JOINT MEETING FOR REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

APRIL 18, 2013

NDA 022219: testosterone undecanoate (proposed trade name, Aveed) for intramuscular injection sponsored by Endo Pharmaceuticals Solutions, Inc., for the replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought a new drug application (NDA 022219) for testosterone undecanoate intramuscular injection (proposed trade name, Aveed) intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone sponsored by Endo Pharmaceuticals, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA BRIEFING PACKAGE
TABLE OF CONTENTS

I. Summary Memorandum

II. Clinical Background Document

III. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Consultation and Appendices

IV. Division of Risk Management, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology (OSE) Briefing Document- Risk Management Considerations

V. Division of Epidemiology II, Office of Surveillance and Epidemiology (OSE), Office of Pharmacovigilance and Epidemiology (OPE) Briefing Document- Epidemiology: Evaluation of Anaphylaxis and Pulmonary Oil Microembolism Reporting Rates

VI. Nonclinical Briefing Document

VII. Clinical Pharmacology Briefing Document

VIII. References

SUMMARY MEMORANDUM

Date: March 22, 2013

From: Audrey Gassman, MD
Deputy Director, Division of Reproductive and Urologic Products, Office of New Drugs, CDER, FDA

To: Members, Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Committee

Subject: Overview of the FDA Background Materials for NDA 22-219, Aveed (testosterone undecanoate) for intramuscular injection

Introduction

Thank you for your participation in the joint meeting of the Advisory Committee for Reproductive Health Drugs Advisory Committee (ACRHD) and the Drug Safety and Risk Management Committee (DSaRM) to be held on April 18th, 2013. As advisory committee members, you will be asked to provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) regarding whether testosterone undecanoate injection should be approved for marketing in the United States. Endo Pharmaceuticals Solutions, Inc. is seeking the approval of testosterone undecanoate injection (proposed tradename, Aveed) for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Aveed will be administered at a dose of 750 mg via intramuscular injection of 3 mLs of solution, followed by a repeat dose of 750 mg after 4 weeks, then 750 mg doses every 10 weeks thereafter.

Severe post-injection reactions reported with the use of testosterone undecanoate injection have been identified during the review of this NDA. Committee members will be asked to weigh the benefits of treatment against this risk in their deliberations.

This memorandum summarizes key issues central to the discussion at this joint Advisory Committee meeting. The FDA background package will provide more detailed discussions of these issues.

Background

The principal endogenous androgens, testosterone and dihydrotestosterone, promote normal growth and development of the male sex organs, and promote and maintain the development of the normal secondary male sex characteristics. These characteristics include the male pattern hair growth, laryngeal enlargement, vocal cord thickening, male body composition (e.g., body musculature, fat distribution), and growth and maturation of the prostate, seminal vesicles, penis, and scrotum.

Male hypogonadism refers to a condition in which the endogenous secretion of testosterone is insufficient to maintain serum testosterone levels within the normal

range and is characterized by low serum testosterone concentrations. Hypogonadism in adult men may vary with respect to the clinical presentation; some symptoms associated with this condition include decreased sexual desire and regression of male secondary sex characteristics. Some conditions that may lead to a hypogonadal state in men include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's syndrome, exposure to chemotherapy or heavy metals ("primary hypogonadism") and pituitary-hypothalamic injury secondary to radiation, trauma, tumors or other idiopathic causes ("hypogonadotropic hypogonadism"). Approved testosterone products are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.

In the U.S., approved testosterone replacement products are available in several formulations: orally administered formulations, transdermal patch, gel, and solution, a buccal bioadhesive system, an oral tablet, a subcutaneous implant, as well as two products for intramuscular injection. The subject of this NDA, testosterone undecanoate, is formulated as an intramuscular injectable that allows for a longer interval between treatments (injections every 10 weeks compared to every 2-4 weeks with the available injectable products).

Regulatory history for testosterone undecanoate injection

The Division of Reproductive and Urologic Products (the Division) has relied on pharmacokinetic (PK) data (i.e., serum concentrations of testosterone) from a single open-label, uncontrolled clinical study as demonstration of efficacy for a testosterone replacement therapy indicated for adult males with conditions associated with a deficiency or absence of endogenous testosterone. The primary PK efficacy endpoint is the average total serum testosterone concentration (i.e., Cavg) over the dosing interval. The desired outcome for an individual study subject is a Cavg value for total testosterone that is within the normal range (e.g., 300-1000 ng/dL). To demonstrate efficacy for a product, at least 75% of subjects are expected to have a total testosterone Cavg within the normal range, and the lower bound of the two-sided 95% confidence interval around the point estimate should not be lower than 65%.

In the original NDA, submitted on August 24, 2007, efficacy of the testosterone undecanoate (TU) 750 mg dose administered every 10 weeks with a loading dose of 750 mg at Week 4 was evaluated in Study IP157-001, Part C. Pharmacokinetic data from this study demonstrated efficacy for TU administered in this regimen. Additional studies, including earlier studies conducted in Europe and a study conducted with a different dosing regimen, were also submitted as supportive information.

The safety profile of TU intramuscular injection was generally comparable to other testosterone drug products approved as testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone except for reports of severe post-injection reactions that included anaphylaxis and pulmonary oil microembolism (POME). These reports raised significant safety concerns regarding the

risk/benefit profile for the use of TU intramuscular injection for the proposed indication. The 2007 application was determined to be not approvable by the Agency on June 27, 2008.

The Applicant provided a Complete Response on March 2, 2009 with additional safety data to address the Division's concerns regarding these severe immediate post-injection reactions. Although additional safety data were provided in this submission, the Division continued to be concerned that the risk/benefit profile for TU was not favorable and issued a Complete Response letter on December 2, 2009.

Product Information

Testosterone undecanoate is a long-acting depot formulation of testosterone in castor oil and benzyl benzoate. Testosterone undecanoate is an ester of testosterone that 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.

Nonclinical Pharmacology/Toxicology

The toxicology of testosterone is well understood. Testosterone is a non-mutagenic rodent carcinogen (increases cervical and uterine tumors and liver tumors), and a teratogen which causes masculinization of female fetuses, female animals, and adult females with acceleration of pubertal changes in juvenile males. Because of the extensive clinical and nonclinical data available on testosterone, nonclinical evaluation of TU was limited to assessing binding affinity for the human androgen receptor, ADE (absorption, distribution and elimination) in rats, local toxicity after a single intramuscular injection in pigs, potential for toxicity after repeated intramuscular dosing in rats, and genotoxicity.

Preclinical findings for TU included: little potential for pharmacologic activity without being metabolized, a long half-life at the injection site with expected ADE, toxicities after repeated dosing generally related to expected pharmacology or the result of large injection volumes, and negative results for *in vitro* and *in vivo* genotoxicity assays. In summary, no significant safety concerns associated with TU administration were identified in the nonclinical program, other than toxicities related to expected pharmacology and injection site trauma.

Clinical/Statistical

Overview of the Clinical Program

Following intramuscular injection of 750 mg of TU, serum testosterone concentrations reach a maximum after a median of 7 days (range 4 – 42 days), and then slowly decline.

Data from Study IP157-001, Part C, demonstrated that intramuscular injection of TU generated mean steady state testosterone concentrations in the eugonadal range for 10 weeks.

The overall clinical development program for TU injection was similar to those of other testosterone products seeking an indication of testosterone replacement therapy. Endo Pharmaceuticals Solutions Inc. submitted the results from a single Phase 3 study (Study IP157-001, Part C) to support the marketing approval of TU injection (proposed tradename Aveed) at a dose of 750 mg for testosterone replacement therapy in adult men with a deficiency or absence of endogenous testosterone. Efficacy of the 750 mg dose was also supported by the findings from two additional pharmacokinetic studies (Study IP157-001, Parts A and B) and 5 other small studies (n=14-96 per study) that were previously conducted in Europe.

Efficacy Overview

A single multi-center, open-label, uncontrolled clinical study (Study IP157-001, Part C) enrolled 130 patients at 31 US clinical sites. Subjects received 750 mg (3 mL) of TU by IM injection at initiation of treatment, at Week 4 of treatment, and every 10 weeks thereafter. Of the 130 patients enrolled, 116 (89%) received 4 injections and completed through the 4th injection visit (Week 24)[1]. The primary efficacy endpoint was defined as the percentage of subjects that had an average serum concentration of total testosterone within the normal range (300–1000 ng/dL). Ninety four percent (94%) of subjects (110 of 117) had serum total testosterone Cavg values within the 300-1000 ng/dL range. The 95% confidence interval around this point estimate was 90%-99%. Of the 7 patients who did not meet this criterion, 6 failed due to a Cavg below 300 ng/dL, and one failed due to a Cavg above 1000 ng/dL.

After review of Study IP157-001, Part C, the Agency concluded that the Applicant had demonstrated that this TU 750 mg dosing regimen met the regulatory requirement for efficacy for a testosterone replacement indication.

Safety Overview

The Complete Response submission contained safety data from 18 clinical and postmarketing studies conducted in 3,556 subjects that were treated with varying dose regimens of TU injection, including studies in men treated with the product for testosterone replacement or male contraception. In addition, the Applicant provided postmarketing safety assessments from a worldwide database that extends back to the original approval of TU in 2003. Sold under the tradename NEBIDO in most markets, TU intramuscular injection has been approved for marketing in more than 90 countries and is marketed in approximately 72 countries. The approved dosing regimen of TU in Europe is 1000 mg via intramuscular injection of 4 mLs of solution.

[1] There was one patient who was missing a Day 70 concentration value; efficacy was analyzed using imputed data for the last value for that patient to bring the total number of subjects in this study to 117.

In Study IP157-001 (Part C), Aveed was associated with adverse events and laboratory changes consistent with an injectable testosterone replacement therapy. The most commonly reported adverse events (>2%) were acne, fatigue, cough, injection site pain, nasopharyngitis, pharyngeolaryngeal pain, arthralgia, insomnia, prostatitis and sinusitis. In Part C, a total of 21.5% of patients reported at least 1 adverse event of interest. These included serum prostate specific antigen increased, prostate exam abnormal, prostatitis, prostate intraepithelial neoplasm, acne, urine flow decreased, nocturia, mood swings, aggression, hemoglobin/hematocrit increased, hyperlipidemia, and injection site reaction. Between 1 and 6 subjects reported each of these adverse events of interest, although none of these events were regarded as a new safety trend for testosterone undecanoate.

The occurrence of severe post-injection reactions was evaluated from available safety data obtained in these studies and from the postmarketing experience. These severe reactions have been classified as either pulmonary oil microembolism (POME) or anaphylaxis. POME is generally attributed to the castor oil substance in the TU formulation, while anaphylaxis could be due to the excipient benzyl benzoate or to the castor oil; both are known allergens, although allergy to testosterone itself is also a possibility. The reported reactions occurred during or within minutes from the time of the intramuscular injection and have been reported to occur after administration of both the 750 mg and 1000 mg doses. Clinical differentiation of anaphylactic reactions vs. POME is extremely difficult because of overlapping symptoms between the two events and also because of the use of different criteria for the purposes of establishing a diagnosis. No deaths have been reported after these severe post-injection reactions, but resuscitations and hospitalizations have been required in some cases. Detailed discussions of these severe post-injection reactions are found in the briefing documents.

In summary, cases of severe post-injection reactions (POME) were identified in the original NDA submission and also during the post-marketing experience. These cases have been assessed and confirmed, although some debate exists regarding which criteria should be used to classify these severe events and how best to determine postmarketing reporting rates. Although cases of severe post-injection reactions have been very rarely reported with other injectable testosterone products, it is not possible to directly compare reporting rates across products in a reliable manner.

Risk Management

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or

biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent severe adverse events.
- The product has severe risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about severe risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be patient to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific severe risk listed in the labeling. Accordingly, section 505-1(f)(2) of the FDCA specifies that ETASU:

- Must be commensurate with specific severe risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar severe risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

The key severe risk observed with the use of testosterone undecanoate in this clinical development program was the occurrence of severe post-injection reactions. Various strategies to manage or mitigate this risk with the marketed use of Aveed were the focus of several discussions between the Applicant and the Agency. These strategies have

included a range of approaches from “labeling only” to alternate approaches that would be required in a REMS.

The Agency is aware that requiring a REMS for a product can impose substantial burdens on patients, providers and the overall healthcare system. The magnitude of the burden depends on the elements of the REMS, the tools that will be utilized to implement those elements, the number of patients affected, and the ability of the Applicant and healthcare providers to implement the elements. In addition, compliance with the REMS elements must be monitored closely and corrections must be made when necessary.

Concerns were raised during these discussions about the potential burdens of various REMS elements and whether a particular strategy was feasible and could adequately mitigate the risk of POME and anaphylaxis in Aveed users.

Risk/Benefit Assessment

Testosterone replacement therapies have been approved for use in adult males with conditions associated with a deficiency or absence of endogenous testosterone including products that are administered via the intramuscular route. Available data have demonstrated that Aveed replaces serum testosterone to the normal range in adult men. For this injectable testosterone product, the extended dosing interval may increase the likelihood of patient compliance. Aside from the risk of severe post-injection reactions, Aveed is associated with the typical adverse events reported for an injectable testosterone therapy.

There is a risk of severe post-injection reactions (POME and anaphylaxis) associated with the use of TU. The incidence of these reactions in clinical study database was small but consistent over time and there was a suggestion of a dose-response relationship. The presence of postmarketing reports for both POME and anaphylaxis indicates that these events continue to occur, but the inability to obtain accurate patient exposure information prevents an assessment of the magnitude of this risk. There are no known approaches to predict or prevent the occurrence of an Aveed-related severe post-injection reaction for any patient. It is unclear whether a “slowly administered” intramuscular injection or a 30 minute post-injection wait time in the healthcare provider’s office will entirely mitigate this risk. Finally, although several risk mitigation strategies have been discussed during drug development, the burden of these strategies to patients, providers and the overall healthcare system must be considered, and the likelihood that they will adequately mitigate the risk of POME and anaphylaxis in Aveed users is unknown.

FDA Issues:

We ask the members of the two advisory committees to focus on the benefits and risks of testosterone undecanoate injection given all of the available data. The preliminary points that we ask you to consider include:

1. Given the severe post-injection reactions that were reported with testosterone undecanoate in clinical studies and postmarketing data, do you believe that Aveed is safe for the proposed indication? Please provide a rationale for your response.

2. Discuss whether the Applicant's proposed Instructions for Use in product labeling would be sufficient to ameliorate the risk of severe post-injection reactions. If not, are there other measures you would recommend?

3. Does the available information provided in the briefing materials and presentations support marketing of Aveed for the proposed indication?
    a. If you voted "Yes", please provide your rationale.
    b. If you voted "No", please provide your rationale.

Clinical Background Document for Joint Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory committee
April 18, 2013

NDA 022-219

Testosterone Undecanoate Intramuscular Injection

(Proposed trade name: Aveed)

Endo Pharmaceuticals, Inc.

Proposed Indication:

Testosterone replacement therapy (TRT) in males for conditions associated with a deficiency or absence of endogenous testosterone: primary or hypogonadotropic hypogonadism (congenital or acquired)

Proposed Dosing Regimen:

3 mL (750 mg) to be injected intramuscularly at initiation, 4 weeks, and every 10 weeks thereafter

Table of Contents

TABLE OF TABLES **3**

TABLE OF FIGURES **4**

1. BACKGROUND **6**

1.1 OBJECTIVE OF MEETING AND OVERVIEW OF DEVELOPMENT PROGRAM 6
1.2 DESCRIPTION OF PRODUCT 6
1.3 TREATMENT OF MALE HYPOGONADISM 6
1.3.1 Male hypogonadism *6*
1.3.2 Current Treatment of male hypogonadism *7*
1.4 REGULATORY HISTORY FOR THE DEVELOPMENT OF TESTOSTERONE UNDECANOATE INJECTION (AVEED) 7

2. CLINICAL DEVELOPMENT OF TESTOSTERONE UNDECANOATE INJECTION **10**

2.1 OVERVIEW OF PRODUCT DEVELOPMENT 10
2.2 OVERVIEW OF PHARMACOLOGY AND TOXICOLOGY 12
2.3 OVERVIEW OF CLINICAL PHARMACOLOGY 13
2.4 OVERVIEW OF CLINICAL STUDIES 13

3. EFFICACY OF TESTOSTERONE UNDECANOATE INJECTION **13**

3.1 EFFICACY STUDY DESIGN 14
3.2 EFFICACY STUDY CONDUCT 15
3.2.1 Study Schedule and Conduct *15*
3.2.2 Eligibility Criteria *15*
3.3 EFFICACY ASSESSMENTS AND RESULTS 16
3.3.1 Analysis Populations *16*
3.3.2 Efficacy Endpoints and Results *17*
3.4 OVERALL SUMMARY OF EFFICACY FOR TESTOSTERONE UNDECANOATE INJECTION 22

4. SAFETY OF TESTOSTERONE UNDECANOATE INJECTION **23**

4.1 OVERVIEW OF THE SAFETY DATABASE FOR TESTOSTERONE UNDECANOATE INJECTION 23
4.2 COMMONLY REPORTED ADVERSE EVENTS IN CLINICAL TRIALS OF TESTOSTERONE UNDECANOATE INJECTION 23
4.3 IMMEDIATE POST-INJECTION REACTIONS - REGULATORY HISTORY / IMPORTANT CLINICAL ISSUES 28
4.4 IMMEDIATE POST-INJECTION REACTIONS –REPORTING RATES AND CASE NARRATIVES 33
4.4.1 Immediate Post-injection Reactions - Reporting Rates (POME and Anaphylaxis) *33*
4.4.2 Immediate Post-injection Reactions – Case Narratives *34*
4.4.3 Summary of Differences between the Sponsor's Internal Review and More Recent Review by the Sponsor's "Independent Adjudicators" *60*
4.4.4 Summary of Search Results and Analysis of the FDA's Adverse Event Reporting System (FAERS) for Immediate Post-injection Reactions with U.S. Approved Injectable Testosterone Products from January 1, 1969 through January 29, 2013 ..... *64*
4.5 SUMMARY OF SAFETY FOR USE OF TESTOSTERONE UNDECANOATE INJECTION 65

Table of Tables

TABLE 1 CLINICAL AND POSTMARKETING STUDIES OF TESTOSTERONE UNDECANOATE INJECTION 10
TABLE 2 IP157-001 PART C STUDY POPULATIONS 16
TABLE 3 IP157-001 PART C2 STUDY POPULATION 16
TABLE 4 PART C: DESCRIPTIVE STATISTICS FOR INJECTION 3 SERUM TOTAL TESTOSTERONE (NG/DL) PHARMACOKINETIC PARAMETERS, PHARMACOKINETIC POPULATION 17
TABLE 5 PART C: NUMBER (%) OF PATIENTS (AND TWO-SIDED 95% CONFIDENCE INTERVAL) MEETING SERUM TOTAL TESTOSTERONE C_{AVG} CRITERIA FOR A RESPONDER DURING THE 3RD INJECTION INTERVAL, PHARMACOKINETIC POPULATION 18
TABLE 6 PART C2: DESCRIPTIVE STATISTICS FOR INJECTION 2 SERUM TOTAL TESTOSTERONE (NG/DL) PHARMACOKINETIC PARAMETERS, TOTAL PATIENT SAMPLE/PHARMACOKINETIC SAMPLE 18
TABLE 7 PART C2: NUMBER (%) OF PATIENTS MEETING SERUM TOTAL TESTOSTERONE C_{MAX} CRITERIA FOR SUCCESS DURING THE 2ND INJECTION INTERVAL, TOTAL PATIENT SAMPLE / PHARMACOKINETIC SAMPLE 18
TABLE 8 PART C: NUMBER (%) OF PATIENTS MEETING SERUM TOTAL TESTOSTERONE C_{AVG} CRITERIA FOR SUCCESS DURING THE 3RD AND 4TH INJECTION INTERVALS, PHARMACOKINETIC AND STEADY-STATE PK POPULATIONS 19
TABLE 9 PART C, PART C2: NUMBER (%) OF PATIENTS MEETING SERUM TOTAL TESTOSTERONE C_{MAX} CRITERIA FOR SUCCESS, PHARMACOKINETIC POPULATION, STEADY-STATE PK POPULATION AND TOTAL PATIENT SAMPLE/PHARMACOKINETIC SAMPLE..... 19
TABLE 10 OTHER SECONDARY ENDPOINTS OF EFFICACY 22
TABLE 11 SAFETY DATA INTEGRATION OF CLINICAL AND POSTMARKETING STUDIES..... 23
TABLE 12 INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS THAT OCCURRED IN ≥ 3% OF THE POPULATION, SUBJECTS TREATED WITH TU IN STUDY IP157-001 PART C AND PART C2..... 23
TABLE 13 INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS THAT OCCURRED IN ≥ 3% OF THE POPULATION, SUBJECTS TREATED WITH TU IN IP157-001 ALL PARTS COMBINED, BY DOSE 24
TABLE 14 OVERALL INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS THAT OCCURRED IN ≥ 3% OF THE POPULATION IN ANY POOL OF STUDY, SUBJECTS TREATED WITH TU IN US AND EUROPEAN CLINICAL STUDIES..... 25
TABLE 15 INCIDENCE OF ALL TREATMENT-EMERGENT ADVERSE EVENTS, SUBJECTS TREATED WITH TU IN EUROPEAN POSTMARKETING STUDIES (39732 [NEO601 IPASS], AWB0105, CZECH NEO, NB02, TG09, AND 14853)..... 26
TABLE 16 REGULATORY HISTORY RELATED TO IMMEDIATE POST-INJECTION REACTIONS ... 31
TABLE 17 COMPARISON OF POSTMARKETING REPORTING RATES OF POME IDENTIFIED BY SPONSOR'S "INDEPENDENT ADJUDICATORS" VERSUS POSTMARKETING REPORTING RATES IDENTIFIED BY THE SPONSOR'S INTERNAL REVIEWERS (SHOWN IN PARENTHESES)..... 33
TABLE 18 COMPARISON OF POSTMARKETING REPORTING RATES OF ANAPHYLACTIC REACTIONS IDENTIFIED BY SPONSOR'S "INDEPENDENT ADJUDICATORS" VERSUS POSTMARKETING REPORTING RATES IDENTIFIED BY THE SPONSOR'S INTERNAL REVIEWERS (SHOWN IN PARENTHESES)..... 34
TABLE 19 LIST OF 137 CASES OF SEVERE POSTMARKETING POST-INJECTION REACTIONS TO TESTOSTERONE UNDECANOATE INJECTION..... 36
TABLE 20 SPONSOR'S ADJUDICATION OF CASES OF POME..... 60
TABLE 21 19 CASES NOT IN CONCORDANCE OF 228 CASES OF POME ASSESSED BY THE SPONSOR'S INTERNAL REVIEW AND CITED IN THE CR OF 9-NOV-2012 61
TABLE 22 14 "IND" CASES NOT IN CONCORDENCE OF 228 CASES OF POME ASSESSED BY THE SPONSOR'S INTERNAL REVIEW AND CITED IN THE CR OF 9-NOV-2012 61

TABLE 23 SPONSOR'S ADJUDICATION OF CASES OF ANAPHYLACTIC REACTION 62
TABLE 24 38 CASES NOT IN CONCORDANCE OF 79 CASES OF ANAPHYLACTIC REACTION ASSESSED BY THE SPONSOR'S INTERNAL REVIEW AND CITED IN THE CR OF 9-NOV-2012 63
TABLE 25 2 YES / 2 IND CASES NOT IN CONCORDENCE OUT OF 79 ANAPHYLAXIS IN CR (29-NOV-2012) 64
TABLE 26 CASES OF SEVERE POST-INJECTION REACTIONS IDENTIFIED FROM A SEARCH OF FAERS FOR U.S. APPROVED INJECTABLE TESOTERONE PRODUCTS - JANUARY 1, 1969 THROUGH JANUARY 29, 2013..... 65

Table of Figures

FIGURE 1 STUDY DESIGN FOR IP157-001 PART C..... 15
FIGURE 2 STUDY DESIGN FOR IP157-001 PART C2..... 15
FIGURE 3 STUDY IP157-001 PART C: MEAN (SD) SERUM TESTOSTERONE CONCENTRATION (NG/DL) DURING THE 3RD INJECTION INTERVAL PK POPULATION 20
FIGURE 4 STUDY IP157-001 PART C: COMPARISON OF SERUM TOTAL TESTOSTERONE CONCENTRATIONS (NG/DL) DURING THE 3RD AND 4TH INJECTION INTERVALS, PHARMACOKINETIC AND STEADY-STATE PHARMACOKINETIC POPULATIONS..... 20
FIGURE 5 STUDY IP157-001 PART C2: MEAN (SD) SERUM TESTOSTERONE CONCENTRATION (NG/DL) DURING THE 2ND INJECTION INTERVAL PK POPULATION 21
FIGURE 6 STUDY IP157-001 PART C: KAPLAN-MEIER ESTIMATE OF THE PROBABILITY OF THE FIRST SERUM TOTAL TESTOSTERONE CONCENTRATIONS < 300 NG/DL DURING THE 3RD INJECTION INTERVAL, PHARMACOKINETIC POPULATION 21

List of Abbreviations and Definitions

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CPA	Cyproterone acetate
CR	Complete Response
CRF	Case report form
CSR	Clinical study report
DHT	Dihydrotestosterone
DRUP	Division of Reproductive and Urologic Products
ENG	Etonogestrel
EU	European
FAS	Full Analysis Set
FDA	Food and Drug Administration
HCP	Health Care Provider
IM	Intramuscular
ISS	Integrated Summary of Safety
IV	Intravenous
LNG	Levonorgestrel
MedDRA	Medical Dictionary of Regulatory Activities
NDA	New Drug Application
NET-A	Norethisterone acetate
NET-EN	Norethisterone enanthate
PMA	Patient Management Algorithm
POME	Pulmonary oil microembolism
POME-BMQ	POME specific MedDRA Query developed by Bayer Pharma AG
PSUR	Periodic Safety Update Report
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SHBG	Sex hormone-binding globulin
SMQ	Standardised MedDRA Query
SOC	System organ class
Std. Dev.	Standard deviation
T	Testosterone
TE	Testosterone enanthate
TEAE	Treatment-emergent adverse event
TRT	Testosterone replacement therapy
TU	Testosterone undecanoate

1. Background

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the safety and overall risk/benefit profile of testosterone undecanoate injection (Aveed) indicated for replacement therapy in adult men with conditions associated with a deficiency or absence of endogenous testosterone. If approved, Aveed would be an injectable testosterone requiring less frequent injections (6 injections per year) compared to currently available injectable testosterone preparations. The critical safety issue is the occurrence of serious post-injection reactions, including pulmonary oil microembolism (POME) and anaphylactic reactions.

