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***APPLICATION NUMBER:***

**022219Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	March 5, 2014
<b>From</b>	Christine P. Nguyen, MD
<b>Subject</b>	Deputy Director for Safety Summary Review
<b>NDA/BLA #/Supplement #</b>	022219/000
<b>Applicant Name</b>	Endo Pharmaceuticals
<b>Date of Submission</b>	August 29, 2013
<b>PDUFA Goal Date</b>	February 28, 2014
<b>Proprietary Name / Established (USAN) Name</b>	Aveed (testosterone undecanoate) injection
<b>Dosage Forms / Strength</b>	750 mg in 3 mL solution for intramuscular injection
<b>Proposed Indication(s)</b>	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
<b>Action/Recommended Action</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Guodong Fang, MD
Statistical Review	Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Eric Andreasen, PhD; Lynnda Reid, PhD
CMC Review	Yichun Sun, PhD; Moo Jhong Rhee, PhD
Microbiology Review	Vera Viehmann
Clinical Pharmacology Review	Huynjin Kim, PharmD, MS; Myong Jin Kim, PharmD
CDTL Review	Mark S. Hirsch, MD
SEALD	Abimbola Adebawale, PhD; Eric Brodsky, MD
OSE/DMEPA	Justine Harris, RPh; Lisa Vo Khosla, PharmD, MHA
OSE/DRISK	Suzanne Berkman-Robottom, PharmD; Cynthia LaCivita, PharmD; Claudia Manzo, PharmD
OMPI/DMPP	Shawna Hutchins, MPH, RN; Melissa Hulett, MSBA, RN; LaShawn Griffiths, MSHS-PH, RN
OPDP	Trung-Hieu Brian Tran, PharmD, MBA; Christine Corser, PharmD, RAC
OCD/Controlled Substance Staff	Alicja Lerner, MD, PhD; Michael Klein, PhD

OND=Office of New Drugs  
CDTL=Cross-Discipline Team Leader  
CMC=Chemistry, Manufacturing, Controls  
DMEPA=Division of Medication Error Prevention and Analysis  
DMPP=Division of Medical Policy Programs  
DRISK=Division of Risk Management  
OCD=Office of the Center Director  
OMPI=Office of Medical Policy Initiatives  
OPDP=Office of Prescription Drug Promotion  
OSE=Office of Surveillance and Epidemiology  
SEALD=Study Endpoints and Labeling Development

## Summary Review for Regulatory Action

### 1. Introduction

The Applicant, Endo Pharmaceuticals Solutions, Inc., submits this response to the Complete Response (CR) letter issued on May 29, 2013, for NDA 22-219 in which the Applicant sought the approval of testosterone undecanoate for injection (tradename Aveed) as testosterone replacement therapy in adult males with conditions associated with a deficiency or absence of endogenous testosterone. Aveed contains testosterone undecanoate (TU), a testosterone ester, at a dose of 750 mg/3 mL to be injected intramuscularly at the start of therapy, a second injection 4 weeks later, and then every 10 weeks thereafter.

Multiple formulations of testosterone replacement therapy (TRT) are available in the U.S. These include transdermal patch, gel, and solution; buccal bioadhesive system; an oral tablet; a subcutaneous implant; as well as two products for intramuscular injection. The two injectable products (testosterone enanthate and testosterone cypionate) require injection approximately every 2 to 4 weeks. Aveed is formulated as an intramuscular injectable that allows for a longer interval between treatment injections (every 10 weeks).

This Complete Response resubmission comprises the fourth review cycle for Aveed. The efficacy of Aveed was demonstrated in the original NDA submitted in August 2007. However, safety concerns over post-injection serious pulmonary microembolism (POME) events and anaphylaxis rendered the benefit-risk balance unfavorable and has precluded the approval of Aveed to date. In this resubmission, the Applicant proposed a risk evaluation and mitigation strategy with Elements to Assure Safe Use (ETASUs-REMS) to ensure that the benefits of Aveed outweigh the risk of serious post-injection reactions and revised labeling to better define, to the extent possible, a population for whom Aveed would be an appropriate TRT. The ETASUs-REMS and revised labeling, along with updated postmarketing safety data, sufficiently addressed the deficiencies in the May 2013 CR letter.

This memorandum provides the basis for the regulatory action for Aveed.

### 2. Background

Male hypogonadism is a clinical syndrome of insufficient or absent endogenous testosterone secretion, as reflected by low serum testosterone concentrations, and associated clinical features. Clinical presentations of hypogonadism in adult men may vary and include regression of male secondary sex characteristics, decreased muscle mass, and osteoporosis. Some causes of primary male hypogonadism include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's syndrome; secondary causes include pituitary-hypothalamic injury due to brain radiation, trauma, or tumors or other idiopathic causes. Primary and secondary male hypogonadism is treated with testosterone replacement therapy.

Multiple dosage forms of testosterone have been approved in the U.S. as TRTs. Each dosage form has its own formulation-specific advantages and disadvantages. For example, the transdermal gel easy to use (applied topically), but requires daily dosing and carries a boxed warning of the risk of secondary exposure to women and children. Currently, two injectable

testosterone products are approved in the US (testosterone enanthate, approved in 1953, and testosterone cypionate, approved in 1979). The dose regimen for both of these injectable testosterone esters is 50 mg to 400 mg injected every 2 to 4 weeks, or 13 to 26 injections per year. The regimen for Aveed consists of an initial load of an injection at the beginning of treatment and a second injection 4 weeks later, followed by maintenance therapy every 10 weeks thereafter. Treatment with Aveed requires 6 injections annually.

Testosterone undecanoate (TU), the testosterone ester in Aveed, for injection has been approved outside the US since November 2003. Currently, TU is approved in over 100 countries and marketed in 78 countries. It is sold under the tradename Nebido in most countries. Nebido is approved as TRT for male hypogonadism at dose regimen of TU 1000 mg/4 mL injected every 10 to 14 weeks. The dose (TU 1000 mg) and injection volume (4 mL) in Nebido are higher than Aveed, which contains TU 750 mg in 3 mL.

The following overview of the regulatory history of Aveed (TU 750 mg/3 mL) has been adapted from the memos of DBRUP deputy director (Audrey Gassman, MD) dated May 29, 2013, and the cross-discipline team leader (Mark S. Hirsch, MD) dated May 28, 2013, and February 28, 2014. See Dr. Hirsch's February 2014 CDTL memos for details of previous review cycles.

