# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-543**

# PHARMACOLOGY REVIEW

# *PHARMACOLOGY/TOXICOLOGY COVER SHEET*

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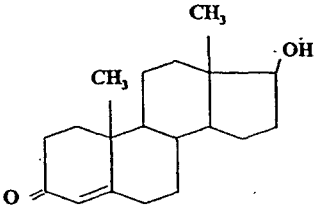
| **NDA NUMBER:** | 21-543 |
| **REVIEW NUMBER:** | 1 |
| **SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:** | N000/08 August 2002 |
| **INFORMATION TO SPONSOR:** | Yes (X) No ( ) |
| **SPONSOR AND/OR AGENT:** | Columbia Laboratories Inc.<br>220 South Orange Avenue, 2nd floor<br>Livingston, NJ 07039 |
| **MANUFACTURER FOR DRUG SUBSTANCE :** | MiPharm S.p.A<br>Milano, Italy |
| **REVIEWER NAME:** | Suzanne R. Thornton |
| **DIVISION NAME:** | DRUDP |
| **HFD #:** | 580 |
| **REVIEW COMPLETION DATE:** | 28 January 2003 |
| **DRUG:** | |
| **TRADE NAME:** | not yet determined |
| **GENERIC NAME (LIST ALPHABETICALLY):** | testosterone |
| **CODE NAME:** | NA |
| **CHEMICAL NAME:** | Androst-4-en-3-one, 17-hydroxy-,(17β) |
| **CAS REGISTRY NUMBER:** | 58-22-0 |
| **MOLE FILE NUMBER:** | not indicated |
| **MOLECULAR FORMULA/MOLECULAR WEIGHT:** | $C_{19}H_{28}O_2$/288.43 |
| **STRUCTURE:** | |

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| **RELEVANT INDS/NDAS/DMFS:** | I60,906 |
| **DRUG CLASS:** | endogenous steroid |

**CLINICAL FORMULATION:** Testosterone, magnesium stearate, colloidal silicon dioxide, talc, polycarbophil, carbomer 934P, lactose monohydrate (Pharmatose 200M), starch, anhydrous lactose, hydroxypropyl methylcellulose. All components are USP or NF.

**ROUTE OF ADMINISTRATION:** buccal

**PROPOSED USE:** Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

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

**STUDIES REVIEWED WITHIN THIS SUBMISSION:** None were submitted.

**STUDIES NOT REVIEWED WITHIN THIS SUBMISSION:** None were submitted.

# *Executive Summary*

## I. RECOMMENDATIONS

A. RECOMMENDATION ON APPROVABILITY: From a pharmacology/toxicology standpoint, the NDA is approvable.

B. RECOMMENDATION FOR NONCLINICAL STUDIES: None at this time.

C. RECOMMENDATIONS ON LABELING: None at this time.

## II. SUMMARY OF NONCLINICAL FINDINGS

A. BRIEF OVERVIEW OF NONCLINICAL FINDINGS:

Testosterone has been extensively studied in animals and in humans. When given orally, testosterone is extensively metabolized due to a high first-pass metabolism. Alternative and approved routes of administration for testosterone include i.m. injections and transdermal patches. These alternative routes of administration, while they have been shown to be safe and effective, are limited by the inconvenience and pain associated with the injections and skin irritation and/or contact dermatitis associated with the transdermal patches. Buccally administered testosterone offers advantages over the approved routes of administration in that it circumvents the first-pass metabolism and therefore leads to higher sustained serum testosterone levels.

Testosterone and its esters are not mutagenic in the Ames test or the SHE cell assay, but are embryolethal in pre- and post-implantation embryos and causes virilization in female offspring.

B. PHARMACOLOGIC ACTIVITY: Testosterone is an endogenous steroid secreted by the testes (Leydig cells) and adrenal gland.

C. NONCLINICAL SAFETY ISSUES RELEVANT TO CLINICAL USE:

There are no safety concerns for testosterone due to the extensive experience, both in animals and humans. Two potential safety concerns are local toxicity/tolerance and the components of the buccal tablet. No non-clinical local toxicity/tolerance studies were conducted, but data were collected during the human clinical trials (see medical officer review). Commonly reported adverse events, all reported at a low incidence, included application site erythema, edema, pain, irritation, gingivitis, buccal mucosal roughening, and oral pain. The components of the buccal tablet, especially colloidal silicon dioxide, [redacted] polycarbophil, hydroxypropylmethylcellulose, and [redacted] starch are used in other products administered buccally, as well as by other routes including oral and topical/dermal. Further, a literature review of the components does not provide sufficient evidence for a safety concern. In this light, there are no non-clinically relevant safety issues for the proposed clinical use.

## III. ADMINISTRATIVE

A. REVIEWER SIGNATURE: _____

B. SUPERVISOR SIGNATURE: CONCURRENCE - _____

NON-CONCURRENCE - _____
(see memo attached)

C. cc: list:

**Bibliography** (as cited by the Sponsor)


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/s/

Suzanne Thornton
1/29/03 10:28:25 AM
PHARMACOLOGIST

Alexander W. Jordan
1/29/03 10:37:47 AM
PHARMACOLOGIST

NDA 21-543

**45 DAY MEETING CHECKLIST**

**(Answer Yes or No to the questions below)**

**FILEABILITY:**

On initial overview of the NDA application:

**PHARMACOLOGY AND TOXICOLOGY:**

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? **Yes**

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin? **Yes**

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can being? **Yes**

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)? **No studies were conducted, but literature article citations were provided.**

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should be required? **Not applicable.**

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? **No pharmacology appropriate labeling is included. Additions to the proposed labeling including the addition of Carcinogenesis, Mutagenesis, Impairment of Fertility Section will be requested.**

(7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor? **Yes**

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? **No animal studies were conducted to support the buccal route. All data were generated from human clinical studies.**

(9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? **Not applicable.**

(10) Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? **Not applicable.**

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. **Yes**

Reviewing Pharmacology Officer Date

Supervisory Pharmacology Officer Date

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/s/

Suzanne Thornton
9/23/02 08:03:21 AM
PHARMACOLOGIST

Alexander W. Jordan
9/25/02 08:44:18 AM
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