The primary source of clinical efficacy data come from two parts of one, U.S., open-label, Phase 3 clinical trial (Parts C and C2 of Study IP157-001). The safety data come from Study IP157-001 and 17 other postmarketing clinical studies, as well as from postmarketing case reports.

1.2 Description of Product

Testosterone undecanoate (TU) is an ester of testosterone. Aveed contains testosterone undecanoate (750 mg), refined castor oil (885 mg/3 mL), and benzyl benzoate (1,500 mg/3 mL). It is to be administered as a 3 mL, intramuscular injection in the following regimen: 1 injection at initiation, a second injection 4 weeks later, followed by chronic administration every 10 weeks thereafter.

The same TU drug product is marketed worldwide under the tradename Nebido by Bayer Pharma AG. TU is also marketed under the tradename Reandron in some countries. The first marketing authorization for Nebido was granted by Finland on November 25, 2003 and the first launch was 2004 in Finland. Nebido is currently authorized to be marketed in 94 countries and is marketed in more than 70 countries. Nebido is administered as a 4 mL injection at a dosing interval not shorter than 12 weeks.

A key issue described in current Nebido labeling is shown here:

- **Section 5.2 Injection-based pulmonary oil microembolism**: In worldwide clinical trials involving more than 20,000 injections, pulmonary oil microembolism reactions were reported at a rate of 4.45 per 10,000 injections. [ISS: section 4.2.5.1.2.2]

Testosterone undecanoate injection has not been approved in the US.

1.3 Treatment of male hypogonadism

1.3.1 Male hypogonadism

Male hypogonadism is a clinical condition characterized by abnormally low levels of circulating testosterone (e.g., serum total testosterone levels <300 ng/dL), in the presence of 1 or more clinical symptoms. Such symptoms can include diminished libido, erectile dysfunction, impaired mood, loss of muscle mass and function, and osteoporosis. Male hypogonadism is classified

based on primary and secondary causes. Primary hypogonadism, congenital or acquired, may be due to numerous causes, including defects of the testes, testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range. Secondary (hypogonadotropic) hypogonadism, congenital or acquired, may be due to idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

1.3.2 Current Treatment of male hypogonadism

For several decades, testosterone replacement therapy (TRT) has been used clinically to treat primary and secondary male hypogonadism. The goals of TRT are to achieve normal physiologic levels of testosterone throughout the dosing cycle and to help manage the symptoms associated with androgen deficiency.

There are a number of testosterone preparations currently available for testosterone replacement. These include topical gels, a topical solution, and a transdermal patch. There is also an orally administered formulation, a subcutaneous pellet, and a buccal mucoadhesive. Finally, there are intramuscular injections of testosterone

Intramuscular (IM) administration of testosterone esters is a well-established approach to TRT in hypogonadal men. Testosterone enanthate or testosterone cypionate are commercially available, FDA-approved preparations for IM injection. With these preparations, levels of total testosterone within the normal physiological range can be achieved for 2 to 4 weeks following a single injection. The short-acting TRTs for IM injection are associated with supraphysiological testosterone levels right after patients receive their dose and sub-therapeutic testosterone levels at the end of each dosing interval.

1.4 Regulatory History for the Development of Testosterone Undecanoate Injection (Aveed)

Regulatory History of NDA 022-219 (Aveed)

	Sponsor	FDA
Original NDA Submission in 2007-2008	**Original NDA submitted on August 24, 2007** Pulmonary oil micro-embolism (**POME):** reported in 2 patients in clinical trials: these 2 events were described as sudden (and in one case, severe) urge to cough, cough, and dyspnea immediately following injection. In post-marketing safety update reports (PSURs), the 120-day Safety Update, and a Summary Report of "cough fits", a total of 66 European postmarketing cases were detected.	**"Approvable" action taken on June 7, 2008 with Chemistry, Manufacturing, and Clinical deficiencies.** • "There are reports of serious, immediate post-injection AEs in men who have received TU intramuscular injections." • "These reports, although the exact etiology has yet to be determined, are consistent with anaphylaxis and POME." The Applicant was requested to provide additional safety information to determine the incidence of serious post-injection POME and allergic reactions and to characterize the nature and etiology of the anaphylaxis-like events.
Complete Response (CR) Submitted on March 2, 2009	**Complete Response submitted on March 2, 2009** Safety data submitted from 2,834 subjects who had received 16,191 injections in 12 completed and 5 ongoing clinical trials. There was just 1 report of serious POME (0.035%) and no reports of systemic allergic reaction. Approximately 125 cases of post-injection reactions (POME and anaphylaxis) were reported in postmarketing experience. A proposed Risk Evaluation and Mitigation Strategy (REMS), consisting of a Medication Guide and a Communication Plan, was included.	**CR action taken on Dec. 2, 2009, with Clinical deficiency of continuing safety concerns regarding reports of serious, immediate, life-threatening post-injection reactions and their impact on the risk/benefit profile.** The proposed REMS was considered not sufficient to ensure that the benefits of Aveed injection outweighed the risks associated with use of Aveed. The Division identified 2 potential remedial actions: • Identify which components of the drug product may be contributing to the immediate post-injection reactions, and reformulate the product; or • Identify a population of adult males who require testosterone replacement therapy (TRT) and in whom the additional potential risks associated with the use of TU injection as currently formulated would be acceptable. In addition, a safety update including worldwide postmarketing safety reports was requested.
From 2009 CR through 2010	Subsequent to the December 2009, CR action, the **Sponsor requested that FDA provide a list of cases** of post-injection reaction that led to the CR action. In April 2010, the Sponsor requested a **Type A meeting** to discuss a potential path forward. The Sponsor proposed to narrow the target population and restrict distribution of Aveed.	In December 2009, **DRUP provided a list** of patients from CIOMS reports who sustained postmarketing post-injection adverse reactions either immediately or soon after injection. On May 24, 2010, **FDA met with Sponsor in Type A meeting** to discuss potential path forward (narrowed target population with restricted distribution).

2011	February 16, 2011 & May 26, 2011 – The sponsor requested a **Type C meeting** and submitted a briefing package, respectively, which included a revised, proposed REMS with Elements To Assure Safe Use (ETASU). The REMS was specifically designed to restrict the distribution of Aveed to certain populations.	On June 27, 2011, **FDA met with Sponsor in Type C meeting**. After further consideration and internal FDA discussion, the Agency determined that the proposed REMS with ETASU was not appropriate for Aveed. DRUP recommended that the Sponsor resubmit the NDA and the application would likely be discussed at an Advisory Committee Meeting.
2012 prior to second Complete Response (CR)	In November 2011, the Sponsor requested another **Type C meeting** to receive feedback on preparing the resubmission. A major issue was identification and analysis of postmarketing reports of POME and anaphylactic reaction. The meeting was granted but was **cancelled by the Sponsor after receiving FDA response**. The Sponsor provided proposals for case identification and classification: • Exact terms were provided for searching the postmarketing database for cases of POME and anaphylaxis • Anaphylaxis will be defined using the "Rüggeberg" definition of anaphylaxis developed in Europe from the Brighton Collaboration Anaphylaxis Working Group	On January 14, 2012, **FDA conveyed preliminary responses to the Type C meeting questions**. The Sponsor was requested to provide: (1) the exact terms to be used for searching postmarketing databases for cases of POME and anaphylaxis; (2) specific criteria to use to define POME and anaphylaxis, as well as the specific process to use adjudicating cases generated by search. DRUP reviewed the Sponsor's proposals in collaboration with the Office of Surveillance and Epidemiology (OSE) and Division of Pulmonary, Allergy and Rheumatology Products (DPARP). DRUP stated: • The MedDRA terms to be queried to cull potential cases of POME and anaphylaxis are reasonable • FDA uses a clinical definition of anaphylaxis (Sampson Criteria) developed by NIAID and the Food Allergy and Anaphylaxis Network when evaluating potential cases of anaphylaxis • Individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis irrespective of Sponsor's medical review or adjudication.
Second CR Submitted on November 29, 2012	**Second CR submitted on November 29, 2012** Sponsor formally requested an AC meeting as part of the review process of this submission	**AC Meeting scheduled for April 18, 2013**

2. Clinical Development of Testosterone Undecanoate Injection

2.1 Overview of Product Development

The development program for testosterone undecanoate injection for TRT consisted of a single U.S. Phase 3 study (Study IP157-001), six European Phase 1, Phase 2 and Phase 3 studies, 5 European male contraception studies, and 6 International postmarketing studies (Table 1)

Table 1 Clinical and Postmarketing Studies of Testosterone Undecanoate Injection

	Indication Sample Size	Title	Type	Study Design	Treatment
US Clinical Study (N = 524)					
IP157-001 Part A Part B Part C Part C2 Completed	Hypogonadism (TU 750 mg, n =272; TU 1000 mg, n=252; Overall, n = 524)	A 2-arm, open-label, randomized, multicenter pharmacokinetic and long-term safety study of intra-muscular (IM) injections of testosterone undecanoate (TU) 750 mg and 1000 mg in hypogonadal men. This was a 5-part protocol that included 2 IM treatment arms in Part A, 2 IM treatment arms in Part B, a single IM treatment arm in Part C, a single IM treatment arm in Part C2 and 2 subcutaneous (SC) treatment arms in Part D.	Phase 3	Open-label, randomized, 2-arm, active-controlled, multiple-dose	**Part A:** TU 750 mg IM; TU 1000 mg IM; **Part B:** All subjects TU 1000 mg IM initial dose followed by 2-arms: TU 750 mg IM; TU 1000 mg IM; **Part C:** TU 750 mg IM; **Part C2:** TU 750 mg IM; **Part D: SC** TU 1000 mg (Part A pts) TU 750 mg (Part C pts)
European Clinical Studies (N = 201)					
JPH01495 Completed	Hypogonadism (n = 14)	Study to investigate the PK of TU after single IM injection	Phase 1	Open-label, single arm, single dose	TU 1000 mg IM
JPH04995 Completed	Hypogonadism (n = 14)	Study to investigate the PK and efficacy of TU after multiple IM injections in hypogonadal men	Phase 2/3	Open-label, single arm, multiple dose	TU 1000 mg IM
ME98096 Completed	Hypogonadism (n = 26)	Open-label study to evaluate safety and PK parameters of total and free testosterone after repeated IM administrations of TU 1000 mg (5 injections over 36 weeks) in hypogonadal male subjects	Phase 2	Open-label, single arm, multiple dose	TU 1000 mg IM
ME97029 Completed	Hypogonadism (n = 36)	Study to investigate the efficacy and safety of TU vs. testosterone enanthate (TE) after IM injection in hypogonadal men	Phase 3	Randomized, open-label, parallel-group, 2-arm, active-controlled, multiple dose	TU 1000 mg IM TE 250 mg IM
306605 Completed	Hypogonadism (n = 96)	Open-label, one-arm study to investigate safety and efficacy of IM injections of TU 1000 mg in hypogonadal men at variable intervals during a 136- to 192-week treatment including PK of TU during steady state in a subgroup of 30 subjects	Phase 3	Open-label, single arm multiple dose	TU 1000 mg IM
303934 Terminated Early[a]	Male Andropause (n = 15)	A monocenter, prospective, randomized, double-blind, parallel-group, placebo-controlled, long term clinical trial to investigate the effects of a long-acting IM	Phase 2	Randomized, double-blind, parallel-group, 2-arm, placebo-	TU 1000 mg IM 4 mL placebo IM

		reparation of TU on andropause-related symptoms		controlled, multiple-dose	
European Male Contraception Studies (N = 407)					
97028 Completed	Male contraception in healthy males (n = 28)	Male contraception with TU vs. combined administration of TU and levonorgestrel (LNG) - a double-blind, randomized, single-center comparative study	Phase 2	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled, multiple-dose	TU 1000 mg IM + oral Placebo TU 1000 mg IM +oral LNG
97173 Completed	Male contraception in healthy males (n = 25)	Male contraception with a sequential regimen of cyproterone acetate (CPA) and TU followed by a lower dose of CPA and TU in normal men	Phase 2	Randomized, double-blind, 3- arm, placebo-controlled, multiple-dose	**Induction Phase:** TU 1000 mg IM+CPA 20 mg/day oral **Maintenance Phase:** 3 Randomized Groups: TU 1000 mg IM+CPA 20 mg/day oral; or TU 1000 mg IM+CPA 2 mg/day oral; or TU 1000 mg IM+daily oral placebo.
98016 Completed	Male contraception in healthy males (n = 14)	A single-center, prospective, 1-arm, uncontrolled study to investigate the efficacy and safety of male contraception with TU and nor-ethisterone enanthate (NET-EN) over 24 weeks	Phase 2	Open-label, single arm multiple dose	TU 1000 mg IM + NET-EN 200 mg IM
99015 Completed	Male contraception in healthy males (n = 42)	Study on efficacy and safety of male contraception with TU and NET combined in different application regimens	Phase 2	Randomized, double-blind, parallel-group, 3-arm, placebo-controlled, multiple-dose	TU 1000 mg IM+NET-EN 200 mg IM TU 1000 mg IM+NET-EN 400 mg IM TU 1000 mg IM+NET-A 10 mg/day oral
42306 Completed	Male contraception in healthy males (n = 298)	A phase IIb, double blind, placebo-controlled, randomized, multicenter, multiple dose trial investigating the efficacy, safety and pharmacokinetics of a subcutaneous etonogestrel (ENG) rod combined with intramuscular TU for male fertility control	Phase 2b	Randomized, double-blind, parallel-group, 7-arm, placebo-controlled, multiple-dose	TU 750 mg IM+LR ENG Implant every 10 weeks TU 750 mg IM+LR ENG Implant every 12 weeks TU 1000 mg IM+LR ENG Implant every 12 weeks TU 750 mg IM+HR ENG Implant every 10 weeks TU 750 mg IM+HR ENG Implant every 12 weeks TU 1000 mg IM+HR ENG Implant every 12 weeks Placebo IM+Placebo Implant
International Postmarketing Studies (N = 2424)					
AWB 0105 Completed	Androgen Deficiency in Men (n = 869)	Efficacy and tolerability of Nebido®	Post-marketing surveillance: prospective, non-interventional	Open-label, single-arm, multiple-dose	TU 1000 mg IM
39732 (NE0601 IPASS) Completed	Hypogonadism (n = 1411)	International, multicenter post authorization surveillance study on the use of Nebido® to assess tolerability and treatment outcomes in daily clinical practice	Post-marketing surveillance: prospective, non-interventional observational	Open-label, single-arm, multiple-dose	TU 1000 mg IM

14329 (Czech NEO) Completed	Hypogonadism (n = 23)	NEO; Observational post-marketing study (Nebido)	Post-marketing surveillance: prospective, non-interventional observational	Open-label, single-arm, multiple-dose	TU 1000 mg IM
NB02 Completed	Hypogonadism (n = 20)	NEBIDO Therapy in Hypogonadal Male Patients With Paraplegia With Osteoporosis Compared With Conventional Osteoporosis	Post-marketing surveillance: prospective, non-interventional observational	Open-label, 3-arm, multiple dose, single center	TU 1000 mg IM
TG09 Completed	Hypogonadism (n = 29)	Efficacy and tolerability of Testogel/Nebido in combination with a standardized exercise and diet programme in hypogonadal male patients with abdominal obesity compared with exercise and diet programme	Post-marketing surveillance: non-interventional observational	Open-label, 2-arm, multiple-dose, single center	TU 1000 mg, Testogel
14853 Terminated Early[b]	Hypogonadism (n = 3)	Effect of exercise alone or in combination with testosterone replacement on muscle strength and quality of life in older men with low testosterone concentrations; a randomized double-blind, placebo controlled study	Post-marketing surveillance: interventional	Randomized, Double blind, parallel-group, 2-arm, placebo controlled, multiple-dose	TU 1000 mg, Placebo

[a] terminated early by Sponsor.
[b] terminated early due to slow recruitment rate.
CPA=Cyproterone acetate; ENG=Etonogestrel; IM=Intramuscular; LNG=Levonorgestrel; NET-A= Norethisterone acetate; NET-EN=Norethisterone enanthate; SC=Subcutaneous; TE=Testosterone enanthate; TU=Testosterone undecanoate.
Source: Integrated Safety Summary

2.2 Overview of Pharmacology and Toxicology

The toxicology of testosterone is well understood. Testosterone is a non-mutagenic rodent carcinogen (increases cervical and uterine tumors and liver tumors), and a teratogen which causes masculinization of female fetuses, female animals, and adult females with acceleration of pubertal changes in juvenile males. Because of the extensive clinical and nonclinical data available on testosterone, nonclinical evaluation of TU was limited to assessing binding affinity for the human androgen receptor, ADE (absorption, distribution and elimination) in rats, local toxicity after a single intramuscular injection in pigs, potential for toxicity after repeated intramuscular dosing in rats, and genotoxicity.

Preclinical findings for TU included: little potential for pharmacologic activity without being metabolized, a long half-life at the injection site with expected ADE, toxicities after repeated dosing generally related to expected pharmacology or the result of large injection volumes, and negative results for *in vitro* and *in vivo* genotoxicity assays. In summary, no significant safety concerns associated with TU administration were identified in the nonclinical program, other than toxicities related to expected pharmacology and injection site trauma.

2.3 Overview of Clinical Pharmacology

The reader is referred to Section 3.3.2 for the pharmacokinetics associated with the to-be-marketed TU injection 750 mg loading dose regimen.

2.4 Overview of Clinical Studies

The Clinical review of NDA 022-219 focused on Parts C and C2 (extension) of Study IP157-001, a single, U.S., Phase 3 study. For safety, the review focused on the information from Study IP157-001, as well as safety information from 12 additional European and International Phase 1-3 studies, and finally, the relevant post-marketing safety experience.

Study IP157-001 was a phase 3, open-label, multicenter clinical trial conducted in the US to evaluate the safety and pharmacokinetics (PK) of testosterone undecanoate injection in hypogonadal men. This study was conducted in 5 parts (Parts A, B, C, C2, and D), with varying dose and treatment regimens. IP157-001 Part C and Part C2 provide pivotal data to support efficacy for U.S. approval. The study was conducted after discussions with DRUP and took into consideration FDA recommendations.

- Treatment in Part A of the study was either TU 750 mg or 1000 mg injected intramuscularly every 12 weeks. Data was presented for Stage 1, which included data through the 5th injection visit.
- Treatment in Part B of the study was TU 1000 mg given intramuscularly at baseline followed by either TU 750 mg or 1000 mg injected 8 weeks later and then every 12 weeks thereafter.
- Treatment in Part C was TU 750 mg given intramuscularly with a second injection ("loading") at 4 weeks and at 10-week intervals thereafter. This loading dosing regimen was selected to provide adequate testosterone replacement over a 10-week dosing interval and to reach steady state conditions sooner than those observed for the treatment regimens in Part A.
    - In Part C, the pivotal measurement was after the 3rd injection (e.g., Stage 1).
    - In Part C2, the pivotal measure was after the 2nd injection.
- Part D was exploratory and was intended to evaluate the PK of TU when given subcutaneously. A total of 21 patients from Part C and 22 patients from Part A crossed over into Part D. No PK parameters were derived from serum total testosterone concentrations measured after SC injections, and no efficacy analysis was performed for Part D

The Efficacy section of this review presents a qualitative integration of complete final results from Part C and Part C2 of Study IP157-001 rather than a pooled analysis of efficacy. In summary, the data characterize the testosterone PK for 3 consecutive injection cycles (2nd, 3rd, and 4th) and provide support for the use of the 750 mg loading dosage regimen as the recommended therapeutic dose.

3. Efficacy of Testosterone Undecanoate Injection

The efficacy of testosterone undecanoate injection as a TRT for conditions associated with male hypogonadism is supported by a single, open-label, pivotal study using the 750mg loading

regimen (Study IP157-001, Part C, C2) in approximately 130 hypogonadal males. Different dosage strengths and different dose regimens were tested during the development program for Aveed, and the results from these additional Phase 2 and Phase 3 studies served as supporting data. In addition, a number of studies have been conducted outside the US both prior to and since the time of initial approval of testosterone undecanoate injection outside the U.S. (in 2004).

In summary, testosterone undecanoate injection 750 mg loading regimen provides acceptable replacement of testosterone. The Sponsor met the current requirement for demonstration of efficacy for this indication.

3.1 Efficacy Study Design

IP157-001 Part C
The primary objective for Part C of the study was to evaluate the PK of testosterone from TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total testosterone.

