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RESEARCH**

APPLICATION NUMBER:

202763Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: N202763
Supporting document/s: <\\CDSESUB1\EVSPROD\NDA202763\202763.enx>
Applicant's letter date: January 13, 2011
CDER stamp date: January 14, 2011
Review Completion: August 24, 2011
Product: Testosterone gel 1%
Indication: Testosterone replacement in hypogonadal men
Applicant: Teva Pharmaceuticals
Review Division: DRUP
Reviewer: Jeffrey D. Bray, Ph.D.
Supervisor: Lynnda L. Reid, Ph.D.
Division Director: Scott Monroe, M.D.
Project Manager: Jeannie Roule

Disclaimer

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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
1.3	RECOMMENDATIONS	3
2	DRUG INFORMATION	3
2.1	DRUG	3
2.2	RELEVANT IND/s, NDA/s, AND DMF/s	4
2.3	DRUG FORMULATION	4
2.4	COMMENTS ON NOVEL EXCIPIENTS	4
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	4
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	5
2.7	REGULATORY BACKGROUND	5
3	STUDIES SUBMITTED.....	5
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	5

1 Executive Summary

1.1 Introduction

This application is for a testosterone gel 1% indicated for hypogonadal men. The applicant submitted a 505(b)(2) NDA application with reliance on the FDA's previous findings of safety and efficacy for similar products. This testosterone gel has a different formulation than other FDA-approved testosterone gels, but otherwise has no unique benefits or risks.

1.2 Brief Discussion of Nonclinical Findings

The applicant submitted no new nonclinical information, and is relying on published studies of testosterone for Approval. Testosterone is the predominant male sex steroid produced by the testes and is responsible for adult male sexual characteristics. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the Labeling. While the formulation is different than other FDA-approved testosterone gel products, the components are at or below the levels in other FDA-approved products.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support **Approval** of testosterone gel 1% for testosterone replacement in hypogonadal men.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Class labeling is appropriate. No significant nonclinical labeling issues were identified nor are significant changes required.

2 Drug Information

2.1 Drug

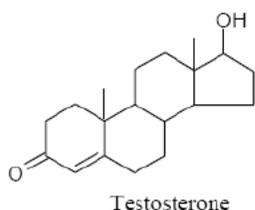
CAS Registry Number: 5949-44-0

Generic Name: testosterone

Chemical Name: (17 β)-17-hydroxyandrost-4-en-3one

Molecular Formula/Molecular Weight: C₁₉H₂₈O₂/288.42

Structure or Biochemical Description



Pharmacologic Class: androgen

2.2 Relevant IND/s, NDA/s, and DMF/s

(b) (4)	(b) (4)
NDA 22-309	(Abbott Labs, AndroGel® 1.62% testosterone gel)
NDA 21-454	(Auxillium, Testim® 1% testosterone gel)
NDA 22-504	(Acrux, Axiron® 1% testosterone solution)
DMF 21546	(Cipla, testosterone)

2.3 Drug Formulation

Product is delivered as 2.5 and 5 g sachets. The recommended starting dose is 5 g corresponding to 50 mg of testosterone and the dose can be titrated up to 10 g/day (100 mg testosterone).

Composition of Testosterone Gel 1% Product at a Dosage of 5 g/day

Ingredient	Function	Amount		Maximal Amount in Approved Products*
		mg	%w/w	
Testosterone, USP	API	50	1	--
Dehydrate alcohol USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Isopropyl palmitate NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Carbomer Homopolymer Type C NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium hydroxide NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified water USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)

*In the Inactive Ingredient Database

2.4 Comments on Novel Excipients

All excipients are at or below the levels in other FDA-approved products.

2.5 Comments on Impurities/Degradants of Concern

Impurities are (b) (4). They are below the specified limits of NMT (b) (4).

(b) (4). However, the amounts of any impurities/degradants in the drug product are (b) (4).



2.6 Proposed Clinical Population and Dosing Regimen

Hypogonadal men will self-administer testosterone gel with 5 to 10 g of drug product daily to the shoulders/upper arms (abdomen was not evaluated). The starting dose is 5 g with the amount to be titrated up to 10 g based on achieving serum testosterone levels of 300-1000 ng/dL. Sachets can be used in combinations that equal the number of grams of gel prescribed.

2.7 Regulatory Background

The applicant submitted a Form 356h with the 505(b)(2) box checked and a Reference List Drug listed as Androgel® (Testosterone Gel) 1%. Initially, the NDA had no Module 4 submitted, but responded to an IR request dated 3/28/2011 with an amendment from the applicant received on 6/13/2011. A scientific rationale for the reliance of Androgel and testosterone for this 505(b)(2) application and the literature references to support the safety of testosterone and similar testosterone gel products (specifically Sections 8.1 and 13.1 of the Labeling) were provided.

3 Studies Submitted

No studies were submitted or reviewed.

11 Integrated Summary and Safety Evaluation

The overall toxicological profile of testosterone products is well established and both animals and humans exhibit similar toxicities. There are extensive nonclinical and clinical data with testosterone products including transdermal applications. Nonclinical data support approval of topical testosterone gel 1%.

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/s/

JEFFREY D BRAY
09/30/2011

LYNNDA L REID
09/30/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202763

**Applicant: Teva
Pharmaceuticals**

Stamp Date: January 4, 2011

Drug Name: testosterone gel 1% NDA Type: 505(b)2

45-Day Filing Review Date: February 27, 2011

74-Day Letter Date: March 29, 2011

Expected Date of Draft Review: May 29, 2011

PDUFA Goal date: November 14, 2011

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?		X	The sponsor did not submit a nonclinical section.
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	n/a		See above.
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	n/a		See above.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?		X	The sponsor will be requested in the 74-day letter to state that the application will rely on the labeling of the reference testosterone product to support the labeling of this testosterone product. Irritation/sensitization studies done in humans.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		
6	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 <u>submitted</u> a rationale to justify the alternative route?	n/a		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	n/a		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	n/a		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Class labeling will be applied.
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	n/a		No issues have been identified; sponsor is using excipients ≤ amounts in FDA Inactive Ingredient Database.
11	Has the sponsor addressed any abuse potential issues in the submission?	X		Ensure consistency among transdermal T products in labeling on potential abuse.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments: To be relayed to sponsor:

To meet the nonclinical requirements for a NDA under a 505(b)(2) application please submit the following:

- 1) scientific justification for your reliance on AndroGel nonclinical data, and
- 2) published literature references to support the nonclinical sections of the labeling, i.e., Sections 8 and 13.

Jeffrey Bray, Ph.D. 1/27/2011

 Reviewing Pharmacologist Date

Lynnda Reid, Ph.D. 1/28/11

 Team Leader/Supervisor Date

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/s/

JEFFREY D BRAY
02/25/2011

LYNNDA L REID
02/25/2011