CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205488Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA #	205488
Applicant Name	Trimel BioPharma SRL
Date of Submission	April 29, 2013
PDUFA Goal Date	May 28, 2014
Proprietary Name / Established (USAN) Name	Natesto (testosterone) nasal gel
Dosage Forms / Strength	Metered dose pump with each actuation delivering 5.5 mg of testosterone
Proposed Indication	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Roger Wiederhorn, M.D.
Statistical Review	Sonia Castillo, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Lynnda Reid, Ph.D.
ONDQA Review	Hitesh Shroff, Ph.D. and Moo Jhong Rhee, Ph.D.
Clinical Microbiology	Bryan Riley, Ph.D. and Stephen Langille, Ph.D.
Clinical Pharmacology Review (Includes Pharmacometrics)	Chongwoo Yu, Ph.D., Myong-Jin Kim, Pharm.D., Jiang Liu, Ph.D. and Yaning Wang, Ph.D.
Biopharmaceutics Review	Kelly Kitchens, Ph.D., Tapash Ghosh, Ph.D. and Richard Lostritto, Ph.D.
DPARP Consult Review	Sofia Chaudhry, M.D., Susan Limb, M.D., and Badrul Chowdhury, M.D., Ph.D.
CDTL Review	Mark Hirsch, M.D.
Environmental Assessment	Raanan Bloom, Ph.D. and Nakissa Sadrieh, Ph.D.
OSE/DMEPA	Manizheh Siahpoushan, Pharm.D., James Schlick, R.Ph., M.B.A., and Carol Holquist, R.Ph. Denise Baugh, Pharm.D., M.B.A. and Lisa Khosla, Pharm.D., M.H.A.
Office of Scientific Investigations	Gopa Biswas, Ph.D., Sam Haidar, Ph.D., R.Ph. and William Taylor, Ph.D.
OPDP	Trung-Hieu Brian Tran, Pharm.D., M.B.A.
OMP/DMPP	Shawna Hutchins, M.P.H, B.S.N., R.N., Melissa Hulett, M.S.B.A., B.S.N., R.N. and LaShawn Griffiths, M.S.H.S.-P.H., B.S.N., R.N.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPARP=Division of Pulmonary, Allergy and Rheumatology Products
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Trimel BioPharma SRL submitted this new drug application (NDA) for intranasal testosterone gel, tradename Natesto. The Applicant is seeking approval through the 505(b)(2) approval pathway by relying, in part, upon published literature for testosterone. This document serves as FDA's decisional memorandum and will mostly focus on the efficacy issues and the unique safety concerns related to the intranasal route of administration.

2. Background

There are several approved testosterone products, including gels and patches applied to the skin, injectable formulations, and a buccal mucoadhesive system. Each formulation has its own advantages and disadvantages but all are approved as replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. If Natesto is approved, it will carry this same indication but will offer a novel route of administration. Additional background is provided, where needed, in the sections below in context of the issues being discussed.

3. CMC/Device

The drug substance in Natesto is testosterone, manufactured by (b) (4) and (b) (4). The Applicant provided letters of authorization to reference these Drug Master Files. The Chemistry/Manufacturing/Controls (CMC) reviewers have determined that both Drug Master Files are adequate.

The Natesto drug product is available in a metered-dose pump that contains 11 grams of gel dispensed as 60 metered pump actuations. Each pump actuation delivers 5.5 mg of testosterone in 122.5 mg of gel. A dose consists of two actuations, one per nostril, for a total delivered testosterone dose of 11 mg.

There are no novel ingredients in the drug product. The inactive ingredients are castor oil ((b) (4)), oleoyl polyoxylglycerides ((b) (4)) and colloidal silicon dioxide ((b) (4)). These are commonly used excipients and are compendial. All components in Natesto are at or below the levels in other FDA-approved products. The CMC reviewers have concluded that there are adequate specifications to assure the identity, strength, purity and quality of the drug product. There are no concerns with impurities and there are no compatibility issues between the drug substance, excipients, and container closure. The CMC reviewers agree with a 24-month expiration dating period.

The Environmental Assessment staff agrees that this application qualifies for a categorical exclusion from the requirement to submit an Environmental Assessment. See the review by Raanan Bloom, Ph.D., for further details.

