CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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/BLA REVIEW AND EVALUATION

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Supporting document/s:	EDR:\\CDSESUB1\EVSPROD\NDA205488\205488.enx
Applicant's letter date:	April 29, 2013
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Product:	Testosterone Intranasal Gel (TBS-1)
Indication:	Testosterone replacement in men for primary and hypogonadotropic hypogonadism
Applicant:	Trimel BioPharma SRL
Review Division:	DBRUP
Reviewer /Supervisor:	Lynnda L. Reid, Ph.D.
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1 Executive Summary

1.1 Introduction

TBS-1 is a gel consisting of testosterone USP (4.5%), castor oil ((b) (4)%), oleoyl polyoxylglycerides ((b) (4)%) and colloidal silicon dioxide ((b) (4)%), delivered intranasal as a testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

1.2 Brief Discussion of Nonclinical Findings

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. Intranasal, toxicology studies were conducted to support this new route of administration. 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.

In the *in vivo* local tolerance studies in rats and rabbits and the 3 month repeat dose toxicity study in rabbits, animals were exposed to TBS-1 through the nasal mucosa, the same proposed route of administration for hypogonadal men. Administration of TBS-1 intranasal for three months at doses up to 6-fold the recommended human dose were not associated with any local or systemic toxicity in the organs examined: nasal turbinates, brain, testes, heart, kidneys, and lungs. Local tolerance studies using an *ex vivo* model and the nasal route of administration in rats and rabbits demonstrated that testosterone in combination with the excipients of the gel (castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide) was non- irritating.

The highest dose used in the toxicology studies were approximately 4 times greater than the proposed daily clinical dose based on three administrations per day.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support **Approval** of TBS-1 for the treatment of male hypogonadism.

1.3.2 Additional Non Clinical Recommendations

None

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1.3.3 Labeling

Current nonclinical recommendations for labeling are provided below. Recommended labeling is consistent with other testosterone products to treat hypogonadism.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------Indications and Usage----------
TRADENAME (testosterone nasal gel) is an androgen indicated for testosterone replacement therapy in adult males for the conditions associated with a deficiency or absence of endogenous testosterone:

1 INDICATIONS AND USAGE
TRADENAME is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

4 CONTRAINDICATION

4.x Pregnancy

TRADENAME is contraindicated in women who are or who may become pregnant, or who are breast-feeding. TRADENAME may cause fetal harm when administered to a pregnant woman. TRADENAME may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to TRADENAME, she should be apprised of the potential hazard to the fetus (see Use in Specific Populations [**Error! Reference source not found.**, **Error! Reference source not found.**]).

5 WARNINGS AND PRECAUTIONS POPULATIONS

5.x Use in Women

Due to lack of controlled studies in women and potential virilizing effects, TRADENAME is not indicated for use in women.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy category X. TRADENAME is contraindicated in pregnant women or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization. If TRADENAME is used during pregnancy, or if the patient becomes pregnant while taking TRADENAME, the patient should be apprised of the potential hazard to the fetus.

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8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, TRADENAME is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, and Impairment of Fertility

Carcinogenicity
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. [see Contraindications (4) and Warnings and Precautions (5.5 and 5.8)].

Mutagenicity
Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays.

Impairment of Fertility
The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment [see Warnings and Precautions (5.8)].

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

CAS Registry Number: 5949-44-0

Generic Name: testosterone

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

Molecular Formula/Molecular Weight: $C_{19}H_{28}O_2$/288.4 (b) (4)

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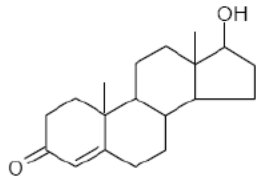
Structure or Biochemical Description



Testosterone

Pharmacologic Class: androgen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND	70,512	Testosterone nasal gel
NDAs:	21-105	AndroGel® 1% testosterone gel
	22-309	AndroGel® 1.62% testosterone gel
	21-454	Testim® 1% testosterone gel
	22-504	Axiron® 1% testosterone solution
DMFs:	(b) (4)	