The **original NDA** for Aveed was submitted on **August 24, 2007**. The pivotal study IP157-001, Part C (referred to as "Part C" study) evaluated the efficacy of Aveed using the to-be-marketed dose and dosing regimen of TU 750 mg in 3 mL administered at Day 1, Week 4, and then every 10 weeks thereafter. The study showed that Aveed administered according to this regimen met the standard of substantial evidence of efficacy for a TRT. In the original NDA, the safety database comprised of a clinical trial safety population of 709 hypogonadal men enrolled in 6 trials and postmarketing experience of TU 1000 mg/mL outside the US since November 2003. The safety profile of Aveed was generally comparable to other approved testosterone products, with the exception of post-injection reactions consistent with pulmonary microembolism (POME) and anaphylaxis. Specifically, immediate post-injection reactions (sudden urge to cough, dyspnea, respiratory distress), occurred in 2 of 709 adult male hypogonadal patients. More concerning, however, was the 66 postmarket cases of immediate post-injection respiratory and hypersensitivity reactions reported in the Periodic Safety Update Reports and other postmarket sources for TU dating from November 2003 to October 2007. Twenty-eight of these cases were serious, 12 required emergency medical care, and 6 required hospitalization. The postmarket cases described symptoms such as cough, shortness of breath, throat tightness, pruritis, tachycardia, and blood pressure changes. In a consult from the Division of Pulmonary and Allergy (now the Division of Pulmonary, Allergy, and Rheumatology Products [DPARP]) to DBRUP dated April 14, 2008, Dr. Charles Lee concluded that there were 4 cases of anaphylaxis in the postmarketing experience of TU. At that time, the applicant disagreed that there were anaphylaxis cases with TU, but rather, attributed all cases to POME that could be mitigated by appropriate injection methods. These clinically significant adverse reactions rendered the benefit-risk calculus of Aveed unfavorable. The Division took an Approvable action on June 27, 2008, based on clinical safety concerns and chemistry deficiencies.

The Applicant submitted the **first Complete Response** on **March 2, 2009**. The chemistry deficiency was satisfactorily resolved. In the CR submission, the Applicant provided safety data from an additional 11 studies (conducted pre- and post-market), comprising a total of 2,125 additional subjects, for a cumulative clinical study safety population of 2,834 subjects in 17 studies. The Applicant also submitted 2 additional safety updates (November 2007 to August 2009), bringing the total duration of postmarketing experience to almost 6 years. From the clinical study safety population, the clinical review team identified 6 additional immediate post-injection severe reactions suspicious for POME or hypersensitivity reactions. These patients experienced convulsion, syncope, or circulatory collapse. From the postmarketing safety updates, the clinical team detected 52 new cases of immediate post-injection reactions; almost all were severe in nature. DPARP was again consulted to evaluate these 52 new cases, and concluded that 20 cases were either anaphylaxis or possible anaphylaxis, and another 8 cases were possible POME. The clinical team determined that the risk of these post-injection serious reactions remained a significant and unresolved safety concern. Although the Applicant proposed a Risk Evaluation and Mitigation Strategy (REMS) consisting of a communication plan (Patient Package Insert, Dear Health Care Professional letter, video demonstrating method of injection), the Division determined the communication plan REMS could not adequately address the risks of post-injection serious POME and anaphylaxis, and issued the second Approvable letter on December 2, 2009, citing clinical safety deficiencies.

In the **second Complete Response** submitted on **November 2, 2012**, the Applicant submitted one clinical study, bringing the total to 18 clinical studies enrolling a total of 3,556 subjects, and additional postmarketing safety updates (November 2009 through April 2012), for a total duration of postmarketing experience to approximately 8.5 years. The Applicant provided extensive analysis of post-injection reactions using agreed-upon search terms, and identified 533 potential cases of POME and 330 potential cases of anaphylaxis. In collaboration with DPARP, DBRUP identified 137 cases meeting the Agency's prespecified criteria for "severe" post-injection reactions of POME and anaphylaxis. Detail discussion on this analysis is found in Section 8 (Safety) of this memo. The Applicant proposed a REMS comprising of a medication guide and a communication plan. A **joint Advisory Committees meeting** with the Advisory Committees for Reproductive Health Drugs and for Drug Safety and Risk Management was convened on **April 18, 2013**. FDA posed the following two voting questions to the Committee members:

- Regarding the question "Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?", the Committees voted 9 "yes" and 9 "no."
- Regarding the question "... please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions," the Committees voted 1 "yes" and 17 "no."

It should be noted that the voting of the Committee members was not based on a restricted distribution REMS with elements to assure safe use (ETASU-REMS) as a risk mitigation

strategy for Aveed, because the Applicant did not propose such a REMS program in their November 2012 CR resubmission. The Committees discussed the need to enhance risk mitigation with a boxed warning and a more stringent REMS program. Some Committee members also opined that the intended population for Aveed should be more narrowly defined, such that the risks of serious post-injection reactions would be acceptable.

The Agency determined the Applicant's proposed REMS program of a medication guide and communication plan could not sufficiently mitigate the risk of post-injection serious POME and anaphylaxis. Subsequently, the Division issued a third Complete Response letter on May 29, 2013, that outlined two major deficiencies:

1. REMS: The proposed REMS submitted on November 29, 2012, which contained a Medication Guide, a communication plan, and a timetable for submission of REMS assessments were inadequate to mitigate the risks of severe post-injection anaphylaxis and pulmonary oil embolism (POME). In order to ensure that the benefits of Aveed outweigh these risks, the revised REMS must include:

- a Medication Guide,
- Elements to Assure Safe Use that consist of certification of healthcare providers and healthcare settings that dispense Aveed injections and an implementation system, and
- Timetable for submission of REMS assessments at 6 months and 1 year from the date of REMS approval, and annually thereafter.

2. Labeling: The proposed indication of Aveed as testosterone replacement therapy in hypogonadal men needed to be better defined to reflect the input from the April 2013 Advisory Committee and to ensure that the benefits of therapy outweigh the risks. To this end, the Agency recommended an additional statement to the INDICATION section: "Testosterone undecanoate injection should be used in patients who require therapy and in whom the benefits (b) (4) outweigh the serious risks of pulmonary oil microembolism and anaphylaxis."

An ETASU-REMS program and revised labeling form the principal basis of this August 2013 CR resubmission, along with additional safety information from a small male contraceptive study and postmarketing safety experience from November 2011 through June 2013.