The Office of Compliance has issued an overall acceptable recommendation for the manufacturing facilities.

There are no outstanding CMC issues. The CMC reviewers recommend approval of the NDA. See the review by Hitesh Shroff, Ph.D., for further details.

4. Nonclinical Pharmacology/Toxicology

The overall toxicological profile of testosterone is well established. The Applicant is abbreviating its nonclinical pharmacology/toxicology program by relying upon published literature. To support the new route of administration, the Applicant conducted local tolerance studies in rats and rabbits and a 3-month repeat-dose toxicity study in rabbits, with all animals exposed through the nasal mucosa. Intranasal administration for 3 months at adequate exposure multiples of the clinical dose was not associated with local or systemic toxicity. Intranasal administration in the single-dose and 2-week local tolerance studies produced no significant nasal irritation. There are no outstanding nonclinical pharmacology/toxicology issues. The nonclinical pharmacology/toxicology reviewer recommends approval of the NDA. See the review by Lynnda Reid, Ph.D., for details.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommend approval of the NDA. See the review by Chongwoo Yu, Ph.D., for further details.

This section of the memorandum focuses only on the clinical pharmacology study in patients with allergic rhinitis. See Section 7 for a discussion of the pivotal phase 3 study.

Seasonal allergic rhinitis: The Applicant conducted an open-label, crossover study in 18 healthy men (14 completers) with seasonal allergic rhinitis. The study had three randomized treatment periods:

- Asymptomatic state
- Symptomatic state induced in an environmental challenge chamber, then left untreated
- Symptomatic state induced in an environmental challenge chamber then treated with the decongestant oxymetazoline. The Applicant chose oxymetazoline because the vasoconstrictor properties have the potential for a significant effect on systemic absorption of Natesto. Each dose of oxymetazoline comprised two puffs in each nostril. Patients received a total of two doses of oxymetazoline 12 hours apart. The morning oxymetazoline dose was given 30 minutes before the morning Natesto dose.

Each subject received three doses of Natesto in each treatment period (a dose at 7 am, another dose at 1 pm and the final dose at 9 pm).

As shown in Table 1, serum testosterone pharmacokinetics were modestly reduced in subjects with symptomatic allergic rhinitis compared to the asymptomatic state. The use of oxymetazoline had minimal additional impact on these pharmacokinetic parameters. For these analyses, Dr. Yu focused on the baseline-uncorrected analyses because 24-hour baseline data were not collected prior to each treatment period. Dr. Yu concluded that these small changes in testosterone pharmacokinetics are not likely to significantly impact the efficacy of Natesto. For further details see Dr. Yu's review as well as the consult review by Sofia Chaudhry, M.D., from the Division of Pulmonary, Allergy, and Rheumatology Products.

Table 1. Baseline-uncorrected testosterone pharmacokinetic parameters in 14 healthy men with seasonal allergic rhinitis

	Untreated Symptomatic State vs. Asymptomatic State	Treated Symptomatic State[1] vs. Asymptomatic State
$AUC_{0\text{-}24hr}$ (ng*hr/dL)	21% ↓	24% ↓
C_{max} (ng/dL)	14% ↓	18% ↓
C_{avg} (ng/dL)	21% ↓	24% ↓

[1]Treated with oxymetazoline

Biopharmaceutics: During development, the Applicant determined the *in vitro* release rate of testosterone from the gel. The Biopharmaceutics reviewers found the Applicant's *in vitro* release test method and the proposed interim specifications of the *in vitro* release test method to be acceptable and recommend approval of the NDA. (b) (4) [redacted] See the review by Kelly Kitchens, Ph.D., for further details.

6. Clinical Microbiology

The clinical microbiology reviewers recommend approval of the NDA. Natesto is a non-sterile nasal product that does not contain a preservative. It has adequate microbial limit specifications and meets the acceptance criteria for antimicrobial effectiveness testing. See the review by Bryan Riley, Ph.D., for details.

7. Clinical/Statistical-Efficacy

This section briefly summarizes the design of the phase 3 study and the key efficacy results. See the clinical review by Roger Wiederhorn, M.D., the clinical pharmacology review by

Chongwoo Yu, Ph.D., the statistical review by Sonia Castillo, Ph.D., and the Cross-Discipline Team Leader Memorandum by Mark Hirsch, M.D. for further details.