The secondary objectives for Part C of the study were:

- To evaluate the PK of testosterone over the 10-week interval following the 4th injection, via multiple measurements of serum total testosterone
- To compare serum levels of dihydrotestosterone (DHT), estradiol, and sex hormone binding globulin (SHBG) to simultaneous levels of serum total testosterone over the 3rd injection interval
- To evaluate safety through up to 9 injections in hypogonadal men

IP157-001 Part C2
The primary objective for Part C2 of the study was to evaluate the maximum concentration (C_{max}) of testosterone from TU 750 mg, given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 2nd injection, via multiple measurements of serum total testosterone, in up to approximately 20 hypogonadal men.
In order to provide a complete PK profile of TU 750 mg during the 2nd injection interval, the Day 70 measurement was included in the evaluations.

The secondary objectives for Part C2 of the study were:

- To compare serum levels of DHT, estradiol, and SHBG to simultaneous levels of serum total testosterone.
- To evaluate safety in patients treated with TU 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 6 injections in hypogonadal men.

Part C2 replicated the dosing regimen of Part C, but focused on PK assessment during the 2nd injection interval. Approximately 20 patients were to be enrolled. The total exposure for individual patients was to be approximately 12 months (54 weeks).

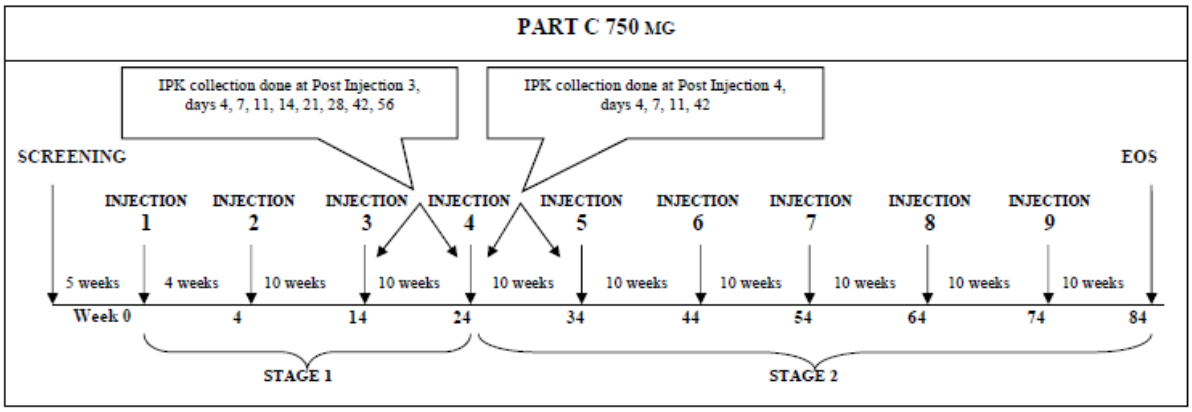
All patients were to have PK assessments during the 2nd injection interval in order to capture C_{max} in the post-loading dose interval. In addition, patients also had a trough PK assessment at the 3rd injection and continued to have trough PK captured at each 10-week dosing interval visit through the remainder of the study. Safety was assessed through 6 injections.

3.2 Efficacy Study Conduct

3.2.1 Study Schedule and Conduct

The Schedule of Events for Part C is displayed in Figure 1.

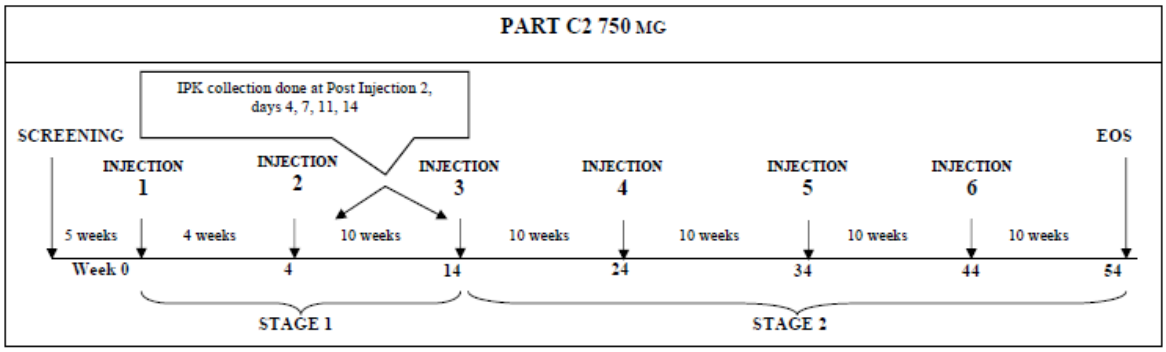
Figure 1: Study design for IP157-001 Part C



EOS = end of study; IPK = Intensive pharmacokinetics

The Schedule of Events for Part C2 is displayed in Figure 2.

Figure 2: Study design for IP157-001 Part C2



EOS = end of study; IPK = Intensive pharmacokinetics

3.2.2 Eligibility Criteria

Patients enrolled in both Parts C and C2 of the study were to be men at least 18 years of age with primary or secondary hypogonadism (morning screening serum testosterone concentration <300 ng/dL). They could not have an American Urological Association Symptom Score ≥15 or significant prostatic symptoms, a screening serum prostate specific antigen level above 4 ng/mL or hyperplasia of the prostate (size >75 cm^3 as measured by transrectal ultrasonography), or

history or suspicion of carcinoma, tumors, or induration of the prostate or the male mammary gland. In addition, the use of any sex hormones within 28 days (e.g., injectable testosterone preparations) or 7 days (e.g., oral, gel, patch testosterone preparations) prior to the screening serum testosterone collection for PK assessment as well as at any time throughout the study was prohibited. Complete inclusion/exclusion criteria were provided in the study protocol.
A lower weight threshold of 65 kg was added as an exclusion criterion in Amendment 8 to account for an inverse relationship between weight and serum testosterone concentration,

3.3 Efficacy Assessments and Results

The Clinical Efficacy section presents a qualitative integration of complete final results of Part C and Part C2 of Study IP157-001 rather than a pooled analysis of efficacy. Part C2 in conjunction with Part C were designed to characterize the PK of the injection intervals of an initial TU 750 mg dose, followed by TU 750 mg given at 4 weeks and then at 10-week intervals thereafter in a repeated-injection setting. In summary, the study characterized 3 consecutive injection cycles (2nd, 3rd, and 4th) of PK behavior of TU 750 mg. This data provided support for the use of this dosage regimen as the recommended therapeutic dose.

3.3.1 Analysis Populations

Table 2: IP157-001 Part C Study Populations

Population	Number of Subjects	Definition
Total Patient Sample	130	All subjects who were enrolled in Part C and given at least 1 injection of study drug
PK Population[a]	117	Subjects who had a minimum of 4 serum total testosterone concentration values during the 3rd injection interval. The 4 values could include the Day 0 and/or Day 70 values from the interval. Additionally, subjects had to weigh at least 65 kg[b] in order to be included in the PK Population. Any subject found to have used other TRT during the study was excluded from the PK population.
Steady-State PK Population	104	All subjects in the PK Population with non-missing 4th and 5th injection serum total testosterone concentrations
Long-Term PK Population	98	All subjects in the Steady-State PK Population with a non-missing 8th injection serum total testosterone concentration

[a] The primary efficacy endpoint was based on the PK population.
[b] One subject with a baseline weight <65 kg enrolled in the study and was excluded from the PK Population. An additional exclusion criterion was added in Amendment 8.
Source: Summary of Clinical Efficacy, Table 3

Table 3: IP157-001 Part C2 Study Population

Population	Number of Subjects	Definition
Total Patient Sample	23	All subjects who were enrolled in Part C2 and given at least 1 injection of study drug

Source: Summary of Clinical Efficacy, Table 4

3.3.2 Efficacy Endpoints and Results

3.3.2.1 Primary Efficacy Results

IP157-001 Part C Primary Efficacy Results:
TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter provided adequate TRT (as measured by C_{avg}) while not providing excessive TRT (as measured by C_{max}). The mean C_{avg} during the pivotal interval (3rd injection) was 494.9 ng/dL (coefficient of variation [CV]: 28.6%), and was within the normal range (i.e., 300 to 1000 ng/dL), with 110 subjects (94.0% [2-sided 95% confidence interval (CI), 89.7%-98.3%]) achieving the normal range for C_{avg}. At all time points measured during the 3rd injection interval, the mean serum total testosterone concentrations remained within the normal range

Table 4: Part C: Descriptive Statistics for Injection 3 Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters, Pharmacokinetic Population

	C-750 mg (N=117)							
	N	Mean	SD	Min	Median	Max	%CV	Geometric Mean
$AUC_{0\text{-}70days}$ (d•ng/dL)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
C_{trough} (ng/dL)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
C_{avg} (ng/dL)	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Source: Summary of Clinical Efficacy

A total of 110 subjects (94.0% [2-sided 95% CI, 89.7%-98.3%]) had C_{avg} between 300 and 1000 ng/dL and were considered responders, and 7 subjects were considered non-responders. Of the 7 subjects who were non-responders, 6 subjects (5.1% [2-sided 95% CI, 1.1%-9.1%]) had a C_{avg} <300 ng/dL (range: 196.5 to 296.9 ng/dL) and 1 subject (0.9% [2-sided 95% CI, 0.0%-2.5%]) had a C_{avg} of 1000.2 ng/dL.

Table 5: Study IP157-001 Part C: Number (%) of Patients (and Two-Sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{avg} Criteria for a Responder During the 3rd Injection Interval, Pharmacokinetic Population

Serum Total Testosterone C_{avg} Criteria	C-750 mg (N=117)	
	N (%)	95% CI
Responder		
C_{avg} within 300-1000 ng/dL	110 (94.0%)	(89.7%, 98.3%)
Not a Responder		
C_{avg} <300 ng/dL	6 (5.1%)	(1.1%, 9.1%)
C_{avg} >1000 ng/dL	1 (0.9%)	(0.0%, 2.5%)

Source: Summary of Clinical Efficacy

IP157-001 Part C2 Primary Efficacy Results:

Table 6: Study IP157-001 Part C2: Descriptive Statistics for Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters after Injection 2, Total Patient Sample/Pharmacokinetic Sample

	C2-750 mg (N=23)							
	N	Mean	SD	Min	Median	Max	%CV	Geometric Mean
$AUC_{0\text{-}70days}$ (d•ng/dL)	23	31475.2	10990.41	17114.4	30436.2	68092.8	34.9	29910.2
C_{trough} (ng/dL)	23	317.4	105.31	135.8	298.9	487.5	33.2	299.1
C_{max} (ng/dL)	23	689.0	266.94	338.6	657.2	1576.3	38.7	646.6
T_{max} (days)	23	8.0	3.27	4.0	7.0	14.0	41.1	7.3
C_{avg} (ng/dL)	23	449.6	157.01	244.5	434.8	972.8	34.9	427.3

$AUC_{0\text{-}70days}$=Area under curve from Day 0 through Day 70; C_{avg}=Average concentration; C_{max}=Maximum concentration; C_{trough}=Day 70 concentration; CV=Coefficient of variation; T_{max}=Time of maximum concentration.
Note: C2-750 mg refers to TU 750 mg.
Source: Summary of Clinical Efficacy

Table 7: Study IP157-001 Part C2: Number (%) of Patients Meeting Serum Total Testosterone C_{max} Criteria for Success During the 2nd Injection Interval, Total Patient Sample / Pharmacokinetic Sample

Serum Total Testosterone C_{max} Observed During 2nd Injection Interval	Criteria for Success[a]	C2-750 mg (N=23) N (%)
≤1500 ng/dL	≥85% of patients	22 (95.7%)
>1500 to <1800 ng/dL	--	1 (4.3%)
1800-2500 ng/dL	≤5% of patients	0
>2500 ng/dL	No patients	0

[a] All 3 criteria for success must have been met in order to reject the null hypothesis in favor of the alternate hypothesis. If any of the 3 criteria did not meet its criteria for success, the null hypothesis could not be rejected.
Note: Percentages based on non-missing data. C2-750 mg refers to TU 750 mg.
Source: Summary of Clinical Efficacy

Comparison of Efficacy Endpoints

In Part C of the study, percentages of "responders", defined as patients with C_{avg} within the normal, was comparable between the 3rd and 4th injection intervals (94.0% and 96.2%,

respectively) (Table 8). A maximum serum T concentration (C_{max}) <1500 mg/dL was achieved in 92.3% of the PK Population and in 92.3% of the Steady-State PK Population (Table 9).

In Part C2, prior to steady state, Cmax was <1500 mg/dL in 95.7% of the Total Patient Sample/PK Sample (Table 9).

Table 8: Study IP157-001 Part C: Number (%) of Patients Meeting Serum Total Testosterone C_{avg} Criteria for Success During the 3rd and 4th Injection Intervals, Pharmacokinetic and Steady-State PK Populations

Serum Total Testosterone	C-750 mg (N=117) 3rd Injection Interval, PK Population		C-750 mg (N=104) 4th Injection Interval, SS PK Population	
	N (%)	95% CI	N (%)	95% CI
Responder				
C_{avg} within 300-1000 ng/dL	110 (94.0%)	(89.7%; 98.3%)	100 (96.2%)	(92.5%; 99.8)
Not a Responder				
C_{avg} <300 ng/dL	6 (5.1%)	(1.1%; 9.1%)	4 (3.8%)	(0.2%; 7.5%)
C_{avg} >1000 ng/dL	1 (0.9%)	(0.0%; 2.5%)	0	

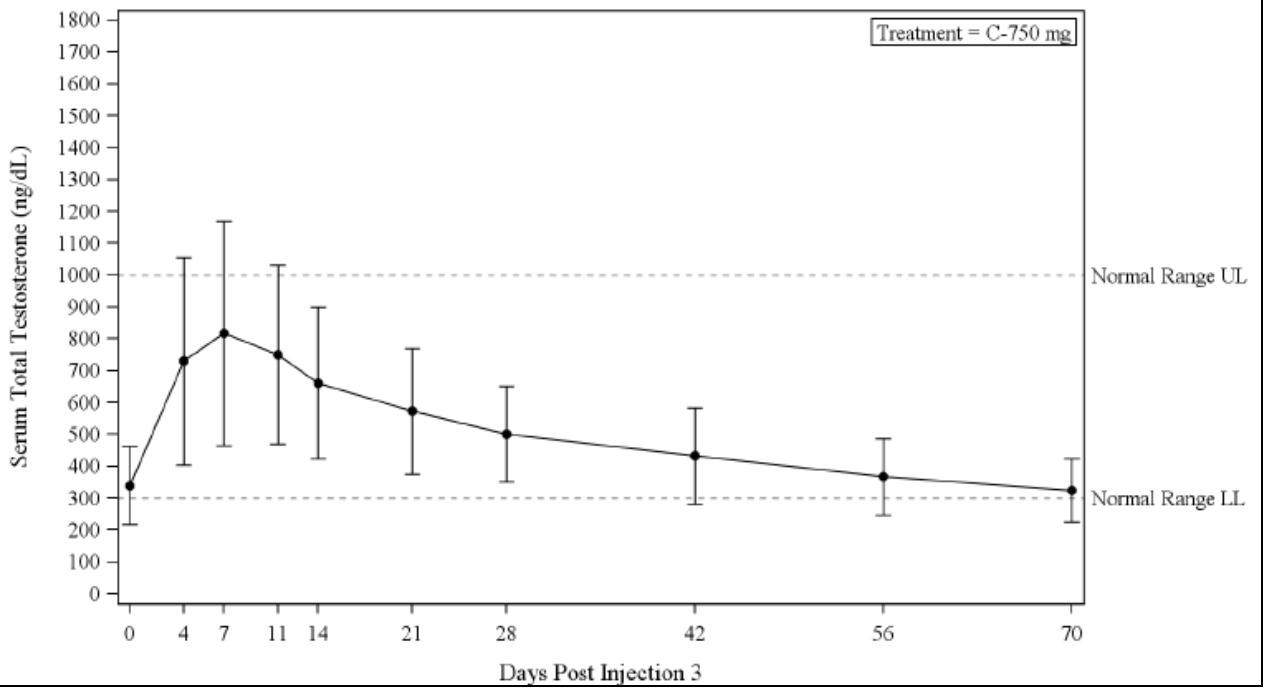
PK=Pharmacokinetic; SS=Steady-state.
Note: Percentages based on non-missing data. C-750 mg refers to TU 750 mg.
Source: Summary of clinical Efficacy

Table 9: Study IP157-001 Part C, Part C2: Number (%) of Patients Meeting Serum Total Testosterone C_{max} Criteria for Success, Pharmacokinetic Population, Steady-State PK Population and Total Patient Sample/Pharmacokinetic Sample

Serum Total Testosterone C_{max} Observed	Criteria for Success[a]	C-750 mg (N=117) 3rd Injection Interval, PK Population	C-750 mg (N=104) 4th Injection Interval, SS PK Population	C2-750 mg (N=23) 2nd Injection Interval, TPS/PK Sample
		N (%)	N (%)	N (%)
≤1500 ng/dL	≥85% of patients	108 (92.3%)	96 (92.3%)	22 (95.7%)
>1500 to <1800 ng/dL	--	9 (7.7%)	4 (3.8%)	1 (4.3%)
1800-2500 ng/dL	≤5% of patients	0	4 (3.8%)	0
>2500 ng/dL	No patients	0	0	0

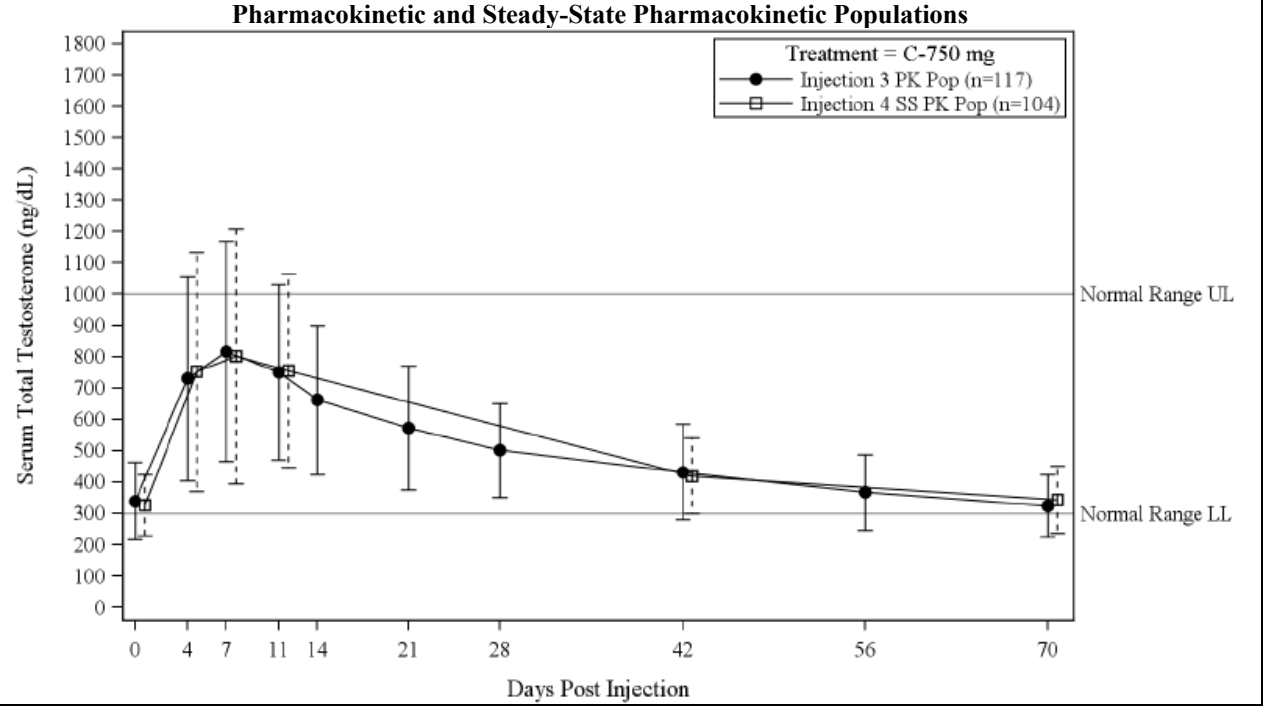
[a] All 3 criteria must have been met in order to reject the null hypothesis in favor of the alternate hypothesis. If any of the 3 criteria did not meet its Criteria for Success, the null hypothesis could not be rejected.
PK=Pharmacokinetic; SS=Steady-state; TPS=Total Patient Sample.
Note: Percentages based on non-missing data. C-750 mg refers to TU 750 mg. C2-750 mg refers to TU 750 mg.
Source: Summary of clinical Efficacy

Figure 3 Study IP157-001 Part C: Mean (SD) Serum Testosterone Concentration (ng/dL) during the 3rd Injection Interval PK Population



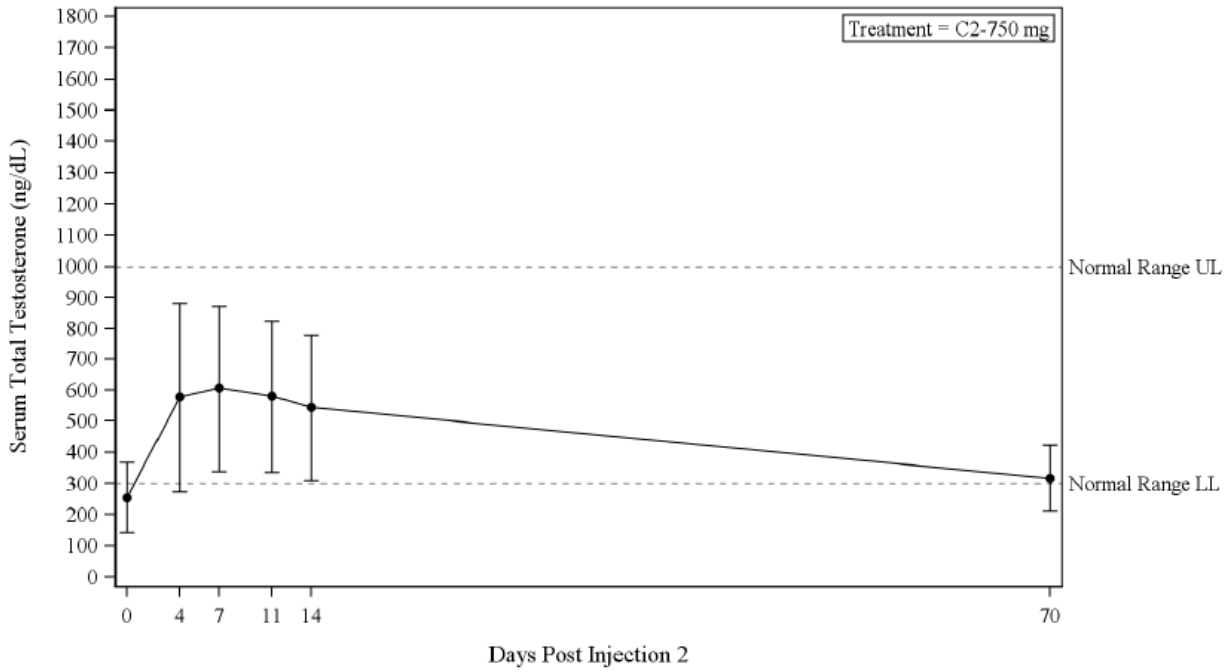
Source: Summary of Clinical Efficacy

Figure 4 Study IP157-001 Part C: Comparison of Serum Total Testosterone Concentrations (ng/dL) During the 3rd and 4th Injection Intervals, Pharmacokinetic and Steady-State Pharmacokinetic Populations



Source: Summary of Clinical Efficacy

Figure 5 Study IP157-001 Part C2: Mean (SD) Serum Testosterone Concentration (ng/dL) during the 2nd Injection Interval PK Population

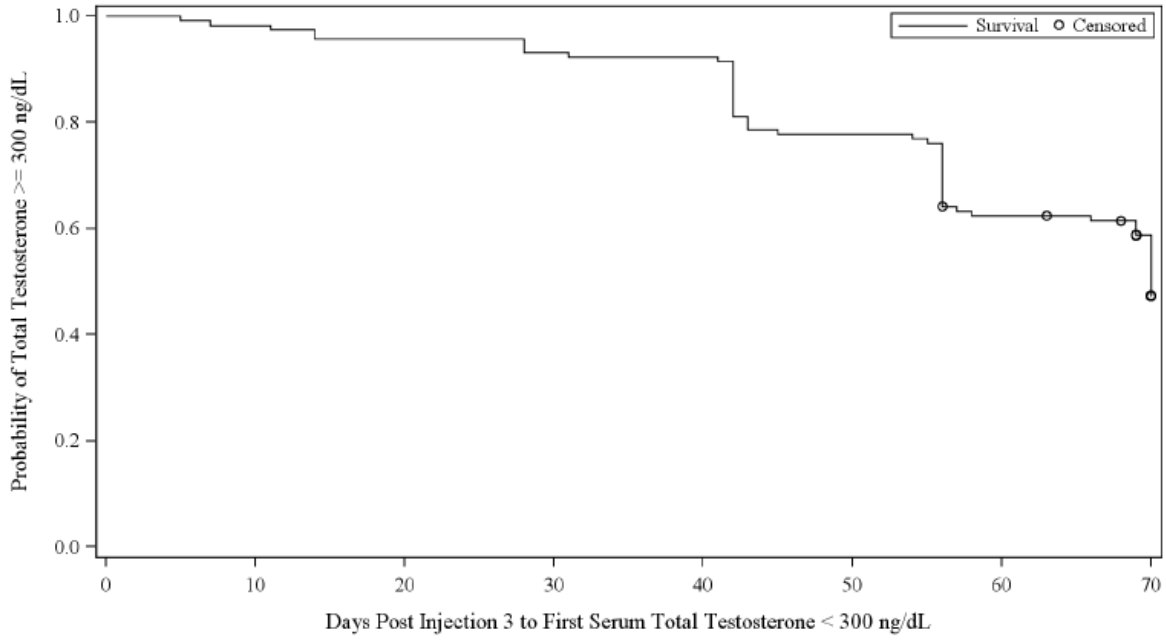


Source: Summary of Clinical Efficacy

3.3.2.2 Secondary Efficacy Results

For the PK Population, the overall median time to the first serum total testosterone concentration <300 ng/dL based on a Kaplan-Meier estimate was 70 days.