2.3 Drug Formulation

TBS-1 is a viscous bioadhesive testosterone intranasal gel consisting of testosterone, castor oil, oleoyl polyoxylglycerides, and colloidal silicon dioxide

Ingredient	Percentage	Daily Dose	Function
Testosterone, USP	4.5%	(b) (4)	Active ingredient
Castor Oil, USP	(b) (4) %	(b) (4)	(b) (4)
Oleoyl polyoxylglycerides (b) (4) NF	(b) %	(b) (4)	(b) (4)
Colloidal silicon dioxide, NF	(b) %	(b) (4)	(b) (4)

2.4 Comments on Novel Excipients

(b) (4), (b) (4) has previously been used in marketed and investigational oral and vaginal preparations. However, the longest approved duration of use was (b) (4) days in the (b) (4) (b) (4) Given the nature of the product and the long history of use of closely related products and various drugs containing (b) (4), it was determined that the negative findings in the 3-month rabbit toxicity study was sufficient to qualify this excipient for use in chronically administered topical products.

2.5 Comments on Impurities/Degradants of Concern

There are no leachables/extractables or other notable impurities of concern in the drug product (See CMC review).

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical dose is 2 actuations (one in each nostril) given three times a day, for a total daily dose of 33 mg testosterone per day.

2.7 Regulatory Background

IND 70,512 was opened on June 30, 2005, to investigate the use of testosterone nasal gel for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) in men whose testosterone levels are <300 ng/dl. NDA 205-488 was filed April 29, 2013, as a 505(b)(2) submission, relying on published literature to assess risks associated with chronic use; reproductive and developmental risks; and risks associated with genotoxicity and carcinogenicity.

3 Studies Submitted

3.1 Studies Reviewed

- 3-Month Rabbit Study Study 227120417
- Local Tolerance – single dose Study 2008040401
- Local Tolerance – repeat dose Study 2008040402
- Local Tolerance – in vitro Study 2008040403

List of Literature Citations – See Appendix 1

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6 General Toxicology

6.2 Repeat-Dose Toxicity

The following Study was reviewed by Dr. Wafa Harrouk under IND 70,512.

Study title:	**3-Month Toxicity Study**
Study no.:	227120417
Study report location:	EDR:\\CDSESUB1\EVSPROD\NDA205488\205488.enx
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	January 4, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Nasobol Gel, batch #E1 014 ([redacted] (b) (4) [redacted] (b) (4)); Nasobol Gel Placebo, batch #E1 016

Key Study Findings: Findings were limited to the high-dose group where irritation of nostrils resulted in scarring & edema in 2/5 of the treated rabbits. Other findings included an increase in liver weight accompanied by a slight increase in glycogenic vacuolation.

Methods

Doses:	0 (sham control, no application), 0 (0.0029 ml/kg placebo volume), TBS-1 at 0.0029, 0.0087 or 0.029 ml/kg representing: 0.093, 0.280 or 0.933 mg/kg, respectively.
Frequency of dosing:	Daily
Route of administration:	Intranasal
Dose volume:	3.6, 12.6 and 56.5 µl/nostril
Formulation/Vehicle:	TBS-1 gel
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	5 males/group
Age:	~11 weeks
Weight:	2.2-3.5 kg
Satellite groups:	None

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Unique study design:	Nasobol gel (aka TBS-1) was administered twice daily into the left nostril and placebo the right nostril by letting the contents of filled syringes fall into each nostril of restrained rabbits: low-dose = 1 small drop; mid-dose = 1 drop; high-dose = 3 drops. [Drops were prequantified pretesting.] After applications, test articles were distributed evenly in the nostrils by massage of the animal's muzzle. During the last month, the number of drops/nostril was increased to a drop for the low-dose, a large drop for the mid-dose, and 4 drops for the high-dose group to account for the increase in body weight. Vehicle control animals were given a small drop during the first 2 months and increased to a large drop during the last month.
Deviation from study protocol:	Nothing significant

Observations and Results

Mortality

None

Clinical Signs

Rabbits were monitored for bleeding of nose, irritation and any other clinical signs twice daily. Animals were monitored for clinical signs (skin appearance, general and motor activity & breathing) before and after application.