The open-label, multicenter, phase 3 study (TBS-1-2011-03) was conducted in the United States and randomized 306 men in a 3:1 ratio to Natesto 11 mg (5.5 mg in each nostril) twice daily (n=228) vs. Natesto 11 mg (5.5 mg in each nostril) three times daily (n=78). Patients who started on twice daily dosing were to be uptitrated to three times per day dosing on Day 45 if the Day 30 estimated serum testosterone Cavg was less than 300 ng/dL. To estimate the Day 30 Cavg, serum testosterone was collected 1 hour before and 20 minutes after the morning Natesto dose. If the sum of these two testosterone measurements was less than 755 ng/dL, the patient was considered to have an estimated Cavg <300 ng/dL. (b) (4)

Inclusion criteria included age 18-80 years, body mass index 18.5-35 kg/m^2, and two fasting morning testosterone concentrations <300 ng/dL (obtained after washout for those patients on other testosterone therapies). Exclusion criteria included a history of nasal surgery, history of nasal fracture within the preceding 6 months (or at any time if there was a severely deviated anterior nasal septum), active allergic rhinitis, mucosal inflammatory disorders, sinus disease, and other nasal disorders (e.g., polyps, recurrent epistaxis). Patients on other intranasal medications were excluded. The randomized population had a mean age of 54 years (80% <65 years old). Most (90%) were Caucasian. The mean body mass index was ~30 kg/m^2. The mean duration of hypogonadism was 4.6 years and most patients (72%) had a diagnosis of primary hypogonadism. The mean testosterone concentration during screening was 200 ng/dL. Most patients (73%) were naïve to testosterone therapy.

The phase 3 study used the to-be-marketed Natesto formulation. The key efficacy analyses were conducted at Day 90 based on 24-hour total testosterone pharmacokinetic profiles. Per Dr. Yu, the bioanalytical methods used to measure the key efficacy parameters were adequate. The study used the standard efficacy parameters and success criteria that we routinely require for testosterone therapies:

- The primary efficacy endpoint was the total testosterone Cavg on Day 90 (calculated by dividing the Day 90 $AUC_{0\text{-}24hr}$ by 24). At least 75% of patients were to have Cavg in the range of 300-1050 ng/dL. The associated 95% confidence interval was to have a lower bound of at least 65%.

- There were three key secondary efficacy endpoints, all based on total testosterone Cmax on Day 90:
    - ≥85% of patients were to have Cmax ≤1500 ng/dL
    - <5% of patients were to have Cmax 1800-2500 ng/dL
    - No patients were to have Cmax >2500 ng/dL

These efficacy analyses were calculated using a modified intent-to-treat population defined as patients who received randomized study drug and who had at least one valid post-baseline efficacy measurement. Missing data were imputed using last-observation-carried-forward. About 90% of randomized patients completed the 90-day treatment period with about 94-95% of randomized patients having valid post-baseline data. As discussed in the statistical review by Dr. Castillo, the protocol did not specify which treatment group from the phase 3 study would be used to establish efficacy. The clinical and clinical pharmacology review teams concluded that efficacy should be evaluated in the treatment group that reflects the Applicant's proposed dosing regimen. The Applicant initially proposed that patients start on twice daily dosing (b) (4). However, (b) (4)

Table 2. Primary efficacy results based on the Applicant's originally proposed dosing regimen. Modified intent-to-treat population with last-observation-carried-forward (LOCF) for missing data. (adapted from Dr. Yu's Tables A-1-14 and A-1-20 and Dr. Castillo's Table 3.2)

Day 90	Prespecified Criteria for Success	Randomized to BID Dosing		
		Remained on BID	Uptitrated to TID	Remained on BID or Uptitrated to TID
N		(b) (4)		
Cavg 300-1050 ng/dL, n (%)	≥75%			
Lower Bound of the 95% CI for Cavg	≥65%			

BID = twice daily dosing; TID = three times per day dosing; CI = confidence interval

The review team shared these efficacy concerns with the Applicant during the NDA review. The Applicant subsequently decided to submit an amendment to the NDA proposing only a three times per day dosing regimen for all patients. We determined that this submission, which included supporting data, qualified as a Major Amendment, and extended the user fee goal date by three months.

