary:	Androgel™
Nonproprietary/Established/USAN:	Testosterone gel
Code Name/#:	T-gel
Chem.Type/Ther.Class:	3S

PARMACOLOGICAL CATEGORY/INDICATION: Androgen/Hormonal replacement therapy in males
DOSAGE FORM: Gel
STRENGTHS: 25, 50 mg (1% gel; 2.5 g/packet & 5.0 g/packet)
ROUTE OF ADMINISTRATION: Topical
DISPENSED: _x_ Rx _____ OTC
SPECIAL PRODUCTS: ___ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

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a. Androst-4-en-3-one, 17-hydroxy-,(17β)-
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see Chemistry Review #1 for structure.

Molecular formula: $C_{19}H_{28}O_2$
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SUPPORTING DOCUMENTS:

Type.Number	Subject	Holder	Status	Review Date	Letter Date
IND ———	Androgel (testosterone)	Unimed Pharmaceuticals	Active	N/A	N/A
DMF ———	Testosterone	———	Adequate	1/18/00	

RELATED DOCUMENTS:
none

PATENT STATUS:
none

CONSULTS:

1. The EER was sent to Compliance on September 23, 1999. The overall recommendation from Office of Compliance is pending (see Chemistry Review #1).
2. The proposed trademark, Androgel, was consulted to OPDRA on December 2, 1999. They have determined that the use of Androgel would be acceptable (see Appendix A).

REMARKS/COMMENTS:
The January 21, 2000 amendment contains draft foil sachet and carton labels.

The February 11, 2000 amendment contains additional information on the primary packaging material.

The February 15, 2000 amendment contains the sponsor's response to the Agency's January 24, 2000 Information Request Letter.

The February 18, 2000 amendment contains acceptance of the 18 months expiry date, acknowledgement of prior approval supplement when the foil laminate supplier is changed, and additional system suitability data.

CONCLUSIONS & RECOMMENDATIONS:
This NDA is approvable pending acceptable cGMP status of the drug product manufacturing and packaging facilities.

cc:
Orig. NDA #21-015
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

R/D Init by: 2/22/00
filename: nda21045.2 (doc)

/S/ 2/22/00
David T. Lin, Ph.D.
Review Chemist

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ON ORIGINAL

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-015
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 19-JAN-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-APR-1999	29-APR-1999	12-MAY-1999
Amendment	17-JUN-1999	18-JUN-1999	22-JUN-1999
Amendment	19-NOV-1999	22-NOV-1999	29-NOV-1999
Amendment	09-DEC-1999	10-DEC-1999	11-DEC-1999

NAME & ADDRESS OF SPONSOR:

Unimed Pharmaceuticals, Inc.
2151 E. Lake Cook Road
Suite 210
Buffalo Grove, IL 60089

DRUG PRODUCT NAME:

Proprietary:	Androgel™
Nonproprietary/Established/USAN:	Testosterone gel
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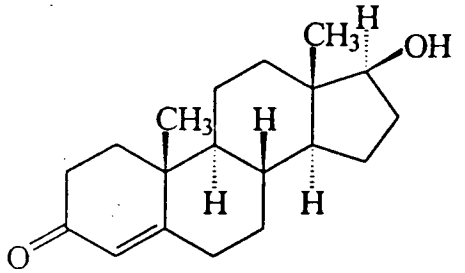
b. 17β-Hydroxyandrost-4-en-3-one



Molecular formula: $C_{19}H_{28}O_2$
Molecular weight: 288.43
CAS # 58-22-0

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND ———	Androgel (testosterone)	Unimed Pharmaceuticals	Active	N/A	N/A
DMF ———	Testosterone	———	Adequate	1/18/00	

RELATED DOCUMENTS:
none

PATENT STATUS:
none

CONSULTS:

1. The EER was sent to Compliance on September 23, 1999. The overall recommendation from Office of Compliance is pending (see Appendix A).
2. The proposed trademark, Androgel, was consulted to OPDRA. The recommendation is pending.

REMARKS/COMMENTS:
Androgel is a clear, colorless hydroalcoholic gel containing 1% testosterone, USP. Testosterone is a well characterized androgen. This NDA has been submitted for the use of a topical gel for hormone replacement therapy in hypogonadal males. This formulation provided continuous delivery of testosterone for 24 hours following single daily applications.

The June 17, 1999 amendment contains microbial testing data.

The November 19, 1999 amendment contains updated stability data and various other minor CMC changes.

The December 9, 1999 amendment contains minor changes to the method validation reports.

CONCLUSIONS & RECOMMENDATIONS:
This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

cc:
Orig. NDA #21-015
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

/S/ 1/19/00

David T. Lin, Ph.D.
Review Chemist

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filename: nda21045.1 (doc)

/S/ 1/19/00

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