Figure 6 Study IP157-001 Part C: Kaplan-Meier Estimate of the Probability of the First Serum Total Testosterone Concentrations < 300 ng/dL During the 3rd Injection Interval, Pharmacokinetic Population



Source: Summary of Clinical Efficacy

In regard to other secondary endpoints:

Table 10 Other Secondary Efficacy Endpoints

PK	Part C	Part C2
C_{avg} **$AUC_{0\text{-}70days}$** **C_{trough}**	During the 3rd injection interval mean C_{avg} was 494.9 ng/dL and was within the normal range (i.e., 300 to 1000 ng/dL) with 110 subjects (94.0%) achieving this range; mean $AUC_{0\text{-}70days}$ = 34645.6 d•ng/dL, and mean C_{trough} = 323.5 ng/dL. During the 4th injection interval mean C_{avg} was 514.3 ng/dL and was within the normal range (i.e., 300 to 1000 ng/dL) with 100 subjects (96.2%) achieving this range; mean $AUC_{0\text{-}70days}$ = 35999.5 d•ng/dL, and mean C_{trough} = 342.8 ng/dL.	During the 2nd injection interval mean C_{avg} (prior to steady state) = 449.6 ng/dL and was within the normal range (300 to 1000 ng/dL); mean $AUC_{0\text{-}70days}$ = 31475.2 d•ng/dL, and mean C_{trough} = 317.4 ng/dL.
C_{max}	During the 3rd injection interval mean C_{max} was 890.6 ng/dL; no subjects had a C_{max} value >2500 ng/dL or between 1800 and 2500 ng/dL; 108 subjects (92.3%) had a C_{max} value ≤1500 ng/dL. During the 4th injection interval, mean C_{max} was 837.6 ng/dL; no subjects had a C_{max} value >2500 ng/dL; 4 subjects (3.8%) had a C_{max} value between 1800 and 2500 ng/dL; and 96 subjects (92.3%) had a C_{max} value ≤1500 ng/dL.	Prior to steady-state, mean C_{max} was 689.0 ng/dL following the initial dose at Week 4. The 2nd injection interval was investigated to confirm that the loading dose did not result in high C_{max} values. No subject had a C_{max} value >2500 ng/dL or between 1800 and 2500 ng/dL; and 22 subjects (95.7%) had a C_{max} value ≤1500 ng/dL during the 2nd injection interval.
C_{trough}	Mean trough concentration of serum total testosterone was within the normal range (300 to 1000 ng/dL) at Week 4 and remained within the normal range at each trough time point through Week 74 after the first injection.	Mean trough concentrations of serum total testosterone were within the normal range at Week 14 and remained within the normal range at each subsequent trough time point through Week 44 after the 1st injection.

In an analysis by subgroup, adequate TRT was provided by IM injection of TU 750 mg regardless of age, race, body mass index (BMI), and prior TRT use.

For Part C and Part C2, the post-baseline mean serum concentrations of DHT and estradiol closely paralleled those for total testosterone.

3.4 Overall Summary of Efficacy for Testosterone Undecanoate Injection

Treatment with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter was found to provide adequate TRT (300 to 1000 ng/dL) in hypogonadal men weighing >65kg (as measured by testosterone C_{avg}), while not providing excessive TRT (as measured by C_{max}). Steady-state was achieved by the 3rd IM injection of TU 750 mg.

Thus, the primary efficacy objectives of the Phase 3 study were met.

4. Safety of Testosterone Undecanoate Injection

4.1 Overview of the Safety Database for Testosterone Undecanoate injection

The safety database for testosterone undecanoate injection consists of clinical trials for testosterone replacement and TU injection as part of male contraception. Additional data was obtained from overseas postmarketing studies and postmarketing experience. An overview of the available safety information is outlined in the table below:

Table 11 Safety Data Integration of Clinical and Postmarketing Studies

Study Pool	Study Number	Total Number of Subjects in the Pool
US Study IP157-001 Parts C and C2	IP157-001 Parts C and C2	153
US Study IP157-001 All Parts	IP157-001 Parts A, B, C, C2 and D	524
European Clinical Studies	JPH01495, JPH04995, ME98096, ME97029, 306605, 303934	201
Male Contraception Clinical Studies	97028, 97173, 98016, 99015, 42306	407
International Postmarketing Studies	39732 (NEO601 IPASS), AWB0105, Czech NEO, NB02, TG09, and 14853	2424
Number of Subjects Included in Adverse Events of Interest Investigations		
Adverse Events of Interest (Pulmonary Oil Microembolism [POME], Anaphylaxis, and Injection Site Reactions)	IP157-001 (All Parts), JPH01495, JPH04995, ME98096, ME97029, 306605, 303934, 97028, 97173, 98016, 99015, 42306, 39732 (NEO601 IPASS) AWB0105, Czech NEO, NB02, TG09, and 14853	3556

Source: Integrated Safety summary

4.2 Commonly Reported Adverse Events in Clinical Trials of Testosterone Undecanoate Injection

U.S. Study IP157-001 Parts C and C2:

In IP157-001 Parts C and C2, most TEAEs were attributable to the system organ class (SOC) of Infections and Infestations (47 subjects [30.7%]). The most commonly reported TEAEs (occurring in ≥5% of subjects) were sinusitis (11 subjects [7.2%]), PSA increased (10 subjects [6.5%]), prostatitis (10 subjects [6.5%]), arthralgia (9 subjects [5.9%]), insomnia (9 subjects [5.9%]), and acne (8 subjects [5.2%]).

Table 12 Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 3% of the Population, Subjects Treated with TU in Study IP157-001 Part C and Part C2

MedDRA SOC (Body System)/ Preferred Term	Number (%) of Subjects TU-750 mg (N=153)
At Least One Treatment-Emergent Adverse Event	104 (68.0%)
Infections and Infestations	**47 (30.7%)**
Sinusitis	11 (7.2%)
Nasopharyngitis	7 (4.6%)
Bronchitis	6 (3.9%)
Upper Respiratory Tract Infection	6 (3.9%)

General Disorders and Administration Site Conditions	**31 (20.3%)**
Fatigue	7 (4.6%)
Injection Site Pain	7 (4.6%)
Musculoskeletal and Connective Tissue Disorders	**30 (19.6%)**
Arthralgia	9 (5.9%)
Back Pain	6 (3.9%)
Pain In Extremity	5 (3.3%)
Investigations	**24 (15.7%)**
Prostatic Specific Antigen Increased	10 (6.5%)
Reproductive System and Breast Disorders	**20 (13.1%)**
Prostatitis	10 (6.5%)
Psychiatric Disorders	**19 (12.4%)**
Insomnia	9 (5.9%)
Anxiety	5 (3.3%)
Injury, Poisoning and Procedural Complications	**18 (11.8%)**
Muscle Strain	5 (3.3%)
Skin and Subcutaneous Tissue Disorders	**15 (9.8%)**
Acne	8 (5.2%)
Vascular Disorders	**11 (7.2%)**
Hypertension	5 (3.3%)

Note: Subjects are counted once within each SOC (Body System) and Preferred Term. Treatment-emergent adverse events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0. Source: Summary of Clinical Safety

U.S. Study IP157-001 All Parts:

In IP157-001, all parts combined, most TEAEs in both treatment groups were attributable to the SOC of Infections and Infestations (TU 750 mg, 84 subjects [30.9%]; TU 1000 mg, 83 subjects [32.9%]); the other most commonly reported TEAEs included: prostatic specific antigen increased (TU 750 mg, 20 subjects [7.4%]; TU 1000 mg, 10 subjects [4.0%])

Table 13 Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 3% of the Population, Subjects Treated with TU in IP157-001 All Parts Combined, By Dose

MedDRA SOC (Body System)/ Preferred Term	Number (%) of Subjects		
	TU-750 mg (N=272)	TU-1000 mg (N=252)	Overall (N=524)
At Least One Treatment-Emergent Adverse Event	198 (72.8%)	195 (77.4%)	393 (75.0%)
Infections and Infestations	**84 (30.9%)**	**83 (32.9%)**	**167 (31.9%)**
Sinusitis	19 (7.0%)	13 (5.2%)	32 (6.1%)
Upper Respiratory Tract Infection	15 (5.5%)	15 (6.0%)	30 (5.7%)
Nasopharyngitis	14 (5.1%)	14 (5.6%)	28 (5.3%)
Bronchitis	12 (4.4%)	8 (3.2%)	20 (3.8%)
Urinary Tract Infection	6 (2.2%)	10 (4.0%)	16 (3.1%)
Musculoskeletal and Connective Tissue Disorders	**53 (19.5%)**	**69 (27.4%)**	**122 (23.3%)**
Arthralgia	12 (4.4%)	11 (4.4%)	23 (4.4%)
Back Pain	13 (4.8%)	10 (4.0%)	23 (4.4%)
Musculoskeletal Pain	6 (2.2%)	12 (4.8%)	18 (3.4%)
Pain In Extremity	9 (3.3%)	9 (3.6%)	18 (3.4%)

Osteoarthritis	2 (0.7%)	8 (3.2%)	10 (1.9%)
Investigations	**51 (18.8%)**	**56 (22.2%)**	**107 (20.4%)**
Prostatic Specific Antigen Increased	20 (7.4%)	10 (4.0%)	30 (5.7%)
General Disorders and Administ. Site Conditions	**50 (18.4%)**	**39 (15.5%)**	**89 (17.0%)**
Fatigue	17 (6.3%)	8 (3.2%)	25 (4.8%)
Injection Site Pain	10 (3.7%)	15 (6.0%)	25 (4.8%)
Reproductive System and Breast Disorders	**43 (15.8%)**	**42 (16.7%)**	**85 (16.2%)**
Prostatitis	15 (5.5%)	14 (5.6%)	29 (5.5%)
Erectile Dysfunction	4 (1.5%)	10 (4.0%)	14 (2.7%)
Gastrointestinal Disorders	**32 (11.8%)**	**46 (18.3%)**	**78 (14.9%)**
Diarrhoea	4 (1.5%)	11 (4.4%)	15 (2.9%)
Nausea	4 (1.5%)	8 (3.2%)	12 (2.3%)
Psychiatric Disorders	**34 (12.5%)**	**35 (13.9%)**	**69 (13.2%)**
Insomnia	12 (4.4%)	12 (4.8%)	24 (4.6%)
Depression	8 (2.9%)	8 (3.2%)	16 (3.1%)
Anxiety	6 (2.2%)	8 (3.2%)	14 (2.7%)
Nervous System Disorders	**28 (10.3%)**	**34 (13.5%)**	**62 (11.8%)**
Headache	6 (2.2%)	8 (3.2%)	14 (2.7%)
Renal and Urinary Disorders	**24 (8.8%)**	**36 (14.3%)**	**60 (11.5%)**
Dysuria	3 (1.1%)	8 (3.2%)	11 (2.1%)
Nephrolithiasis	3 (1.1%)	8 (3.2%)	11 (2.1%)
Skin and Subcutaneous Tissue Disorders	**29 (10.7%)**	**30 (11.9%)**	**59 (11.3%)**
Acne	9 (3.3%)	4 (1.6%)	13 (2.5%)
Respiratory, Thoracic and Mediastinal Disorders	**29 (10.7%)**	**21 (8.3%)**	**50 (9.5%)**
Sleep Apnea Syndrome	10 (3.7%)	4 (1.6%)	14 (2.7%)
Vascular Disorders	**23 (8.5%)**	**18 (7.1%)**	**41 (7.8%)**
Hypertension	16 (5.9%)	10 (4.0%)	26 (5.0%)

Note: Subjects are counted once within each SOC (Body System) and Preferred Term. Treatment-emergent adverse events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0. The events are listed in descending order based on the Overall column SOC. Source: Summary of Clinical Safety.

U.S. Study IP157-001 and European Clinical Studies:

In Study IP157-001 and 5 European clinical studies combined, all TEAEs (by preferred term) which occurred in <3% of hypogonadal subjects treated with TU in all pools of studies are shown in Table 14.

Table 14 Overall Incidence of Treatment-Emergent Adverse Events That Occurred in ≥ 3% of the Population in Any Pool of Study, Subjects Treated with TU in US and European Clinical Studies

MedDRA Preferred Term	Number(%) of Subjects (Overall)			
	IP157-001 Parts C and C2 (N=153)	IP157-001 (All Parts) (N=524)	EU Clinical Studies (N=201)	IP157-001 (All Parts) and EU Clinical Studies (N=725)
At Least One TEAE	104 (68.0%)	393 (75.0%)	145 (72.1%)	538 (74.2%)
At Least One Severe TEAE	22 (14.4%)	80 (15.3%)	27 (13.4%)	107 (14.8%)
Sinusitis	11 (7.2%)	32 (6.1%)	2 (1.0%)	34 (4.7%)

Prostatic Specific Antigen Increased	10 (6.5%)	30 (5.7%)	5 (2.5%)	35 (4.8%)
Prostatitis	10 (6.5%)	29 (5.5%)	5 (2.5%)	34 (4.7%)
Arthralgia	9 (5.9%)	23 (4.4%)	8 (4.0%)	31 (4.3%)
Insomnia	9 (5.9%)	24 (4.6%)	1 (0.5%)	25 (3.4%)
Acne	8 (5.2%)	13 (2.5%)	11 (5.5%)	24 (3.3%)
Nasopharyngitis	7 (4.6%)	28 (5.3%)	34 (16.9%)	62 (8.6%)
Fatigue	7 (4.6%)	25 (4.8%)	0	25 (3.4%)
Injection Site Pain	7 (4.6%)	25 (4.8%)	8 (4.0%)	33 (4.6%)
Upper Respiratory Tract Infection	6 (3.9%)	30 (5.7%)	5 (2.5%)	35 (4.8%)
Bronchitis	6 (3.9%)	20 (3.8%)	7 (3.5%)	27 (3.7%)
Back Pain	6 (3.9%)	23 (4.4%)	9 (4.5%)	32 (4.4%)
Pain In Extremity	5 (3.3%)	18 (3.4%)	2 (1.0%)	20 (2.8%)
Anxiety	5 (3.3%)	14 (2.7%)	1 (0.5%)	15 (2.1%)
Muscle Strain	5 (3.3%)	11 (2.1%)	1 (0.5%)	12 (1.7%)
Hypertension	5 (3.3%)	26 (5.0%)	10 (5.0%)	36 (5.0%)
Diarrhoea	3 (2.0%)	15 (2.9%)	8 (4.0%)	23 (3.2%)
Musculoskeletal Pain	3 (2.0%)	18 (3.4%)	2 (1.0%)	20 (2.8%)
Urinary Tract Infection	3 (2.0%)	16 (3.1%)	4 (2.0%)	20 (2.8%)
Depression	3 (2.0%)	16 (3.1%)	3 (1.5%)	19 (2.6%)
Headache	2 (1.3%)	14 (2.7%)	16 (8.0%)	30 (4.1%)
Blood Triglycerides Increased	2 (1.3%)	8 (1.5%)	7 (3.5%)	15 (2.1%)
Respiratory Tract Infection Viral	1 (0.7%)	5 (1.0%)	12 (6.0%)	12 (1.7%)

Note: TEAEs are listed in descending order for Study157-001 Parts C and C2. Subjects in IP157-001 Parts C and C2 were treated with TU 750 mg (N=153); Subjects in IP157-001 (All Parts) were treated with TU 750 mg (N=272) or TU 1000 mg (N=252); Subjects in EU Clinical Studies (JPH01495, JPH04995, ME98096, ME97029, 306605, 303934) were treated with TU 1000 mg (N=201); and Subjects in IP157-001 (All Parts) and EU Clinical Studies (JPH01495, JPH04995, ME98096, ME97029, 306605, 303934) were treated with TU 750 mg (N=272) or TU 1000 mg (N=453). Subjects are counted once within each Preferred Term. TEAEs occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0.
Source: Summary of Clinical Safety.

International Postmarketing Studies

All reported adverse events in the 6 International Postmarketing studies (n=2424) are presented in Table 25 below.

Table 15 Incidence of All Treatment-Emergent Adverse Events, Subjects Treated with TU in International Postmarketing Studies (39732 [NEO601 IPASS], AWB0105, Czech NEO, NB02, TG09, and 14853)

MedDRA Preferred Term	Number (%) of Subjects with TU 1000 mg (N=2424)	MedDRA Preferred Term	Number (%) of Subjects with TU 1000 mg (N=2424)
At Least 1 TEAE	197 (8.1%)	Dizziness	2 (0.1%)
At Least 1 Severe TEAE	27 (1.1%)	**Sciatica**	2 (0.1%)
PSA Increased	14 (0.6%)	Nipple Swelling	2 (0.1%)
Haematocrit Increased	13 (0.5%)	**Musculoskeletal Pain**	2 (0.1%)
Injection Site Pain	11 (0.5%)	**Aggression**	2 (0.1%)

Headache	7 (0.3%)	**Anxiety**	2 (0.1%)
Acne	6 (0.2%)	Confusional State	2 (0.1%)
Hyperhidrosis	5 (0.2%)	**Depression**	2 (0.1%)
Pruritus	4 (0.2%)	**Hot Flush**	2 (0.1%)
Influenza	4 (0.2%)	Anaemia	2 (0.1%)
BPH	4 (0.2%)	**Atrial Fibrillation**	2 (0.1%)
Myalgia	4 (0.2%)	**Myocardial Infarction**	2 (0.1%)
Hypertension	4 (0.2%)	**Hypertriglyceridaemia**	2 (0.1%)
Cough	4 (0.2%)	Blood Cholesterol Increased	1 (<0.1%)
Haemoglobin Increased	3 (0.1%)	Blood Creatinine Increased	1 (<0.1%)
Weight Increased	3 (0.1%)	**Blood Glucose Increased**	1 (<0.1%)
Chest Pain	3 (0.1%)	Blood Test Abnormal	1 (<0.1%)
Fatigue	3 (0.1%)	Blood Testosterone Increased	1 (<0.1%)
Injection Site Discomfort	3 (0.1%)	**Blood Triglycerides Increased**	1 (<0.1%)
Rash	3 (0.1%)	Haematocrit Abnormal	1 (<0.1%)
Upper Respir. Tract Infection	3 (0.1%)	Haemoglobin Abnormal	1 (<0.1%)
Diarrhoea	3 (0.1%)	**Oestradiol Increased**	1 (<0.1%)
Nausea	3 (0.1%)	Sperm Concentration Decreased	1 (<0.1%)
Gynaecomastia	3 (0.1%)	Weight Decreased	1 (<0.1%)
Pain In Extremity	3 (0.1%)	WBC Count Abnormal	1 (<0.1%)
Oropharyngeal Pain	3 (0.1%)	Hernia	1 (<0.1%)
Polycythaemia	3 (0.1%)	Immedi. Postinjection Reaction	1 (<0.1%)
Hypercholesterolaemia	3 (0.1%)	**Influenza Like Illness**	1 (<0.1%)
Blood Testosterone Decreased	2 (0.1%)	Injection Site Extravasation	1 (<0.1%)
Hematology Test Abnormal	2 (0.1%)	Injection Site Pruritus	1 (<0.1%)
Laboratory Test Abnormal	2 (0.1%)	**Injection Site Rash**	1 (<0.1%)
Injection Site Reaction	2 (0.1%)	Multi-Organ Failure	1 (<0.1%)
Irritability	2 (0.1%)	Oedema	1 (<0.1%)
Malaise	2 (0.1%)	Sluggishness	1 (<0.1%)
Oedema Peripheral	2 (0.1%)	**Unevaluable Event**[a]	1 (<0.1%)
Pain	2 (0.1%)	Dermatitis	1 (<0.1%)
Pyrexia	2 (0.1%)	Dermatitis Acneiform	1 (<0.1%)
Alopecia	2 (0.1%)	Dermatosis	1 (<0.1%)
Bronchitis	2 (0.1%)	Prurigo	1 (<0.1%)
Pharyngitis	2 (0.1%)	Seborrhoea	1 (<0.1%)
Sinusitis	2 (0.1%)	Eye Infection	1 (<0.1%)
GERD	2 (0.1%)	Hepatitis C	1 (<0.1%)
Infected Bites	1 (<0.1%)	**Insomnia**	1 (<0.1%)
Injection Site Abscess	1 (<0.1%)	Sleep Disorder	1 (<0.1%)
Lower Resp Tract Infection	1 (<0.1%)	Flushing	1 (<0.1%)
Onychomycosis	1 (<0.1%)	**Hypotension**	1 (<0.1%)
Osteomyelitis	1 (<0.1%)	Lymphoedema	1 (<0.1%)
Pharyngotonsillitis	1 (<0.1%)	Peripheral Vascular Disorder	1 (<0.1%)
Staphylococcal Sepsis	1 (<0.1%)	Phlebitis	1 (<0.1%)
Syphilis	1 (<0.1%)	Raynaud's Phenomenon	1 (<0.1%)
Tooth Abscess	1 (<0.1%)	Dyspnoea	1 (<0.1%)