Figure 1 shows the Day 90 pharmacokinetic profile for serum total testosterone with three times per day dosing of Natesto. The median Tmax is 0.7 hours. The regimen maintained serum total testosterone within the range of 300-1050 ng/dL for an average of 16 hours.

Figure 1. Serum total testosterone concentrations (Mean ± SD) on Day 90 with three times per day dosing of Natesto (N=69) in Study TBS-1-2011-03 (from Figure 1 in Dr. Yu's review).

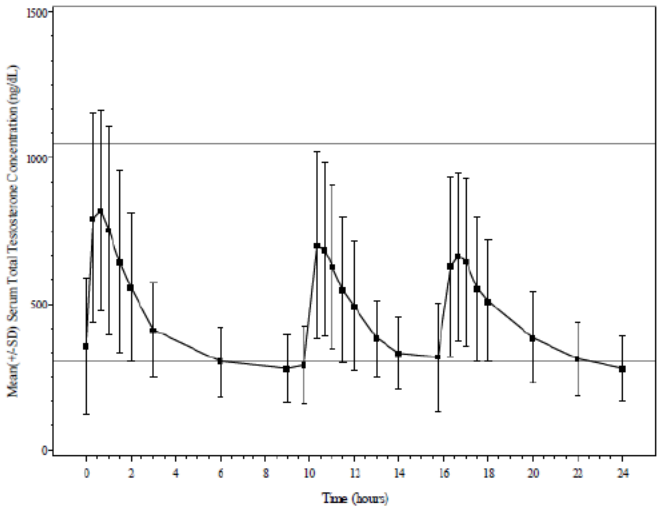

Table 3 summarizes the key efficacy results for the revised dosing regimen and shows that the patients randomized to three times per day dosing of Natesto easily achieved the primary efficacy success criteria for Cavg. The seven patients (10%) randomized to three times per day dosing who did not meet the Cavg success criteria all had Cavg <300 ng/dL.

Dr. Castillo prefers to define the intent-to-treat population as all patients who received at least one dose of study medication with baseline values carried forward for patients with missing post-baseline data. This approach is more conservative than the Applicant's definition, but still meets the pre-specified primary efficacy criteria for success.

Efficacy at Day 30 in patients randomized to three times per day dosing is similar to that seen at Day 90. On Day 30, 84% of these patients had Cavg in the range of 300-1050 ng/dL with a lower bound of 75% for the associated 95% confidence interval. The 16% of patients who were not within the range of 300-1050 ng/dL all had Cavg <300 ng/dL.

A total of (b) (4) patients (b) (4) %) randomized to twice daily dosing were uptitrated to three times per day dosing. Interestingly, only (b) (4) % of these (b) (4) patients achieved (b) (4) Therefore, this uptitrated group does not reflect an all-comers population and should not be used as the primary population for assessing efficacy for the three times per day dosing regimen.

Table 3 also summarizes the key secondary efficacy results on Day 90 for patients randomized to three times per day dosing. Two of these three endpoints were achieved (Cmax 1800-2500 ng/dL in less than 5% of patients and Cmax >2500 ng/dL in no patients). The remaining key

efficacy endpoint (Cmax ≤1500 ng/dL) was achieved in 84% of patients and should have been achieved in at least 85% of patients. This pre-specified criterion would have been met had only one additional patient achieved Cmax ≤1500 ng/dL. I do not think it is reasonable to decline to approve this product based on the impact of a single patient on the outcome of one of three key secondary endpoints.

Table 3. Key efficacy results based on the Applicant's revised dosing regimen. Modified intent-to-treat population with last-observation-carried-forward (LOCF) for missing data. (adapted from Dr. Yu's Tables A-1-14 and A-1-20 and Dr. Castillo's Table 3.2)

Day 90	Prespecified Criteria for Success	Randomized to Three Times per Day Dosing
Primary Efficacy Endpoint		
N		73
Cavg 300-1050 ng/dL, n (%)	≥75%	66 (90%)
Lower Bound of the 95% Confidence Interval for Cavg	≥65%	84%
Key Secondary Efficacy Endpoints		
N with Cmax at Day 90		69
Cmax ≤1500 ng/dL, n (%)	≥85%	58 (84%)
Cmax 1800-2500 ng/dL, n (%)	<5%	1 (1%)
Cmax >2500 ng/dL, n (%)	0	0%