No clinical signs (aspect, activity, coordination, respiration or lesions) were noted for sham controls and vehicle treated controls or Nasobol-treated rabbits in the low- and mid-dose groups.
In the high-dose animals, findings were restricted to the appearance of the rabbit (referred to as aspect by sponsor) where an increase in aspect findings was noted especially towards the last month of the treatment (coinciding with the increase in drop number administered/nostril). Findings were seen in 2/5 rabbits almost daily and included: reddish mucous membrane, small scabs on muzzle, irritation of nostril, which correlated with slight macroscopic irritations. Irritation of nostril and muzzle could be due to the animal scratching their muzzles where some of the dose was still present. No other findings developed into gross pathology findings (e.g., edema, scars) except for the 2 high-dose treated rabbits.

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Body Weights

Weights were recorded daily. No treatment-related effect was noted.

Gross Pathology

All animals in the control and high-dose groups underwent full necropsies.

Consistent with expected testosterone effects on the liver, an increase in liver weight was seen in rabbits in the mid- and high-dose groups. Brain weights also increased with dose but large variations were seen.

Organ Weights

The following organs were weighed in all animals: liver, kidneys, adrenals, testes, epididymides, thymus, spleen, brain, heart, lungs, stomach & colon.

Only increases in brain (not significant), liver (significant), esophagus weight and a decrease in peripheral nerve weights were noted. The only statistically significant finding was seen in the liver weight in mid- and high-dose animals.

Histopathology

Adequate Battery: Yes
Peer Review: No

A complete battery of tissues was collected from all animals but was not examined. Whole rabbit heads (including nasal cavities) were fixed, sliced and examined. The mucous membranes inside the nose, the respiratory tracts and subnasal cavities, testes, brain and any gross abnormalities were examined from all animals.

No changes were seen in the nasal turbinates, brain, testes, heart, kidneys or lungs. A slight increase in centrilobular/midzonal glycogenic vacuolation in the liver was seen in HD-treated rabbits (n=1 minimal, 3 mild, 1 severe) compared to controls (n=3 mild). Kidney findings included multifocal cortical tubular vacuolation (n=2 control, n=2 HD), papillary mineralization (n=1 HD) and focal basophilic tubules (n=1 HD).

Toxicokinetics

Blood samples were collected from the main ear vein of each rabbit on days 0, 45 & 90 of the study. Testosterone (T) and dihydrotestosterone (DHT) immunoassays were used (Kits used from Roche Diagnostics, Germany) to detect drug plasma levels.

T & DHT levels (see Tables on following page): Both hormones showed high variability. T levels did not increase with dose on day 0 but increased on days 45 & 90 of the study. DHT levels did not increase in response to the increase in T.

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Testosterone

Study group	Day of sampling	0	45	90
	Testosterone determination [µg / L = ng / ml]			
Control 1	Average	5.4	5.8	9.6
	SD	2.8	4.6	4.7
	SD %	52.3%	80.4%	49.0%
Control 2 = Placebo	Average	5.4	4.0	6.6
	SD	2.7	1.0	3.2
	SD %	49.6%	26.2%	48.7%
Low dose	Average	4.7	6.0	16.3
	SD	2.8	3.1	15.2
	SD %	59.0%	52.0%	93.2%
Medium dose	Average	4.4	12.8	53.2
	SD	2.8	7.7	20.7
	SD %	63.9%	60.0%	39.0%
High dose	Average	3.8	29.7	112.0
	SD	1.2	24.3	121.5
	SD %	31.9%	81.9%	108.4%

DHT

Study group	Day of sampling	0	45	90
	Testosterone determination [ng / L = pg / ml]			
Control 1	Average	835.4	256.6	1040.4
	SD	668.6	207.1	417.8
	SD %	80.0%	80.7%	40.2%
Control 2 = Placebo	Average	908.0	314.2	1027.4
	SD	537.5	215.9	586.9
	SD %	59.2%	68.7%	57.1%
Low dose	Average	803.0	585.6	1059.0
	SD	859.7	276.2	604.2
	SD %	107.1%	47.2%	57.1%
Medium dose	Average	732.2	271.2	1635.6
	SD	386.1	200.2	887.6
	SD %	52.7%	73.8%	54.3%
High dose	Average	575.4	311.2	1093.2
	SD	283.3	167.8	519.7
	SD %	49.2%	53.9%	47.5%

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7 Genetic Toxicology

Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays.