Abdominal Distension	1 (<0.1%)	Productive Cough	1 (<0.1%)
Abdominal Pain	1 (<0.1%)	**Sleep Apnoea Syndrome**	1 (<0.1%)
Dyspepsia	1 (<0.1%)	Haemoconcentration	1 (<0.1%)
Dysphagia	1 (<0.1%)	Lymphadenopathy	1 (<0.1%)
Gastritis	1 (<0.1%)	**Bradycardia**	1 (<0.1%)
Hyperchlorhydria	1 (<0.1%)	**Cardiovascular Disorder**	1 (<0.1%)
Oesophagitis	1 (<0.1%)	Palpitations	1 (<0.1%)
Peritoneal Adhesions	1 (<0.1%)	Cataract Operation	1 (<0.1%)
Rectal Haemorrhage	1 (<0.1%)	Haemorrhoid Operation	1 (<0.1%)
Reflux Oesophagitis	1 (<0.1%)	Pituitary Tumour Removal	1 (<0.1%)
Tooth Disorder	1 (<0.1%)	Polypectomy	1 (<0.1%)
Carpal Tunnel Syndrome	1 (<0.1%)	Tooth Extraction	1 (<0.1%)
Cerebrovascular Accident	1 (<0.1%)	Transurethral Prostatectomy	1 (<0.1%)
Dementia	1 (<0.1%)	Varicocele Repair	1 (<0.1%)
Paraesthesia	1 (<0.1%)	**Hyperuricaemia**	1 (<0.1%)
Paralysis	1 (<0.1%)	**Contusion**	1 (<0.1%)
Radiculopathy	1 (<0.1%)	**Muscle Strain**	1 (<0.1%)
Somnolence	1 (<0.1%)	Tibia Fracture	1 (<0.1%)
Syncope	1 (<0.1%)	Wrist Fracture	1 (<0.1%)
Breast Tenderness	1 (<0.1%)	Lymphoma Cutis	1 (<0.1%)
Erectile Dysfunction	1 (<0.1%)	**Prostate Cancer**	1 (<0.1%)
Nipple Pain	1 (<0.1%)	Prostatic Adenoma	1 (<0.1%)
Prostatic Disorder	1 (<0.1%)	Skin Papilloma	1 (<0.1%)
Prostatitis	1 (<0.1%)	Adrenal Insufficiency	1 (<0.1%)
Prostatomegaly	1 (<0.1%)	Growth Hormone Deficiency	1 (<0.1%)
Spontaneous Penile Erection	1 (<0.1%)	Hypothyroidism	1 (<0.1%)
Arthralgia	1 (<0.1%)	**Nephrolithiasis**	1 (<0.1%)
Back Pain	1 (<0.1%)	**Nocturia**	1 (<0.1%)
Musculoskeletal Discomfort	1 (<0.1%)	**Urinary Retention**	1 (<0.1%)
Neck Pain	1 (<0.1%)	Tinnitus	1 (<0.1%)
Polymyalgia Rheumatica	1 (<0.1%)	Blepharitis	1 (<0.1%)
Completed Suicide	1 (<0.1%)	Drug Hypersensitivity	1 (<0.1%)
Depressed Mood	1 (<0.1%)		1 (<0.1%)

Note: Subjects are counted once within each Preferred Term. Treatment-Emergent Adverse Events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0.
TEAEs in bold typeface also occurred in hypogonadal subjects treated with TU in the U.S. and European Clinical Studies. Source: Summary of Clinical Safety

4.3 Immediate Post-injection Reactions - Regulatory History / Important Clinical Issues

The **original NDA** contained safety data from a total of 709 male subjects who received testosterone undecanoate injection in 7 controlled clinical studies (including the U.S. Study IP157-001 Parts A, B, C and D; and six European Phase 1-3 studies).

The original NDA also contained 6 periodic safety update reports (PSURs) from Bayer/Schering, the current marketer of testosterone undecanoate injection, that included all spontaneously reported adverse events from approximately 3.5 years of worldwide postmarketing use of testosterone undecanoate injection (specifically November 25, 2003 through June 30, 2007).

The 120-Day Safety Update to the original NDA contained another Bayer/ Schering PSUR (for the time period June 30, 2007 to October 12, 2007), which brought the total duration of postmarketing experience up to 4 years.

An additional Sponsor report was submitted approximately 6 months after NDA submission. The report was included in the NDA materials for FDA review and was entitled "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*".

After reviewing the original NDA, the Division concluded that the clinical trial safety data was consistent with an injectable androgen, <u>except</u> for the occurrence of immediate post-injection reactions in 2 patients. These 2 events were described by the Sponsor as sudden urge to cough, cough, and dyspnea immediately following injection. These two cases, included in original NDA, were:

> **Patient #184 in Study 306605**. A 54-year-old male received his 10th injection of testosterone undecanoate on 3-April-2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug.
>
> **Patient #050-7006 in Study IP157-001 Part C**: A 53-year-old white male received his 3rd injection on 12-July-2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

After reviewing the PSURs and the Summary Report in the original NDA, the Division identified additional clinical trial and postmarketing cases, leading to serious concerns related to the occurrence of immediate post-injection reactions.

Although there were only 2 patients in the original clinical trials with a clear post-injection reactions, the Division's review of the clinical studies submitted with the CR yielded another 6 possible cases, as well as sixty-six (66) postmarketing cases derived from the submitted PSURs and Summary Report. The additional clinical trials cases, identified in the International Postmarketing studies, were listed as post-injection "syncope", "convulsions" and "circulatory collapse" (and three other events) without further detail.

A brief regulatory history associated with the review of these post-injection reactions is provided in Table 16.

Table 16 Regulatory History Related to Immediate Post-Injection Reactions

	Sponsor	FDA
Original submission in 2007-2008	2 patients in clinical trials with reported adverse events of sudden urge to cough, cough, and dyspnea (POME) immediately following injection. PSURs and Summary Reports of "cough fit" included 66 European postmarketing cases	6 additional clinical trials cases of "immediate post-injection reactions" possible (e.g., post-injection convulsions, syncope, cardiovascular collapse, etc). Of the 66 postmarketing cases (April 2004 to Jan 2007), 28 serious cases (42%), 12 hospitalized (18%). After Pulmonary/Allergy (DPARP) consultation, 2 cases deemed to reflect anaphylaxis and 2 other cases, possible anaphylaxis.
Resubmission in 2009	1 serious POME in 2,834 subjects (0.035%) and no systemic allergic reaction events reported. Total number of injections = 16,191 injections in 12 completed and 5 ongoing trials. *Sponsor's analysis:* POME: 5/3905 subjects (0.1425%); Serious POME: 1/3905 subjects (0.0285%); Anaphylaxis: 0	3 additional possible cases from clinical trials: (postinjection "convulsions", "syncope" and "circulatory collapse", respectively). 3 other cases not included. *FDA analysis* 4/2834, 0.14%. Additional PSUR (25-Nov-2007 to 24-Nov-2008) and final Safety Update yielded 52 more postmarketing cases (total >100 cases). Of the new 52 cases, almost all severe and about 20 consistent with anaphylactic reactions.
After 2009 resubmission to 2010	In the postmarketing period 106 total post-injection reactions: POME: 68 cases; Anaphylaxis: 38 cases.	FDA review also yields a final total of 106 post-injection reactions in the postmarketing period - case list conveyed to Sponsor.
2011	Sponsor informed FDA of a total of **400** post-injection reaction reports (160 POME and 240 anaphylaxis). The Sponsor agreed that all 160 POME cases should be included in the analysis, but only 23 of the 240 anaphylactic reactions should be included.	FDA requested the Sponsor provide individual CIOMS reports for all potential cases of POME and anaphylaxis after searching the entire postmarketing safety database irrespective of medical review or adjudication by the Sponsor.

In the clinical review of the 66 postmarketing cases obtained from the original NDA, the manifestations of the events that were evident included: cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, various allergic-type signs and symptoms (rash, pruritis, itching), tachycardia, palpitations, blood pressure changes, and general constitutional symptoms, including headache, malaise, shivering, sweating, weakness and nausea.

The spectrum of signs and symptoms of these serious post-injection reactions frequently overlap between anaphylaxis and POME, making a precise diagnosis difficult in some cases.

Although the Sponsor acknowledges a number of postmarketing cases as anaphylactic reactions, the Sponsor continues to believe that most of the post-injection reactions are POME. Our consultants from the Division of Pulmonary and Allergy Products (DPAP) have conducted an extensive review and despite the inherent limitations of retrospective case review, have categorized the severe post-injection reactions cases as either anaphylactic reaction or POME. The criteria used to defined severe post-injection reactions are delineated in Section 4.4.2 below.

The mechanisms for allergic reactions to Aveed have not been fully elucidated. Two of the excipients in this product, benzyl benzoate and castor oil, appear to have played a role in post-injection adverse reactions: benzyl benzoate as an allergen and castor oil as an oily carrier. In one case, there was skin test documentation of an allergy to the product, and in another case, documentation of a positive skin test to benzyl benzoate. The role played by testosterone undecanoate itself is unknown but some role remains possible. In addition, an injectable estrogen receptor antagonist approved for the treatment of advanced breast cancer, and an approved injectable estrogen replacement product, both of which contain the same excipients as Aveed were associated with post-injection reactions virtually identical to those associated with Aveed (FDA Adverse Events Reporting System; accessed September 25, 2009), and these events are reported in both these products labeling as "anaphylactic or anaphylactoid reactions".

Regardless of the specific mechanism for these post-injection events, and despite difficulty in categorizing them, many of these reactions were reported as severe, and some life-threatening. Severe POME and anaphylactic reactions following intramuscular TU injection cannot easily be differentiated by a health care provider. In most cases, attending health care personnel have reported and treated the incident as an anaphylactic reaction.

Finally, on September 21, 2009, FDA received a report of a full-blown post-injection anaphylactic reaction in a 16 year old male[1]. The Sponsor finds this to be "*the first instance of true anaphylaxis*". We requested another consult from the Division of Pulmonary and Allergy Products (DPAP) and in their draft consult dated November 16, 2009 (and final consult of November 25, 2009), DPAP concluded that 20 cases of these new 52 cases were either anaphylaxis (n=11) or possible anaphylaxis (n=9). Another 4 cases were described as "allergic reactions". DPAP also stated that POME generally lacks cutaneous and mucosal symptoms, such

[1] Ong GS, Somerville CP, Jones TW, Walsh JP.: Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. Case Reports in Medicine 2012; Vol. 2012: Article ID 384054.

as generalized flushing and swollen throat, as reflected in many of the post-injection reaction cases. In light of the findings in the Complete Response and the DPAP consult, the Clinical review team re-assessed the original 66 postmarketing post-injection reactions, and the clinical team finds these cases even more concerning, especially in regard to throat-related symptoms and the potential that they are serious allergic reactions.

4.4 Immediate Post-injection Reactions –Reporting Rates and Case Narratives

4.4.1 Immediate Post-injection Reactions - Reporting Rates (POME and Anaphylaxis)

The postmarketing reporting rates of POME and anaphylaxis cases were analyzed by the Sponsor in the recent re-submission. The Sponsor's first analysis was conducted by internal Endo Pharmaceuticals reviewers and was submitted in the CR on November 29, 2012. The Sponsor's second analysis was conducted by independent adjudicators who were consulted by Sponsor, and this second analysis was submitted on March 5, 2013. Results of the two analyses and comparison of the results are shown in the next two tables.

Table 17 Comparison of Postmarketing Reporting Rates of POME Identified by Sponsor's "Independent Adjudicators" versus Postmarketing Reporting Rates Identified by the Sponsor's Internal Reviewers (shown in parentheses)

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential POME Cases	143 (137)	75 (75)	120 (117)	89 (89)	116 (115)	543 (533)
Number of POME Cases Identified as Yes or Indeterminate	49 (49)	26 (27)	48 (49)	43 (45)	57 (58)	223 (228)
Number of Ampoules Sold	614,586	466,419	587,474	671,668	767,505	3,107,652
Number of Treatment Years	142927.0	108469.5	136621.9	156201.9	178489.5	722709.8
Rate of Cases of POME Identified as Yes or Indeterminate Per 10,000 Ampoules Sold	0.797 (0.797)	0.557 (0.579)	0.817 (0.834)	0.640 (0.670)	0.743 (0.756)	0.718 (0.734)
Rate of Cases of POME Identified as Yes or Indeterminate Per 10,000 Treatment Years	3.428 (3.428)	2.397 (2.489)	3.513 (3.587)	2.753 (2.881)	3.193 (3.249)	3.086 (3.155)

Source: Integrated Summary of Safety (ISS) page 248, Table 88, Submission #10 (November 29, 2012)
Addendum to ISS, page 19, Table 8, Submission #019 (March 05, 2013)

Table 18 Comparison of Postmarketing Reporting Rates of Anaphylactic Reactions Identified by Sponsor's "Independent Adjudicators" versus Postmarketing Reporting Rates Identified by the Sponsor's Internal Reviewers (shown in parentheses)

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential Anaphylactic Reaction Cases	78 (78)	39 (39)	76 (76)	59 (59)	78 (78)	330 (330)
Number of Anaphylactic Reaction Cases Identified as Yes or Indeterminate[a]	9 (24)	7 (9)	7 (11)	10 (16)	12 (19)	45 (79)
Number of Ampoules Sold	614,586	466,419	587,474	671,668	767,505	3,107,652
Number of Treatment Years	142927.0	108469.5	136621.9	156201.9	178489.5	722709.8
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate Per 10,000 Ampoules Sold	0.146 (0.391)	0.150 (0.193)	0.119 (0.187)	0.149 (0.238)	0.156 (0.248)	0.145 (0.254)
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate Per 10,000 Treatment Years	0.630 (1.679)	0.645 (0.830)	0.512 (0.805)	0.640 (1.024)	0.672 (1.064)	0.623 (1.093)

[a] The independent adjudicators used Sampson criteria 1; the Sponsor's internal reviewers used a combination of Sampson criteria, Rueggeburg criteria and special terms.

Source: Integrated Summary of Safety (ISS) page 259, Table 92, Submission #10 (November 29, 2012)
Addendum to ISS, page 22, Table 11, Submission #019 (March 05, 2013)

The "independent adjudicators" identified 223 cases of POME compared to 228 cases identified by the internal reviewers. Thus, the most recent adjudication had little impact (–2%) on POME cases.

However, for anaphylactic reactions, the new adjudication had more of an impact. The "independent adjudicators" identified 45 cases of anaphylactic reaction compared to 79 cases identified by the internal reviewers. The reason for the difference is that the "independent adjudicators" qualified a case of anaphylactic reaction only if it met Sampson's criteria number 1, while the Sponsor's internal review in their most recent CR used a combination of Sampson's criteria, Rueggeburg's criteria and other special terms.

Thus, the analysis of postmarketing reporting rate based upon the "independent" adjudication reduced the rates of anaphylactic reaction per 10,000 ampoules sold and per 10,000 treatment years by 43%.

Overall, however, the total number of severe post-injection reactions, both POME and anaphylactic reaction, was not markedly different between sets of adjudicators.

4.4.2 Immediate Post-injection Reactions – Case Narratives

FDA reviewed all potential postmarketing cases of POME and anaphylaxis that were included in the current resubmission. FDA elected to focus on the severe cases from the series. With this objective in mind, FDA pre-determined the following criteria to define a "case" of severe post-injection reaction to testosterone undecanoate:

Criteria for Defining Severe Post-Injection Reactions to Testosterone Undecanoate:

We categorized any case as a severe post-injection reaction if it occurred within 24 hours of injection and if any of the following criteria were met:

- Any case identified by either FDA or Sponsor as an anaphylactic reaction as a consequence of the reporter using the term "anaphylaxis" or "anaphylactic reaction"
- Any case identified by either FDA or the Sponsor as an anaphylactic reaction by meeting the formal Sampson's criteria
- Any case identified as a serious adverse event (SAE), based upon the FDA standard definition of an SAE
- Any case requiring treatment
- Any case labeled as "Serious" or "Medically Important" by the reporter or by the Sponsor (any case that had a check in box 8-12 of the CIOMS form)
- Any case that FDA believed to be medically significant
- Any case involving syncope or sudden lowering of the blood pressure

In this section of the review, all FDA-adjudicated severe cases are presented (Table 15) and provide narratives for each severe postmarketing post-injection reaction in the testosterone undecanoate series, whether a case of POME, of anaphylaxis, or of either POME or anaphylaxis if a differentiation was not possible. Due to difficulty in distinguishing severe POME from anaphylaxis, the list includes some overlapping cases where POME or anaphylaxis could not be differentiated. The list shows a total of **137 cases**.

Table 19: List of 137 Cases of Severe Postmarketing Post-injection Reactions to Testosterone Undecanoate Injection

	Case #		Case #		Case #
1	200711268BNE	48	201034191GPV	95	2011108338
2	200711270BNE	49	201034195GPV	96	2011110321
3	200711462BNE	50	201034605GPV	97	2011110671
4	200718455GPV	51	201035276GPV	98	2011124098
5	200811461BNE	52	201036559GPV	99	2012004307
6	200812881BNE	53	201037659GPV	100	2012004532
7	200812947GPV	54	201038945GPV	101	2012005684
8	200815181GPV	55	201040373GPV	102	2012005853
9	200815625LA	56	201040508GPV	103	2012007253
10	200818230LA	57	201041966GPV	104	2012014074
11	200818257LA	58	201042008GPV	105	2012014975
12	200819842GPV	59	201045017GPV	106	2012015311
13	200820307GPV	60	201046647GPV	107	2012019653
14	200821519GPV	61	201047159GPV	108	2012020873
15	200821776GPV	62	201047285GPV	109	2012025807
16	200826527GPV	63	2011002167	110	2012025864
17	200826556GPV	64	2011007367	111	2012032972
18	200828604GPV	65	2011009542	112	AT-2007-035468
19	200832838GPV	66	2011011368	113	AU-2007-014016
20	200910048BNE	67	2011014093	114	BR-2007-005496
21	200910221BNE	68	2011014662	115	CH-2007-042227
22	200912079BNE	69	2011016767	116	DE-2004-037302
23	200912293BNE	70	2011018006	117	DE-2005-004016
24	200912294BNE	71	2011022738	118	DE-2005-005199
25	200916799LA	72	2011024048	119	**DE-2005-008140**
26	200919013LA	73	2011025652	120	DE-2005-008181
27	200919765LA	74	2011025755	121	DE-2005-009283
28	200924735GPV	75	2011039522	122	DE-2005-015256
29	200929719GPV	76	2011040546	123	DE-2006-002815
30	200930704GPV	77	2011044214	124	DE-2006-003298
31	200932012GPV	78	2011046164	125	DE-2006-008415
32	200933178GPV	79	2011046482	126	DE-2007-004747
33	200940006GPV	80	2011048218	127	DE-2007-023890
34	200940275GPV	81	2011050730	128	DE-2007-030464
35	200940933GPV	82	2011052409	129	GB-2007-006197
36	201010793GPV	83	2011052410	130	GB-2007-000740
37	201014170GPV	84	2011056865	131	GB-2007-023826
38	201018709GPV	85	2011063184	132	NO-2007-008557
39	201019083GPV	86	2011065559	133	SE-2006-004192
40	201020041GPV	87	2011071329	134	SE-2006-017516
41	201020446LA	88	2011074882	135	SE-2006-022330
42	201021482GPV	89	2011083027	136	SE-2007-002541
43	201025167GPV	90	2011087892	137	ZA-2007-035469
44	201028214GPV	91	2011095240		
45	201029358GPV	92	2011090820		
46	201033158GPV	93	2011102083		
47	201034100GPV	94	2011105544		

*Note: Single case in **bold** typeface denotes the only case picked up by the Sponsor's adjudicators, but not by the Sponsor and FDA during previous evaluations.*

Narratives for Cases of Severe Postmarketing Post-injection Reactions to Testosterone Undecanoate Injection*

*Note: Unless stated, the indication for use of testosterone undecanoate was not reported.

Case 200711268BNE: A UK male patient of unknown age was given Nebido injection by his wife, a practicing nurse. He began coughing immediately afterward and was unable to get his breath, and also experienced a burning sensation in his mouth and chest. The patient required urgent hospitalization for 2 days with presumed embolism. The patient recovered.

Case 200711270BNE: A UK male patient with unknown age was given Nebido injection in a general practitioner's (GP's) office and began to cough immediately. He was unable to get his breath, he felt a burning sensation in his mouth and chest, and he collapsed. He was hospitalized for 2 days, and recovered. The Sponsor's analysis included that the injection was given whilst the patient was standing, the drug not warmed, and the drug was also given quickly.

Case 200711462BNE: On 30-Nov-2007, immediately after an injection, a 44-year-old UK male patient experienced cough, shortness of breath, and flushing, considering serious due to it being an important medical event. The patient recovered after 1 day.

Case 200718455GPV: On 25-Sep-2007, during Nebido injection, a 68-year-old German male patient showed symptoms of an allergic reaction including tingling sensation and sensation of numbness in his lips and mouth. This was considered severe as a medically important event. He was treated with H1 and H2-blocking agents and stayed in the doctor's office for 3 hours under observation. The complaints resolved within 6 hours after administration of Nebido.

Case 200811461BNE: On an unknown date, a 55-year-old UK male patient was given his 3rd injection of Nebido, he immediately complained of a metallic taste in his mouth, and he began to sweat profusely and experienced a "burning up" sensation. His blood pressure soared to 275/175 mmHg during the event, but 30 minutes after the injection, the patient's BP stabilized at a normal level. Due to a sharp increase in the patient's blood pressure for about 30 minutes after the injection, the event was considered as serious by the reporter due to medical significance.

Case 200812881BNE: On 01-Oct-2008, 2 months after an initial injection of testosterone undecanoate for Noonan syndrome (primary testicular failure) and immediately after a second injection of Nebido, a 27-year-old UK male patient experienced bronchospasm, cough, wheeze, and flushing. The patient was treated with salbutamol nebulizer and recovered after 20 minutes. The Sponsor's analysis was that the event constellation may be indicative of POME or of a hypersensitivity reaction.

Case 200812947GPV: A 38-year-old Swedish male patient with lack of testosterone due to radiotherapy received Nebido twice. After his first injection, the patient experienced a mild allergic reaction. Six months later in February 2007, another injection was given in a hospital and the patient developed a "severe allergic reaction" (severe throat swelling) and "potential heart failure". These events were reported to be life-threatening. The patient recovered shortly after treatment but information about treatment was not given. Nebido therapy was discontinued.

Case 200815181GPV: A 52-year-old German male patient of unknown age was given Nebido on (b) (6), and he experienced heat sensation in the neck and tickling in the throat, severe dyspnea, and muscle twitching. Later, the patient lost consciousness for about 20 seconds. Shock positioning and intravenous fluids were administered. The patient was admitted for "clarification". The next day, about 28 hours later, the patient was discharged with a light headache.

Case 200815625LA: The 60-year-old male from Brazil started receiving Nebido at 4mL every 3 months in July 2007. On (b) (6), instantaneously after Nebido's injection, the consumer experienced "anaphylactic reaction" including throat itching followed by cough, glottis spasm and glottis edema. The patient was treated with adrenaline and intravenous corticosteroids, oxygen and an antihistamine orally. He stayed in a hospital under observation, and after 6 hours he recovered and was discharged.