In the phase 3 study, there were no patients randomized to three times per day dosing or uptitrated to three times per day dosing who developed testosterone Cmax >2500 ng/dL on Day 90. There were three patients who had Cmax >2500 ng/dL on Day 30 (two on twice daily dosing and one randomized to three times per day dosing). However, all three patients had Day 90 Cmax values <2500 ng/dL. The only patient who had Cmax >2500 ng/dL on Day 90 had been randomized to twice daily dosing and was still using twice daily dosing on Day 90. The Applicant attributed the elevated Cmax in this patient to a possible post-treatment effect from prior use of finasteride (a 5-alpha reductase inhibitor, which inhibits conversion of testosterone to dihydrotestosterone). Although the low dihydrotestosterone/testosterone ratio supports this possibly, finasteride is an unlikely explanation for these findings. First, finasteride had been discontinued two months prior to initiation of Natesto (and five months prior to the Day 90 Cmax measurement). Also, as noted by Dr. Wiederhorn, prior finasteride use would not explain why the Cmax on Day 90 (3570 ng/dL) was considerably higher than the Cmax on Day 30 (1390 ng/dL). In any event, this isolated finding is not sufficient to preclude approval.

The Clinical Pharmacology and Clinical teams have reviewed the estradiol data and serum dihydrotestosterone/total testosterone ratios on Day 90 and have concluded that these results are consistent with that typically seen with other approved testosterone products.

8. Safety

After the Day 90 primary efficacy timepoint, patients could enter a 90-day extension period followed by a 180-day extension period. The same Natesto dose used on Day 90 was

continued during the two extension periods. A total of 274 patients (90% of the 306 randomized patients) completed Day 90 of the phase 3 study. These 274 patients entered the first 90-day extension period, 75 of whom completed the extension period and entered the second 180-day extension period.

As noted by Dr. Hirsch, 283 patients were exposed to Natesto for at least 90 days, 247 patients were exposed for at least six months, and 67 patients were exposed for at least one year. For the three times per day dosing regimen, 152 patients were exposed for at least 90 days, 69 patients were exposed for at least 180 days and 18 patients were exposed for at least 360 days.

General Safety: As discussed by Drs. Wiederhorn and Hirsch, there were some adverse events, such as increased hematocrit and increased prostate specific antigen that were reported among Natesto-treated patients in the phase 3 study. The lack of a placebo group precludes the ability to definitively conclude that these adverse events are related to treatment; however, the nature of these adverse events is consistent with the known pharmacological effects of testosterone. I agree with Dr. Wiederhorn that this general adverse event profile is similar to that of other drugs in the class. From a general safety perspective, I agree with Dr. Wiederhorn that there is sufficient long-term patient exposure to Natesto given that the adverse event profile of testosterone products is well known and that Natesto achieves testosterone concentrations that are generally in the lower one-half of the reference range (mean Cavg 421±116 ng/dL on Day 90 in patients randomized to three times per day dosing). Natesto will have class labeling with respect to these types of adverse reactions.

Nasal Adverse Reactions: Nasal safety was assessed in the phase 3 study based on adverse event reporting and based on physical examinations, including monthly nasal endoscopy performed by an otorhinolaryngologist. The clinical team as well as Dr. Chaudhry, from the Division of Pulmonary, Allergy, and Rheumatology Products, reviewed the nasal safety data in detail. Dr. Chaudhry determined that the available database is sufficient to evaluate nasal safety given that Natesto is associated with a low incidence of nasal irritation. There were no serious adverse nasal events in the phase 3 study or its extension periods, and few patients discontinued due to nasal adverse events. Nasal adverse events reported at some point during the phase 3 study or its extension periods included nasopharyngitis, rhinorrhea, epistaxis, nasal discomfort, parosmia, nasal scab, upper respiratory tract infection, nasal dryness and nasal congestion – each reported in fewer than 10% of patients. Most of the reported nasal adverse events were minor. Potentially more severe nasal adverse events such as nasal ulceration occurred in isolated patients and there were no reports of more significant irreversible toxicity like nasal septal perforation. Dr. Chaudhry did not identify evidence of a dose-related increase in nasal toxicity with three times per day dosing compared to two times per day dosing. Dr. Chaudhry also reviewed the nasal endoscopy findings and concluded that no patients had exam findings of concern. Nonetheless, Dr. Chaudhry recommends that the risk of nasal irritation be included in the product labeling.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee. The Application did not raise efficacy or safety issues needing input from an external advisory panel.