### 3. CMC/Device

Aveed contains testosterone undecanoate in castor oil and benzyl benzoate. An ester of testosterone, testosterone undecanoate is metabolized to active testosterone by cleavage of the undecanoic acid side chain, presumably via serum esterases. The dosage form is an oily solution of 250 mg TU/mL (equivalent to 157.9 mg testosterone/mL) intended for intramuscular injection. An injection volume of 3 mL contains 750 mg of testosterone undecanoate, 885 mg of refined castor oil, and 1500 mg of benzyl benzoate.

No new CMC information was submitted in this CR resubmission. Labeling, carton container, carton labeling have been adequately addressed from a CMC perspective. The Office of Compliance issued an overall acceptable recommendation on February 24, 2014. In the



review dated February 25, 2014, the CMC review team (Yichun Sun, PhD; Moo Jhong Rhee, PhD) recommended approval from the ONDQA perspective. The CMC team did not recommend any postmarketing studies.

***Comment:** I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 60 months. There are no outstanding CMC issues that preclude approval.*

## 4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this CR resubmission. The nonclinical pharmacology/toxicology review team (Eric Andreasen, PhD; Lynnda Reid, PhD) confirmed that the Applicant's nonclinical program, references, published literature, and general knowledge of testosterone have provided reasonable assurance of the safety of TU in hypogonadal men in a review dated October 15, 2013. The team's labeling recommendations have been addressed. The team did not recommend any postmarketing studies.

***Comment:** I concur with the conclusions reached by the pharmacology/toxicology review team that there are no outstanding pharm/tox issues that preclude approval.*

## 5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this CR resubmission. The clinical pharmacology review team's labeling recommendations have been addressed. In the review dated February 26, 2014, the team (Huynjin Kim, PharmD, MS; Myong-Jin Kim, PharmD) recommended approval from a clinical pharmacology. The team did not recommend any postmarketing commitment or requirements.

Two noteworthy clinical pharmacology issues discussed in prior reviews and again during the most current review cycle follow:

- Lower body weight/body mass index and higher testosterone exposure: Analysis of serum testosterone concentration from the Phase 3 Part C study of 130 hypogonadal men receiving Aveed suggested a trend of an inverse relationship between body weight and serum testosterone concentrations. For instance, in patients weighing  $\geq 100$  kg, the mean ( $\pm$ SD) serum testosterone average concentration was  $426 \pm 104$  ng/dL. A higher serum testosterone average concentration ( $568 \pm 139$  ng/dL) was observed in patients weighing 65 to 100 kg. However, these serum testosterone concentrations were all within the normal range (300 – 1000 mg/dL).

There were 2 subjects weighing  $< 65$  kg, one of whom had elevated maximum concentration ( $C_{max}$ ) of 2,888 ng/dL and average concentration ( $C_{avg}$ ) of 1,164 ng/dL.

The Applicant proposed

(b) (4)

Study

population pharmacokinetic data on testosterone exposure and body weight and body mass index thresholds will be presented in the Clinical Pharmacology section of labeling. I concur with this approach.

- Serum testosterone undecanoate concentrations: TU is detectable in serum of Aveed-treated patients. Maximum TU concentrations were observed on Day 4 and was nearly undetectable 42 days following injection of Aveed. Pharmacokinetic information of TU will be included in the Clinical Pharmacology section of labeling (Section 12). It should be noted nonclinical studies have shown that TU itself has little potential for clinical androgenic activity.

***Comment:** I concur with the conclusions reached by the clinical pharmacology review team that there are no outstanding clinical pharmacology issues that preclude approval.*

## 6. Clinical Microbiology

The clinical microbiology team recommended approval from a clinical microbiology perspective in the review dated April 29, 2009 (during the second review cycle). No new microbiology information was submitted in this resubmission, and the clinical microbiology reviewer (Vera Viehmann) concluded “no product quality microbiology issues” in a “No Action Indicated” statement dated September 26, 2013.

***Comment:** I concur with the conclusions reached by the clinical microbiology review team that there are no outstanding clinical microbiology issues that preclude approval.*

## 7. Clinical/Statistical-Efficacy

There were no outstanding efficacy issues to address in this review cycle. The clinical and statistical review teams concluded that the Applicant had provided substantial evidence of efficacy in the original November 2007 NDA submission. No new efficacy data have been submitted since the original NDA submission, and the teams’ conclusion regarding efficacy has remained unchanged.

Briefly, the pivotal phase 3 study was a multi-center, open-label, single-arm, uncontrolled study (Study IP157-001, Part C) that enrolled 130 adult male patients with morning screening testosterone concentrations < 300 ng/dL from 31 US clinical sites. The majority of patients were White (76%) with a mean age of 54 years, a mean body index of 32 kg/m<sup>2</sup>, and an average screening total testosterone serum concentration of 214 ng/dL.

Patients received 750 mg of TU by IM injection at initiation of treatment, at week 4, and every 10 weeks thereafter. The primary efficacy endpoint was the proportion of patients with an average serum total testosterone concentration within the normal range (300 to 1000 ng/dL) at steady state, which occurred during the third injection interval. Overall, 110 of 117 completers (primary analysis population), or 94%, achieved an average total serum testosterone concentration ( $C_{avg}$ ) within the normal range, with the 95% confidence interval of 90% to 99%. Of the remaining 7 patients, 6 had  $C_{avg}$  below 300 ng/dL and 1 had levels above 1000



ng/dL. Nine of 117 patients (8%) had maximum serum testosterone concentration ( $C_{\max}$ ) > 1500 ng/dL and no patient had  $C_{\max}$  > 1800 ng/dL.

DBRUP has accepted testosterone pharmacokinetic data from a single, open-label, single arm study in hypogonadal men as primary evidence of efficacy for a TRT product, such as Aveed. The accepted criteria of efficacy for a TRT are:

1. *Primary endpoint*: the proportion of subjects achieving serum testosterone  $C_{\text{avg}}$  within the normal range (300-1000 ng/dL) is at least 75%, with a lower bound of the 2-sided confidence interval of at least 65%, and
2. *Key secondary endpoint*: serum testosterone  $C_{\max}$  cannot be excessively high:  $C_{\max} \leq 1500$  ng/dL in  $\geq 85\%$  of patients, 1800 – 2500 ng/dL in  $\leq 5\%$  of patients, and > 2500 ng/dL in no patients.