Case 200818230LA: This 58-year-old male from Brazil has been receiving Nebido for an unknown amount of time when he experienced an "anaphylactic reaction" and was hospitalized. No other information was provided.

Case 200818257LA: This 53-year-old male from Brazil on 31-Aug-2008 experienced profuse sweating, arterial blood pressure decreased, nausea and pain at injection site during Nebido injection. He recovered from these events 4 hours after injection. During the same period patient experienced heaviness of head. He did not recover from this event.

Case 2008-19842GPV: During an injection with Nebido, this 67-year-old Swedish male patient experienced a "light fall" in his blood pressure (from 140/80 to 125/70 mmHg) and sweating. The BP regressed spontaneously within a few minutes. The patient received one additional Nebido injection after this event without experiencing any problems.

Case 200820307GPV: This 72-year-old male patient from Malaysia experienced non-stop coughing for about 10 minutes, and his face turned blue (cyanosis) immediately following an injection of Nebido. He also reported suffering from dizziness and numbness of his face. The patient's symptoms of cough and cyanosis recovered after 10 minutes; dizziness and numbness of the face recovered on an unspecified date.

Case 200821519GPV: On (b) (6), after half a dose of Nebido injection had been given, this 21-year-old Swedish male patient experienced severe chest pain radiating towards his throat and neck, cold sweating and coughing. The injection was stopped. Since the discomfort did not disappear, the patient was given 0.5 mL adrenaline, betamethasone and oxygen. The event was reported as serious as chest pain was considered a medically important event. The condition improved gradually and the patient recovered without sequelae, and he was transmitted to the ER for observation.

Case 200821776GPV: This 33-year-old Denmark male patient had undergone a unilateral orchiectomy and also had received radiotherapy to the other testicle. In July 2006 he started treatment with Nebido. On 08-May-2008, directly after an injection of Nebido, the patient experienced a life-threatening allergic reaction with symptoms of breathing problems and cough. The patient was treated with salbutamol inhalation treatment and an antihistamine (cetirizine). After one hour, all of the patient's symptoms disappeared. The patient's initial blood pressure of 147/89 decreased to 124/73 mmHg.

Case 200826527GPV: This 72-year-old German male patient experienced severe coughing, choking fit, facial dysesthesia, and temporary palsy of mouth (7th nerve paralysis) and face musculature during the injection of Nebido on 15-Sep-2008. After injection of half a vial, the administration of Nebido was discontinued. The complaints persisted over 25 minutes after the injection. The patient recovered within 30 minutes. This reported event was considered serious by the reporter due to medical importance.

Case 200826556GPV: This 76-year-old German male patient with a history of diabetes, hypertension, dyslipidemia and longtime metabolic syndrome received Nebido. During the injection, the patient developed severe coughing, dyspnea, and a chocking fit. The injection was discontinued after half a vial. Within 10 minutes after the injection, the patient recovered. The reporting attending urologist stated that the patient had already developed similar events in the context of Nebido administration on 08-Dec-2006. In 2006, the patient had experienced dyspnea, urge to cough and cyanosis.

Case 200828604GPV: This 41-year-old German male patient had been under treatment with Nebido for six years for Klinefelter's syndrome. In Aug-2008, during a Nebido injection, the patient developed a tingling sensation which started in the lungs and ascended to the nose. Furthermore, he suffered from feeling of tightness in the region of the thorax, dry cough, burning eyes, and flushing symptoms, considering a possible anaphylactic reaction. Thirty minutes after treatment with prednisone, an antihistamine (dimethindene maleate) and ranitidine, the patient recovered. A testosterone cypionate prick test was performed on 09-Oct-2008 and was negative after 20 minutes and also negative after 24 hours. In addition, a dermatological test (prick test) was performed in Nov-2008, using the single ingredients provided by the company (testosterone, castor oil and benzyl benzoate). The *in vivo* diagnostic did not show any signs of type I sensitization.

Case 200832838GPV: On 08-Dec-2008, after 2.6 mL of Nebido was injected slowly, this 58-year-old South Korean male patient experienced moderate chest pain, cough, dyspnea, and dizziness. The patient recovered with treatment (no further specified) on the same day.

Case 200810048BNE: This 39-year-old UK male patient had been given Nebido for 1 year and 4 months. On (b) (6), when 2 mL from a 4 mL Nebido vial was just being injected, the patient suddenly complained of throat closing, coughing, tingling tongue, and difficulty breathing. Facial swelling, tongue swelling, shortness of breath and tremor were observed. The injection was stopped and needle removed. Adrenaline 0.5 mg was administered IM. The patient's BP was monitored and oxygen was given whilst awaiting the ambulance. On arrival at hospital, the patient was asked to sit to transfer to a chair, but on doing so started with tremors. Adrenaline was repeated (20 min after the first dose). Whilst in hospital, he remained symptom free and no further treatment was given.

Case 200910221BNE: A 44-year-old UK male patient was given Nebido for low testosterone on 08-Jan-2009. After the injection, he experienced chest tightness, cough, sweatiness, and throat tightness. The event was considering serious by the reporter as it was an important medical event. Nebido was withdrawn and the patient recovered the same day.

Case 200912079BNE: This UK male patient with unknown age received Nebido injection on unspecified date. One hour after the injection, the patient felt funny and experienced cough fits. He was treated with antihistamines, and improved.

Case 200912293BNE: This 53-year-old UK male patient started Nebido treatment in Dec-2007. After receiving his 6th dose in 2009 (12 weeks ago), the patient experienced a "mild anaphylactic shock". He felt burning in his throat and couldn't breathe very well. He recovered. In early (b) (6), after receiving another Nebido injection, this time at the hospital, the patient experienced closed throat, tight burning throat, dyspnea, feeling hot and sweaty, red face. The nurse reported "*pulse rate thready, irregular – quickly returned to normal, bronchospasm and SOB, range from 68 to 90 SBP fluctuating from normal ranges very briefly then settling at 142/87." The reporter thinks the event may be treated with hydrocortisone. The situation was steadily worsening some 5 – 30 minutes then eased.*" The nurse also reported that the patient was positioned and calmed and recovered 45 to 60 minutes later with supervision.

Case 200912294BNE: This 32-year-old UK male patient received Nebido for 2 years. On (b) (6) the patient's mother who is a nurse administered the injection to the patient. Having received the injection, the patient immediately felt odd, experienced a tightening of the throat, shortening of breath, and flushing. His mother reported that it was a bit like a panic attack. The patient was admitted for observation on that day. The event of anaphylactic shock (SOB, flushing and bronchospasm) lasted 1 hour. It is unclear what treatment, if any, the patient received.

Case 200916799LA: This male patient from Ecuador of unknown age reported symptoms of skin rash and difficulty breathing immediately after administration of Nebido by a pharmacist. The patient was treated with intravenous hydrocortisone and recovered. The patient had received Nebido for 3 months prior to this injection. No other information was given. The reporting physician considered the event possible anaphylactic shock.

Case 200919013LA: This 75-year-old male patient from Brazil had been receiving Nebido for male hormone replacement due to his benign pituitary tumor. On (b) (6), the consumer received a Nebido injection in a pharmacy and a few minutes later, he experienced bad taste in mouth, malaise, cough, hot feeling in body, body formication, pain between his fingers, redness on his face and burning sensation on his skin. He was taken to a hospital and received parenteral adrenaline, corticosteroid and an anti-allergic drug. The consumer recovered on the same day.

Case 200919765LA: This 33-year-old man from Honduras received Nebido for male hypogonadism. In Jun-2009, patient had his first application of Nebido. Nebido was still being administered IM (there was approximately 1 mL left in the syringe) when the patient started complaining about difficulty to breath. This difficulty intensified and the patient became cyanotic so the treating physician stopped the administration and started administering hydrocortisone IV and an antihistamine (chlorpheniramine). The condition of the patient improved within minutes and then the patient said he needed to cry, started crying and he said he did not known why. Minutes later this need to cry had stopped and the patient left physician's office. Patient also experienced cough and vomiting during the event. That night, at 8 pm, the patient called saying he was having fever (40 Celsius degrees) which was treated with unspecified NSAIDs. The fever had disappeared by midnight. The events (difficulty breathing, cyanosis, crying, vomiting, cough and fever) were considered as allergic reaction. Patient fully recovered from the event.

Case 200924735GPV: This 22-year-old male patient from Sweden with Klinefelter's syndrome started Nebido treatment in Feb-2006. On (b) (6), the patient received an injection from his sister-in-law. During the ongoing injection, the patient suddenly developed dyspnea and his throat became swollen when approximate 1 mL of the drug was left in the syringe. The patient became scared and he shivered with his whole body. The needle was drawn and the injection was stopped. The patient was sent to a hospital and was treated with a corticosteroid, salbutamol, an antihistamine (clemastine), adrenaline intravenously, and ipratropium. The patient stayed in the hospital and recovered.

Case 200929719GPV: This Spanish male patient of unknown age received testosterone undecanoate (Reandron) injection on an unspecified date and experienced hypotension, and was not treated. Patient recovered.

Case 200930704GPV: This 43-year-old German male patient with Klinefelter's syndrome had been treated with Nebido since Aug-2005. On 02-Jun-2009, during a Nebido injection, the patient experienced sensation of heat, urticaria and dyspnea. He was treated with an injection of

an intravenous corticosteroid immediately after the occurrence of the adverse reaction. The symptoms started to subside within 30 minutes. After 1 hour, the event was resolved.

Case 200932012GPV: This 16-year-old Australia male with testicular agenesis received two injections of testosterone undecanoate (Reandron) without problems. On an unspecified date, an IM injection of Reandron was administered as his 3rd dose by a general practitioner. Within 3 minutes, the patient experienced itching of his palms, groin, and feet followed by widespread/ generalized urticaria, tightening in the throat, sweatiness, facial and lips swelling, shortness of breath, constriction of the chest, hypotension, cough and dizziness. The patient was given IV adrenaline, hydrocortisone, antihistamines and IV fluids. The patient recovered without sequelae. The case was described as life-threatening by the reporter. The patient had a history of eczema, asthma, food allergies and other drug allergies. Prior to switching to Reandron, the patient had received a testosterone ester preparation. The patient was referred to the allergist who performed skin prick testing with Reandron, which showed a very positive reaction (type I reaction).

> **Addendum**: In this patient, skin prick testing found a definite reaction to Reandron with a 10×8 mm wheal, but no reaction to testosterone esters gel or saline solution control. Testing of the individual components of Reandron found that non-skin-irritating concentrations of benzyl benzoate resulted in a 10×10 mm wheal and smaller peripheral lesions. Neither castor oil nor TU induced a response.

Case 200933178GPV: This 34-year-old UK male patient was injected with Nebido for transgender hormonal therapy in Dec-2007. On 13-Aug-2009, the patient experienced fat embolism, considered serious by the reporter due to important medical event. No further information is available.

Case 200940006GPV: On 03-Sep-2009, this 70-year-old UK male patient developed shortness of breath, cough, and instant chest pains immediately after injection of Nebido. The symptoms lasted 1-2 minutes. He recovered after 1-2 days. This event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS form was checked as "Other").

Case 200940275GPV: On (b) (6), directly after an injection of Nebido, this 68 year-old German male patient experienced a severe cough attack and dyspnea followed by vomiting and tightness of chest. He was hospitalized. Once in the hospital, the patient was treated with nitroglycerine and his condition improved, but he developed nausea and vomited once. The reported events lasted approximately 4 hours. The patient was admitted due to a suspicion of acute coronary syndrome (ACS, sub-type of unstable angina pectoris). An ECG on (b) (6) revealed horizontal ST depression. An ECG performed 6-hr later showed regression of ST depression. Cardiac enzymes were normal.

Case 200940933GPV: This 37-year-old German male patient with Klinefelter's syndrome started treatment with Nebido in Jul-2008. On 12-Oct-2009, four minutes after a Nebido injection, the patient was sweaty, collapsed (experienced syncope), developed nausea, an urge to vomit, tachycardia and hypotension. The reporter states that the patient had developed an allergic

reaction with shortness of breath and anxieties. The patient was immediately treated with hydrocortisone intravenously. The patient's condition improved. After 7 minutes, all symptoms disappeared.

Case 201010793LA: This 64-year-old Columbian male patient with primary hypogonadism received a Nebido injection on 09-Dec-2009. On the same day, the patient experienced facial rash and cough with expectoration considered serious by the reporter due to medically important event (Box 8-12 of the CIOMS Form was checked as "Other"). The patient improved after 1 day.

Case 201014170LA: This 84-year-old male patient from Mexico received his 2nd Nebido injection on 25-Apr-2010. On an unknown date (the case report was received on 29-Apr-2010), the consumer experienced dyspnea and high arterial blood pressure (up to 190 mmHg). The outcome was unknown. The event was considered serious by the reporter as a consequence of medical significance (Box 8-12 of CIOMS Form was checked as "Other").

Case 201018709GPV: This 40-year-old Austrian male patient started treatment with Nebido for testosterone substitution after orchidectomy. On 25-Feb-2010, following 1 year of Nebido treatment, the patient received a Nebido injection, and 20 seconds later experienced circulatory collapse with a fall in his blood pressure lasting 30 minutes. In addition, he suffered from cough and dyspnea, also lasting 30 minutes. The report does not describe whether any treatment was administered. The outcome was event was reported as improved. The events were considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "other").

Case 201019083GPV: A report received on 08-Mar-2010 described a 46-year-old Swiss male patient who on an unknown date experienced pulmonary fat embolism with fits of cough, and rising warmth of the body after an injection of Nebido. The patient recovered after 10 minutes. No further information was available. The event was considered serious by the reporter due to its medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201020041GPV: This 58 year-old German male patient with prostate adenoma started receiving Nebido injections on Aug-2005. On 21-Jul-2009, during a Nebido injection, the patient experienced tickle of the throat, mild nausea, weakness and cold sweat. No treatment was given, the patient recovered spontaneously after 10 minutes. The event of suspected POME was considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201020446LA: This 60-year-old Mexican male patient started Nebido therapy for panhypopituitarism in 2007. In Jul-2010, 10 seconds after a Nebido administration, the patient experienced a hypersensitivity reaction, including taste of oil in the throat, dyspnea, malaise, drowsiness, and dry cough. He recovered after 1 hour without treatment. On 25-Oct-2010, approximately 3 months later, the patient received another Nebido injection and during the administration, he experienced persistent dry cough, feeling of irritation (like burning) that

started in the throat and spread to the face, nose, ears, mouth and eyes, intense dyspnea, and numbness of the mouth. The event was very intense until about 45 minutes after injection, and gradually resolved spontaneously within 15 minutes. Both episodes of the event were considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201021482GPV: This 63-year-old South African male patient received Nebido treatment for hypogonadism. On 19-Mar-2010, while his 3rd or4th dose of Nebido was being injected into the right gluteus muscle, he experienced cough and dyspnea, became anxious, and wanted to faint (pre-syncope). In addition, he also suffered from tachycardia and a drop in blood pressure. He was given oxygen and hydrocortisone intramuscularly. The patient was not hospitalized, and recovered. This serious event was considered an anaphylactic reaction by the reporter.

Case 201025167GPV: This 51-year-old German male patient with a history of ablation of the right testes due to seminoma experienced cough after his first and 3rd Nebido injections. On 25-Nov-2009, approximate 10 seconds upon injection of Nebido, the patient developed heat sensation in the head, tingling in the finger tips, headache, and attacks of asthma-like cough. The BP was measured at 125/90 mmHg. After IV administration of hydrocortisol, the symptoms subsided with 20 minutes. The event was considered severe POME or hypersensitivity by the reporter.

Case 201028214GPV: This 46-year-old UK male patient received Nebido for testicular hypogonadism starting 2-3 year prior to the event. On 10-Mar-2010, right after an injection of Nebido, the patient experienced a mild anaphylactic reaction where he had breathing difficulties, sweating, a cough fit 2 minutes after the injection, felt hot and sick, felt faint and had to lie flat. No adrenaline was given but the physician gave him prednisone tablets 5 mg, 6 times daily for a total 42 tablets. The patient eventually recovered, but felt very "unwell" after the incident.

Case 201029358GPV: This 52-year-old German male patient used Nebido for the treatment of hypogonadism. On an unspecified date (4 weeks before the report that was received 07-Jul-2010) immediately after a Nebido injection, the patient developed cough, tingling sensation, malaise, sensation of constriction of the chest and redness of the facial skin. The patient recovered after 30 minutes. The event was considered serious by the reporter due to medical significance (Box 8-12 of CIOMS Form was checked as "Other").

Case 201033158GPV: This German male patient of unknown age experienced cough and taste disturbance at the end of a Nebido injection on a unspecified date. The injection was administered in a standing position. The symptoms abated. The patient was not hospitalized. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other"), but no further information was available.

Case 201034100GPV: This 70-year-old German male patient received Nebido treatment for androgen deficiency syndrome since Aug-2007. On 04-Jan-2010, during slow injection of

Nebido, the patient experienced severe "unpleasant" cough and dyspnea. The event lasted about 20 minutes, and subsided. The patient received no remedial therapy. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201034191GPV: This 45-year-old German male patient received Nebido therapy for hypogonadism. On 05-Jul-2010, upon slow Nebido injection, the patient developed severe cough attacks with dyspnea after injection of just 2 mL. The symptoms improved after approximately 20 minutes. Patient received no remedial therapy. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201034195GPV: This German male patient of unknown age experienced unpleasant cough and dyspnea. The patient received no remedial therapy. No further information was available. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 201034605GPV: This 60-year-old German male patient received Nebido injections for androgen deficiency syndrome. On an unspecified date, the patient experienced a severe cough attack with initial dyspnea, followed by a sweating attack and malaise. Duration of the events was reported as about 15 hours. The next morning, the patient recovered. The patient received no remedial therapy. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

The next 4 cases (201034100GPV, 201034191GPV, 201034195GPV, and 201034605GPV) were reported by the same urologist.

Case 201035276GPV: This 45-year-old UK male patient received Nebido for pituitary adenoma starting in 2006. On 15-Jul-2010, the patient experienced an anaphylactic reaction. Nebido was withdrawn, and the patient recovered.

Case 2010 36559GPV: This Swiss male patient of unknown age had a history of orchidectomies for seminoma of both testes for which he received treatment with Nebido. On 12-Aug-2010, at 3 to 5 minutes after the Nebido injection, the patient experienced feeling of heat, cough and dyspnea. The patient received methylprednisolone, an antihistamine (clemastine), and intravenous ranitidine, and he felt quickly better without problems. Allergy tests to the Nebido ingredients turned out to be negative. The Sponsor determined this event was a case of severe POME.

Case 201037659GPV: This 61-year-old Danish male patient with a testicular disorder received Nebido therapy since 22-Jun-2006. On (b) (6), the patient experienced breathing difficulty and coughing after the injection. The patient was hospitalized and recovered.

Case 201038945GPV: This 63-year-old Belgian male patient with a hypophyseal tumor, hypophysectomy and prostatectomy received Nebido therapy for hypogonadism. On (b) (6) one minute after a Nebido injection, the patient experienced shortness of breath. He was transferred to an emergency room and received cortisol intravenously. He stayed in observation for 1 hour and recovered completely.

Case 201040373GPV: This 53-year-old UK male patient received Nebido injection on an unknown date. He experienced an odd taste at the back of his mouth whilst Nebido was still being injected. Almost immediately thereafter, this patient began to cough, developed difficulty breathing, became sweaty, and turned pale. No rash was reported. The patient was given intramuscular adrenaline and he started feeling better after a couple of minutes. An anaphylactic reaction was assumed by the reporter.

> **Addendum**: The patient was skin tested to benzyl benzoate, Nebido and also to "Virormone". A skin prick test and intradermal tests up to 1:10 concentration were performed. There was no evidence of reaction and therefore, symptoms were considered as not suggestive of a type I allergy. The AE term Anaphylactic Reaction was amended to Suspicion of POME.

Case 201040508GPV: This German male patient of unknown age was enrolled in an investigator-sponsored study to evaluate the allergic potential of Nebido (*Study IP157-003, a phase 1, double-blind study to evaluate the allergic potential of Nebido and formulation components in patients who have exhibited anaphylactic-like reactions following intramuscular injection of Nebido*). After the 1st injection of Nebido, the subject developed reddening of the skin, increase in BP, a feeling of flushing, and dyspnea. The severity was mild. The subject was treated with corticosteroids and recovered. A re-challenge was reported as positive. The event was considered serious due to its medical significance. The investigator determined that the reaction in this patient was clearly not POME, but rather a perfect example of a non-allergic hypersensitivity reaction, which was most likely specifically related to study drug.

Case 201041966GPV: On an unspecified date, this 42-year-old Denmark male patient started treatment with Nebido. On an unspecified date, he experienced an anaphylactic shock. The temporal relationship between the event and Nebido was unclear in the report.

Case 201042008GPV: This 61-year-old Swedish male patient received Nebido for hypogonadism on 05-Oct-2010. Approximately one minute after completion of injection, the patient experienced coughing and swollen throat, which were originally considered non-serious. However, the patient kept suffering from coughing and swollen throat with an unchanged intensity for the next 10 days until the symptoms decreased on 19-Oct-2010. After receiving his 2nd Nebido injection on 10-Nov-2010 (about 5 weeks after the 1st injection), the patient experienced a similar reaction to the one he experienced after the initial injection was given. Approximately 1.5 hours after injection, the patient was still suffering from the reaction of coughing and swollen throat. However, no breathing difficulty occurred. The event of swollen throat was upgraded to serious by the reporter due to medical importance.

Case 201045017GPV: This 51-year-old Swiss male patient with testicular hypofunction, essential hypertension, HIV disease, and opioid dependence syndrome received Nebido treatment. On 11-Oct-2010, after his 2nd injection of 0.75 mL Nebido, the patient experienced cough and dyspnea, reported as medically important events (Box 8-12 of the CIOMS Form was checked as "Other"). The injection was stopped after 1 mL, and he was treated with 100 mg prednisone 100 mg orally and two tablets of an antihistamine (desloratadine). After 10 minutes the patient recovered.

Case 201046647GPV: This 38-year-old Italian male patient experienced chest pain, respiratory symptoms, arthralgia, and syncope. No additional details were provided. The time frame between the injection and the occurrence of events was not reported.

Case 201047159GPV: This 63-year-old German male patient was treated with Nebido for testosterone deficiency syndrome. On 21-Sep-2010, the patient received his 2nd Nebido injection, and experienced a life-threatening, immediate hypersensitivity reaction with symptoms of feeling hot (flushing), an irritative cough, and bronchospasm that lasted for 20 minutes. He was treated with IV anaphylaxis therapy, and quickly improved afterwards. Nebido was discontinued.

Case 201047285GPV: This 54-year-old German male patient received Nebido for trans-sexualism. On 26-Jan-2010, the patient experienced irritative cough, a generalized hot feeling, and palpitations that lasted for 20 minutes. It was not reported whether the events occurred during or shortly after injection or later, but the report did mention that Nebido was withdrawn. The event was considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other).

Case 2011-002167: This Ghanaian male patient of unknown age had been using Nebido for about 3 years as part of his hormone replacement therapy for panhypopituitarism. A few seconds after starting his injection of Nebido on 04-Jan-2011, he experienced an overwhelming need to cough, followed by a constriction in his airway and serious difficulty in breathing. This episode of coughing and impaired breathing lasted for about 10 minutes, and was extremely frightening for him. No treatment was performed. The case was considered serious by the reporter due to medical importance (constriction of airway and serious difficulty in breathing).