8 Carcinogenicity

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. [Human data: See Contraindications (4) and Warnings and Precautions (5.5 and 5.8)].

9 Reproductive and Developmental Toxicology

Reproduction: The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment [see Warnings and Precautions (5.8)].

Development: Testosterone is contraindicated in pregnant women or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization.

Although it is not known how much testosterone transfers into human milk, testosterone products are contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation.

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10 Special Toxicology Studies

Study title:	**Study of Local Tolerance, single application**
Study no.:	Study 2008040401
Study report location:	EDR:\\CDSESUB1\EVSPROD\NDA205488\205488.enx
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	April 21, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	NASOBOL [aka TSB-1], batch #100304, 35 mg testosterone/gram of gel

Key Study Findings: no significant findings of local irritation

Methods

Doses:	0.1 ml TBS-1 in left nostril and 0.1 ml Mygliol in right nostril
Frequency of dosing:	Single dose
Route of administration:	Intranasal
Dose volume:	0.1 ml
Formulation/Vehicle:	TBS-1 gel; reference control – neutral oil Mygliol
Species/Strain:	Sprague-Dawley rats New Zealand White rabbits
Number/Sex/Group:	3 males/species
Age:	Rats: ~7 weeks Rabbits: ~10 weeks
Weight:	Rats: 200-300 g Rabbits: 2-2.5 kg
Satellite groups:	None
Unique study design:	For the applications on rats, the inner flexible part of a sterile single usage catheter was used, whereas rabbits received applications directly from a 1 ml syringe. Animals were restrained and test items were left in nostrils for 4 hours.
Deviation from study protocol:	None

Observations and Results

After the applications, animals were observed for appearance of clinical signs such as bleeding from the nose, irritation and any other biologically abnormal reaction. Further assessments included:

- Appearance of the nostrils
- Activity

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- Coordination of motion: paralysis, spasms
- Breathing lesions, edemas
- Appearance of eyes, nose

After 4 hours, animals were euthanized by intracardious injection of T61. Histological evaluations were performed on the mucous membranes and nasal turbinates.

Results: There were no adverse clinical observations during the 4 hour observation period. Histopathologic examination revealed no significant difference between TBS-1 treated tissues and those exposed to the reference compound neutral oil Mygliol.

Study title:	**Study of Local Tolerance, repeated application during 2 weeks**
Study no.:	Study 2008040402
Study report location:	EDR:\\CDSESUB1\EVSPROD\NDA205488\205488.enx
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 21, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	NASOBOL [aka TSB-1], batch #100304, 35 mg testosterone/gram of gel

Key Study Findings: no significant findings of local irritation

Doses:	0.1 ml TBS-1 in left nostril and 0.1 ml Mygliol in right nostril
Frequency of dosing:	Single dose
Route of administration:	Intranasal
Dose volume:	0.1 ml
Formulation/Vehicle:	TBS-1 gel; reference control – neutral oil Mygliol
Species/Strain:	Sprague-Dawley rats New Zealand White rabbits
Number/Sex/Group:	3 males/species
Age:	Rats: ~7 weeks Rabbits: ~10 weeks
Weight:	Rats: 200-300 g Rabbits: 2-2.5 kg
Satellite groups:	None

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Unique study design:	For the applications on rats, the inner flexible part of a sterile single usage catheter was used, whereas rabbits received applications directly from a 1 ml syringe. Animals were treated daily for 2 weeks. After the last application, test items were left in nostrils for 4 hours prior to euthanasia.
Deviation from study protocol:	None

Observations and Results

After the applications, animals were observed for appearance of clinical signs such as bleeding from the nose, irritation and any other biologically abnormal reaction. Further assessments included:

- Appearance of the nostrils
- Aspect (especially skin)
- Activity
- Coordination of motion: paralysis, spasms
- Breathing lesions, edemas
- Appearance of eyes, nose
- Body weight

4 hours following the final administration on day 14, animals were euthanized by intracardious injection of T61. Histological evaluations were performed on the mucous membranes and nasal turbinates.