10. Pediatrics

The Division in consultation with the Pediatric Review Committee (PeRC) agrees with the Applicant's request for a full waiver from conducting pediatric studies under the Pediatric Research Equity Act (PREA). Hypogonadism is rare in children; therefore, studies of Natesto in the pediatric population are impossible or highly impractical.

11. Other Relevant Regulatory Issues

Drs. Wiederhorn and Hirsch did not identify concerns relating to financial disclosures of study investigators.

The Office of Scientific Investigations (OSI) conducted inspections of the analytical portion of the phase 3 study and three clinical sites. OSI found the analytical data to be acceptable. The two issues identified by OSI during the clinical site inspections have been adequately addressed by the review team:

- (b) (4). This raises no concerns and is no longer relevant because the Applicant is now proposing three times per day dosing for all patients.

- One patient had elevated serum transaminases and a markedly elevated serum creatine phosphokinase (7070 U/L or 34-fold increase above the upper limit of normal) on Day 90. The clinical investigator decided that these results were not clinically significant because the patient had been involved in strenuous physical exercise before the clinic visit. This explanation is reasonable. Of note, the patient's creatine phosphokinase had returned to baseline at the next measurement on Day 180. In addition, there is lack of biological plausibility linking the well-known ingredients in Natesto to these findings.

See the OSI reviews by Gopa Biswas, Ph.D., for details.

There are no unresolved regulatory issues.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) found the tradename 'Natesto' to be acceptable from both a promotional and safety perspective. See the review by Manizheh Siahpoushan, Pharm.D., for details.

The review disciplines and the Applicant have reached agreement on all labeling materials. Key aspects of physician labeling include:

- Text in the Dosage and Administration section stating that the drug-drug interaction potential between Natesto and nasally administered drugs other than sympathomimetic decongestants is unknown and not recommended.
- Text in the Dosage and Administration section recommending periodic testosterone measurements. The text will recommend discontinuing Natesto if the total testosterone concentration consistently exceeds 1050 ng/dL and to consider alternative treatment if the total testosterone concentration is consistently below 300 ng/dL. (b) (5) [redacted].
- A Warning and Precaution for nasal adverse reactions and noting the limited long-term data on nasal safety
- A Warning and Precaution recommending against use in patients with chronic nasal conditions and alterations in nasal anatomy as these patients were excluded from the phase 3 study
- A new Warning and Precaution noting postmarketing reports of venous thromboembolism in patients treated with testosterone products, such as Natesto (b) (5) [redacted]
- Class labeling for testosterone products, where appropriate. Natesto is a Schedule III controlled substance like all other approved testosterones.

The finalized labeling incorporates recommendations from the Office of Prescription Drug Promotion (OPDP), the Office of Medical Policy's Division of Medical Policy Programs (DMPP), and from DMEPA. See the reviews by Trung-Hieu Brian Tran, Pharm.D., M.B.A., Shawna Hutchins, M.P.H., B.S.N., R.N., and Denise Baugh, Pharm.D., M.B.A., for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

All review disciplines are recommending approval of this NDA. The consensus among the clinical pharmacology, clinical, and statistical reviewers is that there is sufficient evidence of efficacy with the three times per day dosing regimen. I agree. The clinical team has also concluded that the general safety profile of Natesto is similar to that of other testosterone products, except for local nasal irritation related to the novel route of administration. The nasal irritation is generally mild and can be adequately addressed with labeling alone. Disadvantages of Natesto include the need for three times per day dosing and local nasal irritation. Advantages include the ability to self-administer (compared to injectable products requiring administration by healthcare providers) and no risk of skin reactions or transfer to others (compared to the transdermal products). Based on all the above considerations, Natesto is another reasonable option for replacing testosterone in the hypogonadal male and should be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

HYLTON V JOFFE
05/28/2014