**Efficacy conclusion**: Results from the Aveed Part C study met the above efficacy criteria for a TRT.

## 8. Safety

The safety of Aveed has been extensively reviewed, analyzed, and discussed in the previous three review cycles, including a presentation at the joint Advisory Committees meeting with the Advisory Committees for Reproductive Health Drugs and for Drug Safety and Risk Management in April 2013. The most pertinent safety findings are summarized below (see Dr. Hirsch's CDTL memo dated February 28, 2014, for detailed discussion of Aveed's safety).

The current CR resubmission contains safety data from a small TU contraceptive study in 40 healthy male subjects and updated postmarketing safety experience for TU from November 2011 through June 2013. This additional information does not change Aveed's overall safety profile or alter the risk characterization of post-injection POME and anaphylaxis reactions (see February 20, 2014, review of the clinical reviewer, Guodong Fang, MD).

**Safety Database**: At the time of this CR resubmission, the clinical study database for TU now contains data from 19 clinical studies enrolling a total of approximately 3,600 subjects treated with varying dose regimens of TU injection for different indications, such as male hypogonadism, obesity, and male contraception. The primary study supporting efficacy and safety for Aveed was a multicenter, open-label study evaluating the safety and efficacy (pharmacokinetics) of TU in a total of 524 hypogonadal men conducted in the US (study IP157-001). This study was conducted in several parts; key parts are outlined below:

- a. Part A included a total of **237** adult male subjects, enrolled in two dose arms: 750 mg every 12 weeks ( $n=120$ ) and 1000 mg every 12 weeks ( $n=117$ ). Study Part A has Stage 1 and a long-term extension (Stage 2) out to 13 injections of TU.
- b. Part B included a total of **134** adult male subjects in two treatment groups: *112 patients* received an initial injection of TU 1000 mg, followed 8 weeks later by a loading injection of 1000 mg and then 1000 mg every 12 weeks thereafter, while *22 patients* received an initial injection of 1000 mg, followed 8 weeks

later by a loading injection of 750 mg and then 750 mg every 10 weeks thereafter.

- c. Part C included a total of **117** adult male subjects enrolled in the to-be-marketed dosage regimen (750 mg load for one initial injection followed by the second injection 4 weeks later, and then every 10 weeks thereafter). The Applicant also submitted safety data on another **40** adult male subjects taking the 750 to-be-marketed regimen in a longer-term extension study (referred to as Part C2) up to 9 injections of Aveed.

Study Parts A and C provided the primary clinical study safety data for Aveed. Most of the clinical study data came from 6 international postmarket surveillance, non-interventional studies in a total of 2424 hypogonadal men. Six European phase 1, 2 and 3 studies provided safety data on an additional 201 hypogonadal men treated with TU 1000 mg. The remaining 6 clinical studies were small European male contraception studies investigating TU 1000 mg.

In addition, the worldwide postmarketing experience with TU now spans 9.5 years, from November 2003 to June 2013.

***Comment:** The discussion on the general safety of Aveed focuses on findings from the pivotal study IP157-001 Parts A and C. The discussion on POME and anaphylaxis is based on findings from the clinical study safety database and the 10 years postmarketing experience.*

**General Safety:** The general safety profile of TU is similar to other injectable TRTs, with the exception of post-injection serious POME reactions and anaphylaxis (discussed separately).

**Study Part C:** Two deaths (myocardial infarction, cardiac arrest) occurred in Aveed's pivotal 84-week Part C study. Both patients had underlying cardiovascular disease or major risk factors for cardiovascular disease, such as hypertension and diabetes. In study Part C, of the 8 subjects who experienced at least one non-fatal serious adverse event (SAE), one event (deep vein thrombosis) was considered by the investigator to "possibly" be drug-related. In the second Complete Response, the Sponsor updated the long-term safety results from Study IP157-001 Part C (117 patients), including Part C2 (an additional 40 patients). With dosing out to 9 injections of Aveed, a total of 22 of 157 subjects (14%) reported an SAE. SAEs reported in more than 1 patient were prostate cancer (3), spinal column stenosis (3), intervertebral disc disorders (2), and myocardial infarction (2).

Five patients in study Part C discontinued Aveed because of adverse events (AEs), including acne, mood swings, myocardial infarction (MI), increased estradiol and deep vein thrombosis. In the updated safety results from study Part C and C2 submitted in the second Complete Response, a total of 16 of 157 patients (10%) discontinued Aveed due to AEs. Events reported in more than 1 patient were prostate cancer (3), and 2 patients each of hematocrit increased, mood swings, anxiety, and MI.

One patient in study Part C experienced a non-serious event of POME (10 minutes of coughing without respiratory compromise) immediately after receiving his third injection of

Aveed. The patient recovered without intervention and continued with study drug treatment. Review of laboratory changes did not reveal new safety signals for Aveed from what is already known for a TRT.

Study Part A: Two deaths occurred (homicide in Stage 1, stroke in Stage 2 of study Part A). The stroke fatality was reported in a 68 year old male with significant underlying cardiovascular disease and risk factors. In Stage 1, 18 patients experienced at least one non-fatal SAE, which included atrial fibrillation, knee arthroscopy, spinal stenosis, stroke, tendon rupture, malignant hepatic neoplasm, and coronary artery disease. In the second Complete Response, the Applicant updated the safety results from Study IP157-001 Part A, including both Stages 1 and 2. With continued dosing out to 13 injections of TU (750 mg and 1000 mg), a total of 37 of 237 patients (15%) had an SAE. SAEs reported in more than 2 patients were: coronary artery disease (4), atrial fibrillation (3), stroke (3), prostatitis (3). In Stage 1, 10 patients discontinued due to adverse events; AEs of increased serum prostatic serum antigen (PSA), increased serum estradiol, and increased red blood cells were judged by investigators to be drug-related. With the updated safety results submitted in the second Complete Response (both stages 1 and 2 of study Part A), a total of 22 of 237 patients (9%) discontinued because of AEs. Events reported in more than 1 patient included increase PSA (5), prostatic intraepithelial neoplasia (3), and increased hemoglobin (2).

Common adverse reactions seen with Aveed are as expected for an injectable TRT and included: acne, fatigue, injection site pain, irritability, hyperhidrosis, hemoglobin increased, estradiol increased, insomnia, mood swings, aggression, PSA increased, and disturbance in attention.