Case 2011007367: This 58-year-old Austrian male patient received Nebido for testosterone deficiency syndrome. During the injection on 01-Jun-2010, the patient experienced cough, dyspnea, anxiety, attack of sweating, and a "feeling of constriction in chest", which lasted few seconds. The window was opened, and the patient was laid down on the bed under observation. He recovered after 5 minutes. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011009542: On unknown date, after his 3rd Nebido injection, this 62-year-old South Korean male patient experienced POME with a symptom of cough. After his 1st POME episode,

the patient took three more Nebido injections, which were followed by the new POME episodes. According to reporter, the patient did not recovered from the last episode yet. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011011368: This 41-year-old UK male patient received Nebido for an unknown indication. On 21-Jan-2011, the patient experienced an anaphylactic reaction with symptoms of dyspnea, rash, and throat tightness. The event was considered life-threatening. The event was treated with oxygen, adrenaline, an antihistamine (chlorphenamine), and hydrocortisone. The patient recovered.

Case 2011014093: This German male patient of unknown age received Nebido for an unknown indication. On an unknown date, the patient received an injection that was probably less than 2 mL, and during the injection the patient developed marked symptoms of POME, which was considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011-014662: This 33-year-old Spanish male patient was prescribed Reandron for androgenic insufficiency two years prior to this event. On 20-Jan-2011, he experienced bronchospasm. He was treated with corticosteroid therapy. Reandron was discontinued and the patient recovered from the event.

Case 2011016767: This 42-year-old UK male patient had been on Nebido for 3 years for testicular cancer. In (b) (6), the patient had an anaphylactic reaction immediately after the 2nd injection. He felt his throat closing, cough, difficult breathing, and had an erythematous rash. He received oxygen, an antihistamine, hydrocortisone, adrenaline and prednisolone. The breathing improved with adrenaline. The patient was hospitalized and he recovered. He was discharged home on prednisolone and the antihistamine. Nebido therapy was discontinued.

Case 2011018006: On 19-Apr-2010, after his 3rd application of Nebido, this 61-year-old Swiss male patient experienced an immediate type hypersensitivity reaction, grade III, coughing, dyspnea, wheezes, face edema, rash erythematous, and blood pressure increased. The events lasted for 30 minutes. The patient was treated with an antihistamine (clemastine), hydrocortisone intravenously, and salbutamol. The events were considered serious by the reporter due to medical significance (Box 8-12 of CIOMS Form was checked as "Other").

Case 2011022738: This 57-year-old German male patient received Nebido on 14-Mar-2011. After a Nebido injection, the patient experienced urge to cough, burning sensation of eyes, breathing difficulties, and pressure on trachea. The patient did not receive any treatment and recovered after 30 minutes. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011024048: On 16-Mar-2011, 30 seconds after starting his 3rd injection of Nebido (about 0.5 mL being injected), this 69-year-old Brazilian male patient experienced cough during injection, dizziness, chest pain, profuse sweating, and increased blood pressure. The events lasted about 5 to 7 minutes. The patient recovered from all events. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011025652: This Swedish male patient of unknown age received Nebido for a unknown indication and experienced POME. This event was considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011025755: This 65-year-old male German patient received Nebido for hypogonadism. On 24-Feb-2011, immediately after a Nebido injection, the patient experienced chest pain, dizziness, tingling and burning sensation, increased sweating, malaise, dyspnea and cough. He did not receive any medication to treat the event. Actual symptoms abated after one hour, however, dry cough after athletic activity remained for three weeks after the injection. The events were considered serious by the reporter due to medical significance (Box 8-12 of CIOMS Form was checked as "Other").

Case 2011039522: This German male patient of unknown age received Nebido injection and experienced bronchospasm, cold sweat, and dry cough. It was not reported whether these symptoms appeared directly after the injection. The patient's outcome was not reported. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011040546: This Brazilian male patient of unknown age received a Nebido injection at a drug store. On 12-Mar-2011, approximately 1 to 2 minutes after injection, the patient experienced reduced breathing capacity followed by increased difficulty of breathing (he could not inflate the chest with air). As a consequence of difficulty breathing, the patient experienced dizziness, vertigo, darkness of vision (he saw alternate points of light like a off TV), joint pain (with more intensity in the lower limbs), intense sudoresis in his whole body, weakness, pallor, decreased body temperature, and "total absence of autonomy" (he remained sitting for 15 to 20 minutes). The outcome of the events was reported as recovered /resolved. According to the consumer, during the episode of the adverse events, he thought he would die as a result of these events. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011044214: This unknown-aged male UK patient used Nebido since 2007 for unknown indication. On an unspecified date, after a Nebido injection by a general practitioner, the patient experienced coughing and wheezing. He went to an allergy clinic and the physician suggested it was POME. The symptoms were resolved within hours after the reaction occurred. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011046164: This 34-year-old Spanish male patient had received Reandron for years. On (b) (6), after an IM injection, the patient experienced dyspnea, cough, depressed level of consciousness, muscular weakness, excessive sweating, and pallor. Adrenaline and oxygen were administered and he improved. However, after 30-40 minutes, the symptoms started again and the patient was taken to the hospital where he remained for observation. He recovered the next day and was discharged from the hospital.

Case 2011046482: This 49-year-old male UK patient started Nebido injection (indication for use not reported). After his 1st injection on 07-Jan-2011, the patient reported fatigue and flu-like symptoms. The reaction that occurred after his 2nd injection on 16-Feb-2011 (6 weeks apart) was more severe, with severe flu-like symptoms, headache, dizziness, hot flushes, sweating, aching joints, feeling of faintness, weakness, wheezing, sneezing, chest pain and heart palpitations. The patient sought care from a specialist, who informed the patient of "blood pressure through the roof". The patient felt very poorly for 2 weeks, then quite poorly for 8 weeks. He decided to discontinue Nebido treatment. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011048218: This 48-year-old Italian male patient started Nebido for primary male hypogonadism on 31-May-2011. On 31-May-2011, the consumer experienced dry cough, mild dyspnea, malaise, hyperhidrosis and mild dizziness in the afternoon after a slow injection of Nebido that was self-administered. Nebido injection was discontinued immediately. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011050730, **Case 2011052409**, **Case 2011052410**: These 3 case reports were submitted by a single physician and concerned three Singaporian male patients of unknown age who started Nebido treatment for unknown indications about 3 years ago. During the injection all 3 patients experienced cough. The physician was aware of the possibility of POME. All three cases were considered serious by the reporter due to medical significance (Boxes 8-12 of the CIOMS Forms were checked as "Other").

Case 2011056865: This unknown-aged male German patient started Nebido treatment on an unspecified date. On an unspecified date, the patient experienced allergic reaction and suspicion of POME. The outcome for this event was not reported. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011063184: This 28-year-old South African male patient had been on Nebido treatment for the past 2-3 years for primary hypogonadism. On (b) (6), about 30 seconds after a Nebido injection, the patient complained about a burning sensation in his throat and he started coughing. After about 5 minutes, the patient felt pins and needles on his tongue. He was referred to ER and hospitalized for observation. The outcome of this event was not reported.

Case 2011065559: This 67-year-old Russian male patient started Nebido treatment for age-related androgenic deficit on 27-Jul-2011. On 27-Jul-2011, during a regular injection of Nebido, the patient experienced cough. Nebido treatment was continued and the patient experiencing bronchospasm during the following injection (dyspnea and difficulty breathing) and cyanosis. The injection was stopped. The patient also experienced small bleeding at the injection site. The physician considered that Nebido could have been injected directly into a blood vessel. The events resolved on the same day without treatment.

Case 2011071329: On (b) (6), a few minutes after an injection of Nebido, a 49-year-old Swedish male patient experienced a feeling of pressure on his chest centrally and a slight feeling of cough. The patient was hospitalized with telemetry monitoring and received aspirin. An ECG approximately 10 minutes post-hospitalization showed 0.5-1 mm ST segment elevation in V2-V4. The physician diagnosed POME. The patient felt well and was discharged the same day. Nebido treatment was discontinued.

Case 2011074882: This 60-year-old Brazilian male patient started Nebido treatment on 10-Jun-2008 for androgenic deficiency. On 08-Aug-2011, after a Nebido injection, the consumer experienced dizziness, vertigo, feeling of disappearing, confusion, disorientation, inability to stand, sensitivity alterations, gastrointestinal disorders (peppery taste on mouth, nausea, diarrhea), tiredness, general malaise and hypotension. The physician stated that the patient also experienced injection site bleeding on the buttock, which was believe to reflect unsuccessful and rapid injection. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011083027: This male Russian patient of unknown age took hormonal replacement therapy by testosterone during last 10 years and used Nebido during the last several years. On 07-Sep-2011, the patient experienced a "strange wish to cough" after the 1st mL of Nebido was injected, then severe cough and difficulty breathing after the 2nd mL Nebido was injected. The patient experienced itching after the 3rd mL was injected. Finally, the patient experienced loss of consciousness after the 4th mL was injected. The patient was administered liquid ammonia as corrective therapy. The patient's BP was 100/90 mmHg after the injection. The event was considered serious by the reporter and the patient was recommended to discontinue Nebido.

Case 2011087892: This 50-year-old UK male patient started Nebido for impotence on 12-Apr-2009. On (b) (6), he experienced shortness of breath immediately after an injection of Nebido. He also had burning in his hands and feet, burning in the roof of his mouth, severe pain in his right shoulder and extremity, and was clammy and pale. He lay down and ambulance was called. He was given an antihistamine with little effect, then he was transferred to a hospital. The patient experienced syncope and received aspirin and glycerol trinitrate (GTN) as treatment for this event. The outcome of these events were not specified. The events were considered serious and life-threatening by the reporter.

Case 2011095240: This 72-year-old Austrian male patient began coughing during a Nebido injection about 2-5 seconds after starting the injection. The cough was long-lasting and occurred

twice after Nebido injections despite reporting a correct injection technique. After 2 hours, the patient recovered. Nebido injection was discontinued after the 3rd occurrence of cough and patient was switched to a testosterone gel product. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011090820: On an unspecified date in 2007, after an injection with Nebido, this German male patient of unknown age experienced an anaphylactic shock. No additional information was reported.

Case 2011102083: One minute following injection of Nebido, this 47-year-old UK male patient began to cough fairly immediately, then described some tightening of the throat but no swelling noted, some difficulty breathing but mostly due to cough, also then felt very hot and sweaty. His BP was taken showing 170/105 mmHg. The events lasted 10 minutes. The events were not treated and resolved the same day. The events were considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011105544: This 68-year-old German male patient with a medical history of multiple allergies (to bees, wasps, peanuts, unspecified food) initiated Nebido therapy for hypogonadism on 06-Dec-2007. On 27-Oct-2011, the patient experienced anaphylactic reaction during a Nebido injection, with symptoms of cough, dyspnea, flushes, taste disorders in mouth, and pronounced spasticity. He was treated with glucocorticoids and antihistamine medications. The patient's symptoms lasted for over one hour and slowly improved. His blood pressure remained stable, and no skin irritation was reported. Nebido was discontinued on the same date and the patient recovered after 1 hour.

Case 2011108338: This 42-year-old UK male patient started Nebido treatment on 17-Oct-2011 and experienced acute shortness of breath at the time of the first dose administration. The event resolved within several minutes. The reported event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011110321: This male patient of unknown age from Malta with a medical history of hypopituitarism after brain cancer received Nebido treatment since 2008. His concomitant medications included thyroxine, hydrocortisone. On 30-Sep-2011, the patient experienced violent cough during intramuscular injection of Nebido and was close to collapsing. He also developed a generalized maculopapular rash. Due to their severity, these events were considered life-threatening for the patient by the reporter. He recovered from the events and Nebido was discontinued the same day.

Case 2011110671: This 64-year-old German male patient received Nebido treatment for hypogonadism post orchidectomy. On 15-Nov-2011, 2 minutes after an injection of Nebido, the patient developed dry cough, mild dizziness, nausea, and dyspnea. These symptoms improved after approximately 5 – 10 minutes, and the patient recovered after approximately 20 minutes. No skin reactions occurred, and no treatment was necessary. The event was considered serious

by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2011124098: This 56-year-old Finnish male patient received Nebido treatment for hypogonadism for many years. In 2011, the patient experienced cough, and strange feeling in the throat and mouth after a Nebido injection. One hour later, he recovered. The event was reported as POME and considered serious by the reporter due to medical importance (Box 8-12 of CIOMS Form was checked as "Other").

Case 2012004307: This 50-year-old male patient started using Nebido for hypogonadism. During a Nebido injection on 12-Jan-2012, he experienced cough, furry feeling on tongue, tingling sensation, red eyes, sweating, rash on whole body, and ear pressure. The cough fully recovered shortly after the occurrence, while all other symptoms improved but were reported to have not fully recovered.

Case 2012004532: This Austrian male patient of unknown age experienced dry cough, dyspnea, and hypertensive crisis during an injection of Nebido. The patient's condition recovered 30 minutes later. The event was reported as POME and considered serious by the reporter due to medical importance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2012005684: This 58-year-old Australian male patient started Reandron therapy on 19-Jan-2012. Shortly after the 1st injection, he experienced postural hypotension and presyncope. The patient was reported to have recovered.

Case 2012005853: This 25-year-old German male patient received Nebido. On 27-Jun-2011, he received an injection over 30 seconds and experienced severe cough, sweating and dizziness. He was symptomatically treated and recovered after 25 minutes. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2012007253: This 53-year-old German male patient received several injections of Nebido. On 07-Oct-2011, during an injection that lasted 30 seconds, the patient experienced severe cough, sweating, and dizziness, lasting about 25 minutes. Symptoms were symptomatically treated. The patient recovered. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2012014074: This Austrian male patient of unknown age received Nebido injection for lack of testosterone/hypogonadism. During the injection, the patient experienced dyspnea, hypertensive crisis, paresthesia of the upper limbs, and dry cough. The event led to hospitalization.

Case 2012-014975: This 71-year-old male patient from South Africa received Nebido at a pharmacy, and afterward, he experienced a feeling of faintness, throat tightness (constriction of throat), and cough. He also experienced numbness in the leg for approximately three days.

Case 2012015311: Immediately after his 3rd injection of Nebido, this 76-year-old Nicaraguan male patient with androgenic hypogonadism experienced 2 minutes of cough. Subsequently, he complained of itching in the interscapular region, and a macular papular reaction of the skin. The patient was diagnosed with an allergic reaction and treated with antihistamines. The symptoms resolved. The event was considered serious by the reporter due to medical significance (Box 8-12 of the CIOMS Form was checked as "Other").

Case 2012019653: This Austrian male patient of unknown age received Nebido injection for low testosterone/hypogonadism. On an unspecified date, during the injection, the patient experienced hypertensive crisis, paresthesia of his upper limbs, dry cough, and dyspnea for 30 minutes. Therefore, the patient was hospitalized. His condition recovered and Nebido was discontinued. The event was considered serious by the reporter due to medical significance and hospitalization.

Case 2012020873: This 68-year-old Brazilian male patient received Nebido injection on 29-Dec-2011 for hormone replacement. On an unspecified date after the product was administered, the patient developed an allergic reaction, and was hospitalized for 8 days and treated with unspecified medication. He had not recovered at the time of the report.

Case 2012025807: This unknown-aged German male patient had been using Nebido for several years due to insufficiency of the adenohypophysis. On an unspecified date, the patient experienced anaphylactic reaction with symptoms of cough, dyspnea, swelling of face and eyelids, dizziness, dry throat and mouth which appeared within seconds after an injection and lasted approximately 30 - 60 minutes. The patient was treated with dexamethasone and an antihistamine (clemastine) and subsequently hospitalized. At admission, his complaints resolved. Skin allergy testing was planned. The patient had history of rash and general skin redness of unclear etiology.

Case 2012025864: This 59-year-old Brazilian male patient started Nebido treatment for testosterone replacement on an unspecified date. On 15-Mar-2012, at the end of an injection, the consumer experienced pain in middle of the chest, continuous cough crisis, cold sweating, itching on his scalp, difficulty breathing, redness, malaise, burning in the side of his nose, burning in the buccal and lip mucosa, and itching eyes. The events of pain in the middle of chest, continuous cough crisis, cold sweating, itching on his scalp, difficulty breathing, redness and malaise resolved around 15 to 20 minutes after injection. The other events resolved after 30 minutes. Patient reported that he had never had these events before. He denied hospitalization and remedial therapy. The patient also reported that on previous injections, he had experienced a bad taste in mouth and slight somnolence. Of note, the box for hospitalization in the CIOMS form was checked.

Case 2012032972: This 47-year-old Swiss male patient received Nebido injections since Nov-2005. On 29-Mar-2012, 5 minutes after starting an injection of Nebido, the patient experienced progressive dry cough, followed by symptoms of a low grade Quincke's edema (angioedema). He also experienced generalized rash, intensive sweating, dyspnea, and dizziness. The symptoms lasted for 15 minutes. The patient was treated with an antihistamine (clemastine) and a corticosteroid. The patient recovered after 12 hours.

AT-2007-035468: On 13-Jun-2007, approximately 30 seconds after receiving Nebido injection, this 46-year-old Austrian male patient presented with anaphylactic reaction, a gagging throat irritation and a tickle of the throat. The patient was treated with an antihistamine. The patient recovered after 15 minutes.

AU-2007-014016: On 23-Apr-2007, during the 2nd injection of Reandron, this Australian male patient of unknown age developed severe coughing, as well as bodily shivering shortly after the injection. The injection was stopped approximately halfway and the patient was treated with oxygen, antihistamines and cortisone. The symptoms subsided. The patient was observed for one and a half hours prior to going home.

BR-2007-005496: This 57-year-old Brazilian male patient received his 1st Nebido injection on 05-Feb-2007 for hormone replacement therapy. On 05-Feb-2007, immediately after the Nebido injection, the patient experienced anaphylactic shock with symptoms of glottis edema, breathlessness, and malaise. The patient's breathlessness became worse 30 minutes after injection and he was lying down and treated with corticosteroids, and ventilated with oxygen. The patient experienced malaise during next 3 days. Nebido was withdrawn the same day.

CH-2007-042227: This 60-year-old Swiss male patient received Nebido injection on 07-Sep-2007. During the slow injection, the patient developed cough and respiratory distress. He recovered after 30 minutes. The event was considered serious by the reporter due to medical significance. Box 8-12 of the CIOMS Form was checked as "Other".

DE-2004-037302: On 21-Dec-2004, this 38-year-old German male patient received his first dose of Nebido injection for transexualism. During the injection, the patient experienced hyperventilation followed by pronounced redness in the face, malaise, and shivers. The patient's BP and HR increased. He was treated with prednisolone intravenously and an antihistamine, and kept in the clinic for observation. He left in a relatively recovered state. On the next day (22-Dec-2004), the patient still had late allergic symptoms like feeling of heat in the thighs and upper arms, malaise, and a feeling of fever, but no skin reactions or urticaria. The patient recovered.

DE-2007-004016: This unknown-aged German male patient received his 2nd dose of Nebido injection on an unspecified date. Approximately 15 seconds after the injection, the patient experienced circulatory collapse with unconsciousness for several minutes, nausea, tickling cough, and encopresis.

DE-2005-005199: This 30-year-old German male patient received Nebido treatment for Klinefelter's syndrome. On 31-May-2005, immediately after his 2nd dose of Nebido, the patient experienced medically significant stenocardia (angina), as well as tickle of the throat, shortness of breath, and sweating. The patient was reported to have recovered after 0.5 hours. The events were considered serious by the reporter due to medical significance. Box 8-12 of the CIOMS Form was checked as "Other".

Case DE-2005-008140: On 13-May-2005, this 56-year-old male German patient received his 1st injection of Nebido. He developed tickling of the throat immediately after removal of the needle, and was diagnosed as having a non-serious allergic reaction. The patient was treated with an antihistamine, clemastine.

It is notable that neither the Sponsor nor FDA picked up the preceding case, but it was counted by the independent adjudicators.

DE-2005-008181: On an unspecified date, after receiving an injection of Nebido, this 67-year-old German male patient experienced circulatory collapse with decrease in BP, nausea, retching and fever attacks. The event was regarded as a hypersensitivity reaction. The outcome of the reaction was not reported.

DE-2005-009283: This 54-year-old German male patient received a dose of Nebido injection for hypogonadism. Immediately after the injection, the patient developed cough, flushing, sweating attacks, restlessness, tremor, dizziness, cold sweats, and increased blood pressure up to 150/95 mmHg. The symptoms lasted longer than 20 minutes. The patient was treated with cortisone in the office practice setting and transferred to a hospital. In hospital, he received ranitidine and an antihistamine. After observation, he was discharged the same evening.

DE-2005-015256: After his 2nd Nebido injection, this 61-year-old German male patient experienced a severe cough attack. The event subsided after 10 minutes. The event was considered serious by the reporter due to medical significance. Box 8-12 of the CIOMS Form was checked as "Other".

DE-2006-002815: This 15-year-old German male patient received Nebido treatment for hypogonadism due to Kallmann's syndrome. On 14-Feb-2006, immediately after his 2nd injection of Nebido, the patient developed extremely severe urge to cough, retrosternal pain and mild dyspnea, redness of the eyes and tachycardia. Blood pressure was normal. The patient was treated with an antihistamine, (dimetindene), and prednisolone. The patient recovered. The injection was administered in a reclining position but within less than a minute. The reporting physician suspected a type I hypersensitivity reaction.

DE-2006-003298: This 42-year-old German male patient received Nebido injection quarterly on 3 occasions for hypogonadotropic azoospermia and androgen deficiency after radiation. On an

unspecified date, 3 minutes after his 4th Nebido injection, the patient experienced a hot flush, paresthesia in the area of his mouth and head, increasing dyspnea, cough, and an episode of apnea lasting 1-2 minutes. After 10 minutes, stable cardiovascular conditions returned. The patient recovered in the course of another 10 minutes. The events were considered serious by the reporter due to medical significance.

DE-2006-008415: This 54-year-old German male patient was enrolled in Study 306605 and received his 1st dose of testosterone undecanoate on 15-Mar-2004 for hypogonadism. On 03-Apr-2006, the patient received the 10th dose. Shortly (1 minute) after the injection of the study medication, the patient experienced cough with dyspnea. The event lasted about 15 minutes. The patient recovered without treatment. The investigator confirmed that he considered the event "cough after injection" as serious. Box 8-12 of CIOMS Form was checked as "Other".

DE-2007-004747: This 74-year-old German male patient started Nebido treatment on 14-Jan-2005 for hypogonadism and erectile dysfunction (ED). On 08-Dec-2006, starting at 3 minutes after the slow injection of Nebido, the patient developed pronounced urge to cough, dyspnea and cyanosis. The event lasted for 20 min. The event of cyanosis was reported as life-threatening. The patient recovered. Allergic reaction (hypersensitivity) was suspected by the reporter.

DE-2007-023890: This 57-year-old German male patient received the 1st dose of Nebido injection on (b) (6) for hypogonadism due to pituitary tumor. During the injection, the patient complained that everything turned black and he experienced a headache, sweating and tickling of the palms of the hands and soles of feet. After the injection, the patient developed dizziness, tingling sensation of the upper part of the body and on hands and feet, a sensation of weakness and pressure in head. The patient was treated with 8 mg of an antihistamine (dimetindene maleate) and prednisolone in the ER. In the ER, the patient developed dry mouth, a numbness sensation in his fingers and toes, continued dizzy, the sensation of warmth at the injection site (which was hot, hard, sensitive to pressure and reddened). Cardiac, pulmonary and abdominal examinations were unremarkable. Blood pressure was normal (128/88 mmHg). The patient received an infusion of intravenous fluids E153, ranitidine and cooling of the injection site. The patient's outcome was not reported.