Results:

- In rats, but not in rabbits, some nasal bleeding was observed starting around day 6 in both TBS-1 and Mygliol treated nostrils with no deference in severity between the two treatments. Bleeding in rats was attributed to mechanical trauma during application.
- No changes in aspect, activity, coordination, respiration, body weight gain or lesions
- No significant histological changes

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Study title:	**Study HET-CAM according to the**
Study no.:	Study 2008040403
Study report location:	EDR:\\CDSESUB1\EVSPROD\NDA205488\205488.enx
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 8, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	NASOBOL [aka TSB-1], batch #100304, purity not specified

Key Study Findings: TBS-1 was deemed nonirritating under the conditions tested

Methods

Doses:	0.3 ml
Formulation/Vehicle:	TBS-1 gel; reference control – neutral oil Mygliol
Species/Strain:	Hen eggs
Number/Sex/Group:	4 eggs/test article
Unique study design:	Official method for the assessment of the irritating potential trough application of the chorio-allantois membrane of the Hen's Egg: The eggs were placed into an incubator (37.8ºC/60% humidity) for 10 days. Eggs were turned every 4 hours. After the 10 day incubation, the shell was taken away on the side of the air bag. All the area of the shell membrane was humidified with NaCl 0.9% warmed to 37ºC. The NaCl was then removed and the chorio allantois membrane was visible. Only eggs with an intact chorio allantois membrane were used. Test articles were warmed to 37ºC and laced on t6he chorio allantois membrane for 20 seconds. Eggs were then rinsed with 5 ml NaCl and observed for 5 minutes.
Deviation from study protocol:	None

Results

There were no signs of hyperemia, hemorrhage, coagulation or thrombosis. There were no differences between TBS-1 and neutral oil Mygliol.

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11 Integrated Summary and Safety Evaluation

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. Currently available options for administration of testosterone are transdermal gels and patches, injectables, implantables, and buccal administration.

Local irritation studies and a 3-month repeat dose study in rabbits via nasal instillation support the safety of TBS-1. TBS-1 in rats and rabbits produced no significant nasal irritation or toxicity. Doses in the 3-month study were originally selected to represent 1x, 3x and 10x the maximum anticipated twice daily (bid) clinical dosing regimen. However, the recommended approved dose will be three times daily (TID), resulting in lower, but still considered adequate, exposure multiples in the nonclinical studies.

Nonclinical labeling sections are supported by referenced testosterone literature.

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12 Appendix/Attachments

APPENDIX 1

LIST OF LITERATURE CITATIONS

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/s/

LYNNDA L REID
01/16/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205-488 **Applicant:** Trimel Biopharma **Stamp Date:** April 28, 2013

Drug Name: TBS-1 (testosterone) intranasal gel CIII **NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for RTF: From a Pharm/Tox perspective, the application is fileable.

	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		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	x		
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?	x		
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		Submission includes the following study reports: • 3-month intranasal repeat-dose toxicology study in male rabbits • in vivo and in vitro local tolerance studies • Literature references regarding genotoxicity, carcinogenicity and reproductive/developmental toxicity • Evaluation of Impurities • Evaluation of Excipients • Systemic Exposures
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).	x		Testosterone intranasal gel (TBS-1) was used in the 3-month and local tolerance rabbit studies.

Reference ID: 3330767

	Content Parameter	Yes	No	Comment
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 submitted a rationale to justify the alternative route?	x		
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		3-month study conducted at (b) (4)
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	x		
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		
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	x		
11	Has the sponsor addressed any abuse potential issues in the submission?			NA
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

Any Additional Comments: None

Reference ID: 3330767

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LYNNDA L REID
06/24/2013