**Cardiovascular safety:** The long-term safety of testosterone therapy, including Aveed, with regard to cardiovascular risks is unknown. In the safety database of Aveed, cases of major cardiovascular (CV) events (MI, stroke, deaths from these causes) were sporadically reported in the clinical and postmarketing studies with TU (750 mg and 1000 mg). In the phase 3 safety database of study IP157-001 (all parts) comprising of a total of 524 hypogonadal men treated with TU 750 mg to 1000 mg, two deaths due to stroke and MI were reported. In the same database, 5 and 3 patients experienced nonfatal MI and stroke, respectively. In the database from 6 international postmarket surveillance studies, among the 2424 patients treated with TU 1000 mg/4 mL approved outside the US, 2 had MIs and 1 experienced a stroke. A search of the literature did not yield any publication on CV risk with TU therapy.

These findings do not convey a frank safety signal of CV risk with Aveed. Also, they do not appear to differ from what has been generally seen with other testosterone therapy, that is, occasional cases of MI and stroke reported as adverse events in the drug's safety database. Furthermore, major cardiovascular events have a high background incidence rate in men older than 40, a population similar to patients that use Aveed. Because most studies with TU, including Aveed, are uncontrolled without comparator group, one cannot ascribe drug causality to these relatively common adverse outcomes.

***Comment:** Presently, the FDA is re-investigating under Tracked Safety Issue 865 the association between cardiovascular adverse outcomes and testosterone therapy, prompted by*

*the recent publication of two observational studies<sup>1</sup> suggesting a signal of risk. FDA issued a Drug Safety Communication on January 31, 2014, to inform the public that the agency is re-assessment this potential safety issue.*

*In 2010, DBRUP evaluated the same safety signal after a small, randomized, double-blind placebo controlled efficacy trial in 200 frail older men at high-risk for cardiovascular disease was prematurely discontinued due to an overall imbalance of various CV related AEs (e.g., peripheral edema, arrhythmias, myocardial infarction, stroke). The Division of Cardiovascular and Renal Products (DCRP) reviewed the study and concluded that it had several significant limitations that precluded a definitive assessment of the role of testosterone therapy in the CV events in the study. Their review also concluded that it was questionable whether the study results apply to the population for whom testosterone therapy is indicated.<sup>2</sup>*

*In 2010, FDA's Division of Epidemiology (DEPI) evaluated other data sources on potential CV risks of testosterone, comprising two meta-analyses of randomized, placebo-controlled clinical trials and one systematic qualitative review addressing CV risks associated with testosterone therapy in hypogonadal patients. DEPI concluded that the findings from these studies did not support an association between testosterone therapy and an increased risk of adverse cardiovascular outcomes.<sup>3</sup>*

*In January 2011, DBRUP determined that the overall safety information informing CV risk with testosterone therapy was insufficient to support a regulatory action.*

*Available evidence informing the association of testosterone and CV risks generally lacks key scientific qualities needed to reliably infer the effect of testosterone on CV outcomes. Published studies have reported conflicting results, with some concluding that testosterone may increase CV risks, whereas others found that testosterone had a favorable effect on mortality.*

*At this time, FDA has not yet determined that testosterone use is associated with a higher risk of heart attack, stroke, or death. Given that the Agency thoroughly considered the CV safety concern with testosterone therapy and had concluded that there were insufficient data to support a regulatory action regarding CV risk just 3 years ago; that the Aveed safety database did not show worrisome trends in MACE findings; and that testosterone undecanoate has been marketed for 10 years at doses higher than that of Aveed without known CV concerns, I do not believe that a CV safety risk exists with Aveed to warrant a warning of CV risk in labeling.*

**Post-injection POME and anaphylaxis:** The major safety concern for Aveed is post-injection reactions of serious POME and anaphylaxis. DBRUP has consulted and collaborated with the

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<sup>1</sup> R Vigen et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310:1829.

WD Finkle et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men PLOS One 2014; 9:e85805.

<sup>2</sup> DCRP consult review to TSI 865 (Stephen M. Grant, MD; April 8, 2010)

<sup>3</sup> OSE consult review to TSI 865 (OSE RCM# 2010-720, Fatmatta Kuyateh, MD, May 21 and December 6, 2010)

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) since the identification of immediate post-injection serious reactions in the original NDA submitted in 2007. Refer to consults from DPARP dated April 21, 2008; September 19, 2008; November 25, 2009; June 13, 2011; June 5, 2012; and March 22, 2013 for details. The following discussion on POME and anaphylaxis is summarized from the materials reviewed for the November 2012 second CR resubmission and presented at the joint April 2013 Advisory Committees meeting.

**Clinical Studies:** From clinical study safety database of 3,556 patients enrolled in 18 clinical studies (conducted pre- and post-market), there were 9 cases of POME (in 8 patients) and 2 cases of anaphylaxis associated with TU injections identified by retrospective adjudication using pre-defined criteria. This translates to an estimated incidence rate of 4.6 cases per 10,000 injections for POME and 0.9 cases per 10,000 injections for anaphylaxis. Of note, no cases of POME or anaphylaxis were observed in the male contraceptive study in 40 male subjects submitted in this CR resubmission.

**Postmarketing Experience:** During the first two review cycles, the Applicant and the Agency disagreed on what constituted cases of clinically important POME reaction versus anaphylaxis. Further, the Applicant argued that these post-injection reactions are rare and that careful and slow IM injection, as well as lower volume of injection (3 mL in Aveed as oppose to 4 mL in Nebido), could effectively mitigate these reactions.

In the November 2012 second CR submission, the Applicant extensively searched and analyzed its postmarket safety database spanning over 8 years using search terms for anaphylaxis and POME previously agreed upon by FDA. This search yielded 533 and 330 *potential* postmarket cases of POME and anaphylaxis, respectively. Because the search terms for anaphylaxis are subset of those for POME, essentially all anaphylaxis reports were contained within the 533 POME cases.

DBRUP and DPARP collaborated to establish pre-defined criteria for “severe” cases of post-injection POME and anaphylaxis. These cases included those that occurred within 24 hours of TU injection and met any of the following criteria: identified by the FDA or the Applicant as “anaphylaxis” or “anaphylactic reaction”; labeled as “serious” or “medically important” by the reporter or Applicant; met the formal Sampson’s criteria; met the regulatory definition of serious adverse reaction; required treatment; or involved syncope or lowering of blood pressure.

Together, DBRUP and DPARP reviewed the 533/330 case narratives of potential cases of POME/anaphylaxis and found the following:

- A total of 137 cases of “severe” post-injection reactions of POME and anaphylaxis. Of these, 128 were considered “medically significant,” 32 were either hospitalized or seen in the emergency department, 19 stated drop in blood pressure or syncope, and 9 were described as life-threatening.
- DPARP identified a total of 47 to 68 cases of anaphylaxis, as well as 170 to 191 POME cases, 55 to 76 of which qualified as “severe.” The range of cases is due to overlapping criteria used to identify anaphylaxis by strict (must have mucosal or skin involvement) or



less restrictive criteria set forth by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network.

In the postmarketing safety update provided in this third CR resubmission, an additional 43 cases of POME and anaphylaxis were reported. Five of these cases were serious, three of which were possible anaphylaxis. This additional postmarket information did not provide qualitatively new safety information for Aveed.

A majority of the severe post-injection reactions (~90%) occurred during or within 30 minutes from the time of TU injection. The risk of these post-injection reactions does not appear to diminish with continued treatment; these reactions have occurred after the first injection, as well as after any subsequent injection during the course of therapy. For instance, severe reactions have been reported up to 4 years after previous uneventful therapy. Other than known hypersensitivity to the drug product, there are no identifiable factors that increases or decreases the probability of experiencing these post-injection reactions. To date, no deaths or permanent disability have resulted from these severe post-injection reactions, although some cases required treatment with epinephrine, steroids, and oxygen, emergency department visits, and hospitalizations.

POME and anaphylaxis have different pathophysiology, with anaphylaxis being a hypersensitivity reaction and POME believed to be micro-embolization of oil droplets to the pulmonary microvasculature. Nevertheless, their clinical manifestations can overlap significantly. Both serious POME and anaphylaxis have clinical signs and symptoms involving the upper airway, respiratory, and cardiovascular, and dermatological systems. Symptoms reported with serious POME included severe shortness of breath, severe cough, paresthesias, respiratory distress, cardiovascular symptoms, such as angina, and loss of consciousness. Signs and symptoms of anaphylaxis reactions consisted of dyspnea, rash/urticaria, tightening or closing of throat, cardiovascular collapse, and loss of consciousness. In any case, whether an adverse experience such as respiratory distress is ultimately diagnosed as serious POME or anaphylaxis is not clinically relevant in the acute setting. In practice, medical management would be required and would be based on the nature and severity of a patient's signs and symptoms, regardless of the exact etiology.

**Comment:** The castor oil excipient (b) (4) is believed to directly contribute to the occurrence of POME and anaphylaxis. Anaphylaxis could also be a result of the excipient benzyl benzoate, a known allergen, or possibly to testosterone drug substance itself. It is postulated that POME results from microembolization of the oil drops to the lung vasculature, causing respiratory symptoms. Although other drug products also contain castor oil, the volume of castor oil in TU injection is relatively greater than that of other approved products in the US. The Applicant selected a lower volume (and lower dose) for Aveed (TU 750 mg in 3 mL) compared to Nebido (TU 1000 mg in 4 mL) in an attempt to lower the risk of POME and address FDA's concerns. However, because a vast majority of clinical safety data for TU is obtained with Nebido, it is not possible to determine whether the lower volume of oil-based injection of Aveed is associated with a reduced risk of POME.

*Postmarket sources and published literature have reported only short-term consequences of POME. Acutely, the mechanical occlusion of the pulmonary vasculature from oil microembolization can cause transient pulmonary hypertension, resulting in a wide range of symptoms, from mild cough to circulatory collapse. Oil microembolization can also lead to inflammatory response in the lungs. The long-term consequences of these mechanical and inflammatory changes, whether in serious POME episodes or mild repeated ones, on a patient's cardiopulmonary function are unknown.*

The available clinical study data and postmarketing experience are too imprecise to determine a reliable incidence rate of POME and anaphylaxis for the purposes of labeling. Some reasons include the difficulty in clinically differentiating between serious POME and anaphylactic reactions, the use of different diagnostic criteria for anaphylaxis since 2003 when TU was first approved outside the US, and the challenges in capturing adequate and informative details with postmarket spontaneous reporting of adverse outcomes.

In the consult review dated February 14, 2013 (during the third review cycle), the Division of Pharmacovigilance provided results from a search of FDA's voluntary adverse reporting database (FAERS) for cases of POME and anaphylaxis reported for all approved injectable testosterone products from the time of approval to current date. After adjudication, a total of 33 postmarket cases of severe POME and anaphylaxis were identified in the 44 years since these products have been approved. Nevertheless, due to factors such as inherent limitations of postmarket reporting, unknown drug use information, and differences in time of drug approval, it is not possible to directly compare reporting rates across injectable products in a reliable manner.

### **Risk Mitigation:**

***Labeling (Boxed Warning, Medication Guide):*** Labeling will have a boxed warning for the risk of serious POME and anaphylaxis. DBRUP determined that a boxed warning is warranted based on the conclusion that these post-injection reactions are so serious in proportion to the potential benefit of Aveed that they are essential to be considered in the risk/benefit decision to use Aveed; that the sequelae of these reactions may be minimized by having the patient remain in the health care setting for 30 minutes post-injection; and that FDA has approved Aveed with a restricted distribution REMS. DBRUP has also determined that a Medication Guide is necessary for patient's safe and effective use of Aveed under 21 CFR 208. Aveed has serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Aveed.

***Risk Mitigation and Evaluation Strategies with Elements to Assure Safety Use (ETASUs-REMS):*** After discussion at the April 2013 Advisory Committees meeting, DBRUP and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) determined that Medication Guide and an ETASUs-REMS are required to provide active strategies to minimize the potential serious sequelae to patients from serious post-injection reactions. This was conveyed to the Applicant in the May 2013 CR letter. In the August 2013 CR resubmission the Applicant proposed a REMS with a Medication Guide, Communication

Plan, ETASUs (health care provider certification, health care setting certification), and a timetable of REMS assessment.

The goal of the approved REMS is to minimize the negative outcomes associated with Aveed-induced POME and anaphylaxis. The REMS stipulates that: 1) Aveed is dispensed in certified healthcare settings that have equipment and personnel to manage POME and anaphylaxis, 2) prescribers understand the risk of these post-injection reactions and safe use of Aveed, and 3) patients are informed and understand the need to remain in the healthcare setting for 30 minutes post-injection, the time period when these reactions are most likely to occur. The ETASU elements are:

- 1) Healthcare providers who prescribe or dispense Aveed must be specially certified and;
- 2) Healthcare setting that dispenses Aveed must be specially certified.

The REMS will also have an Implementation System and a timetable of submission of assessments consistent with that of ETASUs-REMS.

The approved Aveed REMS must provide for a controlled distribution system, ensuring a secure distribution chain from the point of manufacture to only certified healthcare settings and certified prescribers. According to the Controlled Substance Act (CSA), all testosterone-containing products are Scheduled III controlled substances. Under the CSA, for a Scheduled III drug, if there is a prescription for a named patient, then a pharmacy would directly dispense the drug to that patient. However, under the REMS, Aveed (a Schedule III controlled substance because it contains testosterone) will not be allowed to be dispensed directly to the patient. At DRISK's recommendation, the Applicant discussed with representatives from the Drug Enforcement Agency on January 24, 2014, to ensure that the distribution of Aveed complies with the regulations under the Controlled Substance Act for a Schedule III substance, while fulfilling the safe use conditions under the Aveed REMS.

**Other REMS-related issues:**

Medication Guide: After further discussions between OND and OSE, it was determined that the Medication Guide will be maintained as a part of labeling under 21 CFR 208 and a concise patient counseling document to specifically address the risk of serious post-injection reactions will be developed and included as part of the REMS. This document will serve as the primary REMS patient education tool, and healthcare providers must agree, as part of the REMS healthcare provider and healthcare setting certification, to provide it to each patient.

Communication Plan: The May 29, 2013, Complete Response letter did not require the Applicant to submit a communication plan. However, the Applicant proposed a communication plan (consisting of a Dear Healthcare Provider (b) (4) ) as part of their August 29, 2013, CR resubmission.

Because Aveed is another testosterone therapy and the third injectable testosterone ester to be approved, OND and OSE considered that a more targeted communication approach was more practical and less burdensome. OND and OSE agreed that a concise, one-page

general introductory information piece to communicate the risks and Aveed REMS program information as a component under the ETASUs, is sufficient. This introductory piece will be available to healthcare providers and healthcare settings requesting general information about Aveed and the Aveed REMS program.

Therefore, the approved Aveed REMS program consists of Elements to Assure Safe Use, including that healthcare providers who prescribe or dispense Aveed are specially certified and healthcare settings that dispense Aveed are specially certified, an implementation system, and a timetable of assessment.

***Comment:*** *I concur with risk mitigation through labeling and the ETASUs-REMS. The Applicant has agreed to the risk mitigation plans outlined by the Agency.*

The Applicant will also conduct enhanced pharmacovigilance for serious POME and anaphylaxis. Serious cases of POME and anaphylaxis from TU, including Aveed, from domestic and foreign sources will be reported as expedited 15-day reports. Analysis and summary of cases of POME and anaphylaxis will be provided in the required quarterly safety updates to FDA.

The CDTL (Mark S. Hirsch, MD) and the clinical reviewer (Guodong Fang, MD) recommended approval of Aveed.

- In his review dated February 21, 2014, Dr. Fang stated, “In the opinion of this Clinical Reviewer, from a clinical perspective, the evidence presented in the original submission and three re-submissions was adequate to support the effectiveness of this product. In regard to safety, the risk related to immediate post-injection reactions, including serious pulmonary oil microembolism (POME) and anaphylaxis has been the major safety concern. In the current re-submission, the Sponsor agreed to a restricted indication and proposed a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU)...this reviewer believes that the major safety concern has been put under control and is resolved for use of Aveed in the proposed population with restricted distribution and proper management in certified clinical health care settings. Therefore, this reviewer recommends an approval action for this application.”
- Dr. Hirsch recommended the following in his CDTL review dated February 28, 2014: “I recommend that the NDA be approved at this time. I am convinced that the new Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) mitigates the potential adverse consequences of the rare serious POME and anaphylaxis reactions such that the benefit of Aveed now outweighs its potential risks in the restricted target population.”

The clinical team did not recommend any postmarket studies or trials.

***Comment:*** *I concur with the recommendations of Drs. Fang and Hirsch.*

**Safety Conclusion:** In summary, the general safety profile of Aveed is expected of an injectable testosterone replacement therapy. The main safety concern that distinguishes Aveed

is post-injection serious POME and anaphylaxis. Culled from safety data obtained from 3,556 clinical study patients and almost 10 years of post-marketing experience, these cases have been extensively analyzed and adjudicated in the previous 3 review cycles. Whether the adverse outcome meets the definition of POME or anaphylaxis is not the primary concern; rather, any post-injection serious reaction requiring medical intervention is the safety concern. The occurrence of post-injection reactions is sporadic, unpreventable, and unpredictable with each TU injection. It is expected that post-injection serious POME and anaphylaxis will continue to occur with the use of TU.

On the other hand, there has been no fatality or permanent disability from serious POME or anaphylaxis in approximately 10 years of postmarketing experience with testosterone undecanoate. A significant majority of these post-injection reactions occurred within a definable time period of during or within 30 minutes after TU injection. And finally, the clinical consequences of serious POME and anaphylaxis could be managed with timely and appropriate medical intervention. The Aveed ETASUs-REMS incorporates all necessary safe use conditions, such as observation of patients for 30 minutes post-injection and availability of appropriate personnel and equipment to manage post-injection reactions, to effectively mitigate the clinical consequences of POME and anaphylaxis reactions.

## **9. Advisory Committee Meeting**

During the review of the Applicant's second CR resubmission, a joint Advisory Committees was convened on April 18, 2013, to discuss the safety concerns of POME and anaphylaxis with Aveed. The Committee members posited that labeling and a Medication Guide/communication plan REMS would not adequately mitigate the risks of anaphylaxis and POME. The Committee members recommended enhancing risk mitigation with a boxed warning and a more directive REMS program. The Committee also recommended that the patient population for Aveed should be better defined, given the availability of other approved testosterone replacement therapies that do not have the same risk of serious post-injection reactions. These discussions contributed to the deficiencies outlined in the May 2013 CR letter. DBRUP does not need input from another Advisory Committee to finalize the regulatory action for this third CR resubmission.

## **10. Pediatrics**

The Applicant previously requested and was granted a full pediatric waiver in July 2009, because studies in children with Aveed would be highly impractical due to too few children with the disease/condition to study. This determination remains unchanged for this CR resubmission. Of note, at the request of the Pediatric Review Committee, the Applicant confirmed that it does not intend to seek pediatric exclusivity for Aveed in a formally submitted letter dated June 15, 2009.



## 11. Other Relevant Regulatory Issues

**Controlled Substance Staff (CSS):** Aveed contains testosterone, a Schedule III controlled substance. In a consult reviewed dated January 24, 2014, the CSS consultants opined that “Section 9 Drug Abuse and Dependence of the label for Aveed NDA 22219 does not provide the consumers (physicians and patients) current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and withdrawal symptoms.” The consultants recommended revisions to section 9 of Aveed labeling to describe the abuse potential of testosterone and safety findings on testosterone abuse, misuse, overdose, and dependence. The consultants also recommended that OSE evaluate evidence of testosterone-related abuse, misuse, overdose, and addiction.

Representatives from OND, OSE, and the CSS staff met on February 5, 2014. It was decided that:

- Revised labeling text in section 9 applies to all testosterone products and is not unique to Aveed.
- OND and OSE need additional time to review the evidence related to testosterone misuse, abuse, and dependence for all testosterone products, including Aveed.
- OND, OSE, and CSS would collaboratively assess the scientific evidence, and regulatory decisions (s) on the matter of testosterone misuse, abuse, and dependence would most likely apply to all testosterone products, including Aveed.

Therefore, labeling revision to section 9 for Aveed will not be instituted at this time, and will be addressed outside of this CR submission, in a joint inter-Office safety review application.

***Comment:** There are no other unresolved regulatory issues.*

## 12. Labeling

Labeling for Aveed consists primarily of class labeling for testosterone products. Important elements specific to Aveed include:

- Boxed Warning to inform the risks of serious POME and anaphylaxis and the existence of the restricted distribution REMS-ETASUs program for Aveed
- Modified Indication statement that adds the statement that Aveed should only be used in patients who require therapy and in whom the benefits of Aveed outweigh the risks of serious POME and anaphylaxis.
- Warning related to the risks of post-injection serious POME and anaphylaxis
- Data contained in sections 6 (Safety) are from the clinical development and postmarketing experience with testosterone undecanoate, including Aveed. Data in sections 12 (Clinical Pharmacology, including information on the effect of body weight on testosterone exposure) and 14 (Efficacy) are findings from the clinical program of Aveed.
- A Medication Guide under 21 CFR 208 to inform patients of the risks of serious POME and anaphylaxis.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the prescribing information, Medication Guide, carton labeling, and container labels for Aveed. DMEPA’s

recommendations have been incorporated into labeling, container label, and carton labeling. DMEPA also found the tradename Aveed to be acceptable (see memos by Justine Harris, RPh, dated October 28, 2013, February 11 and February 14, 2014).

Recommendations for revisions to the Medication Guide provided by the Division Medical Policy Programs and the Office of Prescription Drug Promotion (OPDP) have been addressed (see joint consult review by Shawna Hutchins and Trung-Hieu Brian Tran, dated 2/5/2014).

OPDP reviewed the labeling and REMS materials for inappropriate promotional materials and recommendations were mostly incorporated, as appropriate (see consult reviews by Trung-Hieu Brian Tran, dated 2/12/14 and 2/19/14).

Recommendations by the Study Endpoints and Labeling Development Team (SEALD) have been addressed (see memo by Abimbola Adebawale, MD, dated February 10, 2014).

### **13. Decision/Action/Risk Benefit Assessment**

- **Regulatory Action**

I recommend approval of Aveed as testosterone replacement therapy in hypogonadal men who require testosterone therapy and in whom the benefits of Aveed outweigh the risks of serious post-injection reactions. The Agency finds the REMS-ETASUs program and modified Indication statement in labeling acceptable. Therefore, the Applicant has addressed the deficiencies in the May 2013 Complete Response letter.

- **Risk Benefit Assessment**

Male hypogonadism is a serious condition requiring testosterone replacement therapy. Among the multiple dosage forms of TRTs available in the US, injectable testosterone may be the most appropriate option for certain patients, for reasons such as convenience (avoiding the need for daily administration), no concern for secondary exposure to children, or skin sensitivity to transdermal patches or gels. For these patients, and especially for those who require life long therapy starting at a younger age, Aveed may provide a suitable treatment alternative to the currently approved injectable testosterone products, given Aveed's longer interval of treatment and considerably fewer injections. The Aveed dosing regimen requires 6 injections per year compared to approximately 14 to 26 injections per year with other injectable TRTs.

The efficacy of Aveed as testosterone replacement therapy has been demonstrated in a single pivotal study. Ninety-four percent (94%) of patients achieved the primary endpoint of Cavg in the normal range, with the lower bound of the 95% confidence interval of responder of 90%, when used according to the labeled dosing regimen. Also, the dosing regimen of Aveed did not result in unacceptably high maximum testosterone exposure that would preclude approval.

The primary safety concern of Aveed is post-injection serious POME and anaphylaxis, observed in clinical studies and reported in the postmarket setting. These reactions can occur after any injection, and no known strategies exist to predict *a priori* patients at risk. Although the occurrence of POME and anaphylaxis cannot be predicted or prevented, the time window

that these reactions are most likely to occur is known, and clinical consequences from these reactions can be mitigated by timely medical treatment. The Aveed REMS program is designed to ensure that prescribers are informed, healthcare settings are prepared to manage serious POME and anaphylaxis, and that patients are observed during the 30-minute post-injection when these reactions are most likely to occur. The REMS stipulates conditions of safe use on the part of the healthcare setting, prescribers, and patients. Furthermore, risk mitigation with labeling has been maximized with the inclusion of a boxed warning and a medication guide to guide risk/benefit decision-making for an individual patient. Finally, the indicated population for Aveed has been modified to include only patients who require therapy and in whom the benefits of Aveed outweigh the risks of serious POME reactions and anaphylaxis.

Overall, I believe that the benefit-risk balance for Aveed is now favorable. Aveed has been shown to be efficacious and appropriate safeguards are in place through labeling and ETASUs-REMS to inform and manage the risk of serious POME and anaphylaxis, a risk that distinguishes Aveed among the armamentarium of testosterone replacement therapy.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

Aveed will be approved with a ETASUs-REMS program. Key components of the REMS are certification of prescribers and of health care settings in which Aveed is dispensed and administered.

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

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/s/  
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CHRISTINE P NGUYEN  
03/05/2014