> **Addendum**: In this patient, all skin testing with Nebido, testosterone undecanoate, benzyl benzoate, caster oil, a testosterone gel product, and latex were negative. Total Ig E was 16 kU/L (normal range < 100 kU/L) and Immuno CAP specific Ig E was 0 kU/L for caster oil and 0.07 kU/L for latex on 19 Jul 2007.

DE-2007-030464: This 47-year-old German male patient started Nebido treatment for hypogonadism after orchidectomy. On unspecified dates, twice during his Nebido treatment course, the patient experienced cough after injection. During the last injection on 22-Jun-2007, the patient developed severe dyspnea which was interpreted as laryngospasm. The emergency physician was called but the patient recovered spontaneously within a few minutes. Nebido was discontinued. The event was considered serious by the reporter due to medical significance. Box 8-12 of the CIOMS Form was checked as "Other".

GB-2007-006197: On (b) (6), just minutes after his 2nd Nebido injection, this 67-year-old UK male patient who was post-orchidectomy, experienced an acute anaphylactic reaction with a coughing fit and tightness in the throat. There was no cardiovascular deficit and no wheezing. The patient was treated with an antihistamine (chlorpheniramine) and epinephrine (adrenaline). The event was considered life threatening and involved hospitalization. The patient was reported to have recovered from the event after treatment.

GB-2007-000740: This 54-year-old UK male patient received his 2nd dose of Nebido injection on (b) (6) for the indication of testicular hypogonadism and osteopenia. Approximately halfway through the injection, the patient began coughing, and began to get progressively worse with difficulty breathing and sweating. His pulse was 48 bpm during the episode and the patient was near respiratory arrest. The event was considered to reflect acute laryngeal edema and was life-threatening. The patient was administered two adrenaline injections and high concentration oxygen by face mask with re-breathing bag. The patient was transferred to the hospital via ambulance. The event was considered immediately life-threatening. The patient was reported to have recovered on (b) (6).

GB-2007-023826: This 45-year-old UK male patient started Nebido treatment as a growth hormone in Apr-2005. On (b) (6), after the 2nd dose, the patient suffered respiratory distress and couldn't breathe. In addition, the patient experienced the urge to cough, coughing, inspiratory wheezing, tightening of his throat, a rash on his abdomen with the feeling of itching, and closing of his airway. The event was considered to be a life-threatening anaphylactic reaction. The patient was hospitalized and treated with epinephrine (adrenaline) and an antihistamine (chlorphenamine). At the time of the report, the patient was recovering and the event was resolving.

> **Addendum**: The patient had no known drug allergies, but was allergic to a testosterone gel product (Testogel) and a testosterone patch (Andropatch). The patient took Andropatch in 1996 but discontinued the product due to local irritation and allergic skin reaction. The patient took Testogel in Aug 2003 and the dose was doubled in Mar 2004. The patient then developed a skin allergy to Testogel in Mar 2005.

NO-2007-008557: On 29-May-2006, just before an injection of Nebido was finished (2.5mL were given instead of 3mL), this 35-year-old Norwegian male patient developed dry coughing, itching, and a tingling sensation in his throat, then in his face and head. These events resolved after 5 minutes.

SE-2006-004192: On (b) (6) just one minute after starting the 3rd injection of Nebido, this 44-year-old Swedish male patient with Klinefelter's syndrome experienced burning pain over the lower part of his sternum radiating up to the chin with dyspnea. The administration of Nebido was discontinued and the events lasted for 2-3 minutes. The patient was hospitalized for further observation. No new episodes of chest pain occurred. The patient recovered and Nebido was discontinued on (b) (6). The patient underwent an EKG which showed non-specific ST changes probably of ischemic character. The reporting physician's assessment was that Nebido

might have been administrated intravascularly. The event was considered serious by the reporter due to medical significance and hospitalization.

SE-2006-017516: This 47-year-old Swedish male patient received his 1st dose of Nebido injection for unknown indication on 24-Jan-2006. After the injection, he experienced a swelling sensation in his throat, difficulty breathing and palpitations. The patient's discomfort disappeared spontaneously after 5 minutes. On 30-Mar-2006, immediately after his 2nd injection, the patient again experienced difficulty breathing for a duration of approximately 5 minutes. In addition, he experienced fatigue and cough for several hours. The reporting Swedish health authority assigned the MedDRA code "angioedema" to these symptoms. The event was considered serious by the reporter due to medical significance. Box 8-12 of the CIOMS Form was checked as "Other".

SE-2006-022330: This 38-year-old Swedish male patient received his 1st dose of Nebido injection on 24-May-2006. During the injection, the patient developed angioedema and pruritus. In addition, the patient experienced nausea, malaise, swelling around the eyes and itching of the throat. The patient was treated with hydrocortisone and antihistamine (clemastine). He was discharged home after observation for a few hours. The patient recovered without sequelae from the angioedema and pruritus. In this case, the Sponsor concluded that differentiation between angioedema, hypersensitivity reaction, and POME could not be done conclusively for this report.

SE-2007-002541: On an unspecified date, at the end of his 4th injection of Nebido, this 64-year-old Swedish male patient experienced a feeling of warmth over his chest and head, coughing and reddening of his face. These events lasted for 5 minutes and resolved spontaneously. Nebido was discontinued and therapy was switched to another testosterone injectable product.

ZA-2007-035469: This 29 year-old South African male who was prescribed Nebido presented with an allergic reaction and life-threatening bronchospasm on (b) (6). The event was reported as anaphylaxis. The patient's BP dropped and he collapsed within a minute of receiving Nebido. His BP was 111/74 mmHg, his HR was 100, and his oxygen saturation was 94%. He recovered after treatment with hydrocortisone and an adrenaline nebulizer. He was observed for 2 hours and was well when discharged the same day (with oxygen saturation of 99%). The patient had received one prior dose of Nebido, 3 months before. He was reported to have fainted after his first dose and was very pale afterwards.

For additional details and expert evaluation of these cases, the reader is referred to the consultative review provided by DPARP.

4.4.3 Summary of Differences between the Sponsor's Internal Review and More Recent Review by the Sponsor's "Independent Adjudicators"

For POME

In the analysis of POME, there were minor differences between the original Sponsor's internal review and the more recent report of a case review by the Sponsor's "independent adjudicators". The internal reviewers identified 228 cases of POME, while the independent adjudicators identified 223 cases. The differences in the analyses are summarized in Table 20.

Table 20 Sponsor's Adjudication of Cases of POME

19 Cases Not in Concordance within 228 POME			14 IND Cases Not in Concordance out of 228 POME		
Case Number	Independent Adjudication	Sponsor Adjudication	Case Number	Independent Adjudication	Sponsor Adjudication
200811257GPV	No	Yes	200818230LA	Indeterminate	No
200816518LA	No	Yes	200818754GPV	Indeterminate	No
200824903GPV	No	Yes	201030488GPV	Indeterminate	No
200918244LA	No	Yes	201035276GPV	Indeterminate	No
201014170LA	No	Yes	201041966GPV	Indeterminate	No
201019729GPV	No	Yes	2011-016420	Indeterminate	No
201022548GPV	No	Yes	2011-090820	Indeterminate	No
201043202GPV	No	Yes	2011-105941	Indeterminate	No
201046647GPV	No	Yes	AT-2007-035468	Indeterminate	No
2011-036255	No	Yes	BR-2006-019257	Indeterminate	No
2011-046482	No	Yes	DE-2004-037302	Indeterminate	No
2011-063096	No	Yes	DE-2005-008140	Indeterminate	No
2011-074882	No	Yes	DE-2005-008154	Indeterminate	No
AR-2006-007565	No	Yes	ZA-2007-035469	Indeterminate	No
AT-2006-001317	No	Yes			
BR-2007-015689	No	Yes			
DE-2005-011567	No	Yes			
DE-2007-023890	No	Yes			
SE-2006-022330	No	Yes			

Table 21 presents a summary of the 19 POME cases that were not counted by the Sponsor's independent adjudicators but were counted by the Sponsor's original internal reviewers. Table 22 presents a summary of the 14 POME cases that were not counted by the Sponsor's internal reviewers but were counted by the independent adjudicators

Table 21 19 Cases Not in Concordance of 228 cases of POME assessed by the Sponsor's internal review and cited in the CR of 9-Nov-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200811257GPV	No	Yes	dizzy, sweating, rhinitis
200816518LA	No	Yes	weakness, malaise, sudoresis
200824903GPV	No	Yes	shivering, sweating, red + pustules
200918244LA	No	Yes	shortness of breath
201014170LA	No	Yes	dyspnea and BP high
201019729GPV	No	Yes	difficulty breathing dyspnea
201022548GPV	No	Yes	cough, hoarseness
201043202GPV	No	Yes	shortness of breath
201046647GPV	No	Yes	chest pain, syncope, arthralgia
2011-036255	No	Yes	chest pain, cough
2011-046482	No	Yes	flu-like symptoms, headache, severe fluey, dizziness, hot flush, sweating, feeling faint,
2011-063096	No	Yes	difficulty breathing, dyspnea, and had a grand mal seizure
2011-074882	No	Yes	dizziness, diarrhea, hypotension
AR-2006-007565	No	Yes	dyspnea
AT-2006-001317	No	Yes	Dyspnea, anxiety, fatigue depress
BR-2007-015689	No	Yes	Emotional disorder, burning in chest, dizziness sweating in hands
DE-2005-011567	No	Yes	feeling of a lump in his throat
DE-2007-023890	No	Yes	things turned black, sweating, tingling sensation; headache dizziness, weakness ER
SE-2006-022330	No	Yes	angioedema and pruritus, nausea, malaise, swelling around the eyes and itching of the throat.

Table 22 14 "IND" Cases Not in Concordance of 228 cases of POME assessed by the Sponsor's internal review and cited in the CR of 9-Nov-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200818230LA	Indeterminate	No	"anaphylactic reaction", hospitalized.
200818754GPV	Indeterminate	No	"recurrent pulmonary embolism"
201030488GPV	Indeterminate	No	tickle of the throat
201035276GPV	Indeterminate	No	"anaphylactic reaction", drug withdrawn
201041966GPV	Indeterminate	No	"anaphylactic shock", no details
2011-016420	Indeterminate	No	"allergic reaction"
2011-090820	Indeterminate	No	"anaphylactic shock", no details
2011-105941	Indeterminate	No	"allergic reaction"
AT-2007-035468	Indeterminate	No	tickle in throat, gag irritation
BR-2006-019257	Indeterminate	No	"allergic reaction"
DE-2004-037302	Indeterminate	No	hyperventilation, erythema, shivering
DE-2005-008140	Indeterminate	No	tickling of the throat
DE-2005-008154	Indeterminate	No	"experienced pressing complaints"
ZA-2007-035469	Indeterminate	No	bronchospasm, BP decreased

In the analysis of anaphylactic reactions, there were differences between the original Sponsor's internal review and the more recent review by the Sponsor's "independent adjudicators" that led to 35 fewer anaphylactic reaction cases overall (from 78 original cases to 45 cases).

The internal reviewers identified 79 cases of anaphylactic reaction, while the independent adjudicators identified 45 cases. The differences in the analyses are summarized in Table 23.

Table 23 Sponsor's Adjudication of Cases of Anaphylactic Reaction

38 Cases Not in Concordance of 79 Anaphylaxis in CR (29-Nov-2012)			2 Yes / 2 IND Cases Not in Concordance out of 79 Anaphylaxis in CR (29-Nov-2012)		
Case Number	**Independent Adjudication**	**Sponsor Adjudication**	**Case Number**	**Independent Adjudication**	**Sponsor Adjudication**
200813805LA	No	Yes	200812881BNE	Yes	No
200818257LA	No	Yes	200942732GPV	Indeterminate	No
200821776GPV	No	Yes	2011-002167	Indeterminate	No
200832838GPV	No	Yes	AT-2006-001317	Yes	No
200919765LA	No	Yes			
200939969GPV	No	Yes			
200940006GPV	No	Yes			
2010-000541	No	Yes			
201018386GPV	No	Yes			
201018670GPV	No	Yes			
201020446LA	No	Yes			
201025167GPV	No	Yes			
201028214GPV	No	Yes			
201036559GPV	No	Yes			
201040744GPV	No	Yes			
2011-016426	No	Yes			
2011-030349	No	Yes			
2011-048218	No	Yes			
2011-063184	No	Yes			
2011-070247	No	Yes			
2011-074882	No	Yes			
2011-110671	No	Yes			
AU-2007-014016	No	Yes			
DE-2004-037302	No	Yes			
DE-2005-009283	No	Yes			
DE-2005-011567	No	Yes			
DE-2006-002815	No	Yes			
DE-2007-004747	No	Yes			
DE-2007-004748	No	Yes			
DE-2007-023890	No	Yes			
DE-2007-030464	No	Yes			
GB-2006-006197	No	Yes			
GB-2007-000740	No	Yes			
NO-2007-008557	No	Yes			
SE-2006-017518	No	Yes			
SE-2006-022330	No	Yes			
SE-2007-002515	No	Yes			
SE-2007-002541	No	Yes			

Table 24 presents a summary of the 38 anaphylactic reaction cases that were not counted by the Sponsor's independent adjudicators but were counted by the Sponsor's original internal reviewers. Table 25 presents a summary of the 4 anaphylactic reaction cases that were not counted by the Sponsor's internal reviewers but were counted by the independent adjudicators

Table 24 38 Cases Not in Concordance of 79 cases of Anaphylactic Reaction assessed by the Sponsor's internal review and cited in the CR of 9-Nov-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200813805LA	No	Yes (ST)	Injection site pain, itching, induration
200818257LA	No	Yes	BP decreased, nausea, sudoresis
200821776GPV	No	Yes (ST)	Cough, dyspnea, BP increased; treated
200832838GPV	No	Yes	Cough, dyspnea, dizziness, treated
200919765LA	No	Yes	dyspnea, cough vomiting, treated
200939969GPV	No	Yes (ST)	Skin erythema, pruritis, treated
200940006GPV	No	Yes (ST)	Cough, dyspnea, chest pain
2010-000541	No	Yes	Cough, face erythema
201018386GPV	No	Yes (ST)	Swollen eyes, tongue, gritty sensation
201018670GPV	No	Yes	cough/dyspnea, BP decreased, dizziness
201020446LA	No	Yes	cough/dyspnea, throat irritation, numbness
201025167GPV	No	Yes (ST)	Asthma-like cough, heat sensation, tingling
201028214GPV	No	Yes	cough, dyspnea, dizziness, sweating
201036559GPV	No	Yes (ST)	cough, dyspnea, feeling of hear
201040744GPV	No	Yes	cough, dizziness, perspiration, dyspnea
2011-016426	No	Yes (ST)	allergic reaction dyspnea, cough attacks
2011-030349	No	Yes (ST)	generalized, mouth, tongue itching
2011-048218	No	Yes	cough, dyspnea, dizziness, sweating
2011-063184	No	Yes (ST)	cough, throat irritation
2011-070247	No	Yes	nausea, erythema, malaise
2011-074882	No	Yes	dizziness,, diarrhea, hypotension,
2011-110671	No	Yes	cough, dyspnea, dizziness, nausea
AU-2007-014016	No	Yes	cough, shivering
DE-2004-037302	No	Yes	hyperventilation, erythema, shivering
DE-2005-009283	No	Yes	cough, flushing, sweat, tremor, dizziness,
DE-2005-011567	No	Yes (ST)	throat irritation, vertigo, tachycardia
DE-2006-002815	No	Yes (ST)	cough, chest pain, dyspnea, eye redness
DE-2007-004747	No	Yes	cough, dyspnea, cyanosis
DE-2007-004748	No	Yes	cough, dyspnea,
DE-2007-023890	No	Yes (ST)	dizziness, tingling, numbness sensation
DE-2007-030464	No	Yes	laryngospasm, dyspnea, cough
GB-2006-006197	No	Yes (ST)	cough, tightness in throat
GB-2007-000740	No	Yes	laryngeal edema, cough, dyspnea,
NO-2007-008557	No	Yes	cough, pruritis, tingling sensation
SE-2006-017518	No	Yes (ST)	itching
SE-2006-022330	No	Yes	angioedema, pruritis, nausea, eye swelling
SE-2007-002515	No	Yes (ST)	urticaria generalized, pruritis
SE-2007-002541	No	Yes	cough, erythema

ST: Special Term only, SII = meets Sampson Criterion Number 2 only

Table 25 2 Yes / 2 IND Cases Not in Concordance out of 79 Anaphylaxis in CR (29-Nov-2012)

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200812881BNE	Yes	No	bronchospasm, cough, wheeze, "flushed"
200942732GPV	Indeterminate	No	Malaise, feel hot, cough, stridor
2011-002167	Indeterminate	No	cough, dyspnea, airway constriction
AT-2006-001317	Yes	No	dyspnea, anxiety

4.4.4 Summary of Search Results and Analysis of the FDA's Adverse Event Reporting System (FAERS) for Immediate Post-injection Reactions with U.S. Approved Injectable Testosterone Products from January 1, 1969 through January 29, 2013

Using the same criteria as were used for identifying cases of severe post-injection reactions (severe POME and anaphylactic reactions) for testosterone undecanoate, FDA conducted a search and analysis of the FDA Adverse Event Reporting System[2] (FAERS) for cases of severe POME and anaphylaxis that occurred immediately post-injection with the U.S. approved injectable testosterone products, testosterone enanthate and testosterone cypionate. The search encompassed the dates January 1, 1969[3] to January 29, 2013.

The search and analysis identified a total of 33 cases of severe post-injection reaction for the 44-year period January 1969 to January 2013. The FDA's analysis determined that 14 of these cases reflected severe POME and 19 were anaphylactic reactions.

Among the identified cases, 4 patients were hospitalized, and 3 patients were reported to have experienced a life-threatening event.

The 33 individual cases are outlined in brief in Table 26 below.

[2] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

[3] AERS implementation date

Table 26 Cases of Severe Post-injection Reactions Identified from A Search of FAERS for U.S. Approved Injectable Tesoterone Products - January 1, 1969 through January 29, 2013

Case #	Receipt	Age	Sex	Event Date	Clinical Manifestation
1	1982	63	M	1982	Dermatitis, eczema, dyspepsia, bronchospasm and obstruction
2	1983	50	M	Oct. 1983	Cough, chest pain, discomfort
3	1986	70	M	05/01/1985	Cough, tongue swelling
4	1990	31	M	4/1/1989	Ulticaria, anaphylactic reaction, bronchospasm and obstruction
5	1991	63	M	3/29/1991	Tongue edema, hypersensitivity, malaise, palpitations
6	1991	33	M	1/1/1991	Laryngeal spasm, edema and obstruction, angioedema, anaphylactic reaction, ulticaria
7	1993	42	F	2/19/1993	Anaphylactic reaction, laryngeal spasm+edema, obstruction, diarrhea, sweating
8	1993	40	M	6/24/1993	Dermatitis, eczema, anaphylactic reaction, bronchospasm+obstruction,
9	1993	47	M	12/3/1992	Anaphylactic reaction. Breathing abnormalities, dyspnea, vasodilation
10	1994	55	M	12/1/1993	Dermatitis, eczema, anaphylactic reaction, angioedema
11	1994	40	M	7/1/1993	Anaphylactic reaction, laryngeal spasm + edema, obstruction, bronchospasm, obstruction, urticaria
12	1994	Unk	M	July 1994	Wheeze, urticaria, difficulty breathing
13	1994	35	M	6/29/1993	Dizzy within a few minutes of injection
14	1995	41	M	2/21/1995	SOB, disoriented POME/Anaphylaxis
15	1995	66	M	10/03/1994	Heaviness in chest 10 min after injection
16	1995	38	M	09/13/1994	Laryngeal spasm and edema, obstruction, anaphylactic reaction, dyspnea, pain
17	1996	Unk	M	1996	SOB, palpitations
18	1997	45	M	8/13/1996	Cough, dizziness, hypertension, tachycardia
19	1997	Unk	M	1997	Respiratory difficulty
20	1998	Unk	M	1998	Cough
21	1998	Unk	Unk	1998	Bronchospasm, obstruction, coughing
22	2000	32	M	7/1/1998	Cough, throat irritation
23	2000	48	M	6/1/1999	Laryngeal spasm, edema obstruction
24	2000	47	M	7/7/1999	Coughing, chills
25	2000	47	M	7/14/1999	Cough, chest pain and discomfort
26	2000	62	M	08/16/2000	Syncope upon injection
27	2007	50	M	05/27/2007	Throat swelling, dyspnea, feeling hot, injection site erythema+pain
28	2008	71	M	12/04/2008	Dyspnea, cough, nausea
29	2010	63	M	08/01/2010	Pain, not breathing right, feeling terrible
30	2011	52	M	3/1/2011	Anaphylactic reaction, pharyngeal edema
31	2012	69	M	04/01/2012	Edema, dyspnea
32	2012	53	M	03/15/2012	Difficulty breathing, hives, facial and peripheral edema
33	2012	20	M	11/19/2012	Paresthesia, tingling, wooziness in head, SOB, dyspnea, malaise, dizziness

4.5 Summary of Safety for Use of Testosterone Undecanoate Injection

The overall assessment based on the above safety findings from clinical trials and postmarketing reports is that testosterone undecanoate intramuscular injection product is associated with severe immediate post-injection adverse reactions, which appear to be both anaphylactic reactions and

severe POME. The clinical concern is based largely on the immediacy and severity of these reactions, in particular, the anaphylactic reactions and POME reactions accompanied by throat tightening, dyspnea, cardiovascular changes, and loss of consciousness. While there are a host of lesser symptomologies, such as cough, throat irritation, flushing, nausea, GI disorders, sweating, etc., it is the cases of anaphylactic reaction and severe POME reactions that constitute our major concern. The characteristics of the above 137 cases of serious post-injection reactions, with their sudden onset of difficulty breathing, their throat tightness/fullness developing into potential airway constriction, cough, flushing, cardiovascular, allergic and constitutional symptoms are clinically impressive. In some cases, patients have reported feeling that they would not survive the event, some became apneic or lost consciousness, some required hospitalization, some received emergent treatment, and some cases were described as life-threatening. Respiratory distress and cardiovascular collapse with loss of consciousness were also reported. Some patients also required resuscitation for a catastrophic event, including treatment for anaphylaxis.

Other than the severe post-injection adverse reactions, the remainder of the safety results from clinical studies as well as the International Postmarketing studies of testosterone undecanoate injection reveals expected adverse reactions associated with the pharmacological action of testosterone (e.g., increasing serum PSA, worsening BPH, increasing hematocrit, weight gain, peripheral edema, change in lipid profiles, acne, breast pain, sweating, depression, etc.), and expected local adverse reactions at the injection site (e.g., injection site reactions).

Overall, safety data associated with the use of this testosterone undecanoate product continue to be concerning based upon the occurrence of severe post-injection reactions.

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) CONSULTATION

Date:	March 22, 2013
To:	Mark Hirsch, MD, Cross Disciplinary Team Leader Division of Reproductive and Urologic Products
From:	Stacy Chin, MD, Medical Reviewer, DPARP
Through:	Anthony Durmowicz, MD, Team Leader, DPARP
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPARP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

General Information

NDA#:	NDA# 22-219
Sponsor:	Endo Pharmaceuticals
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	December 11, 2012
Date Received:	December 19, 2012
Materials Reviewed:	NDA 22-219 Resubmission, DPARP Medical Officer Consultations (4/14/08, 5/27/08, 9/18/08, 5/4/09, 11/24/09, 6/9/11)

Introduction

This Division of Pulmonary, Allergy, and Rheumatology (DPARP) medical officer review outlines the safety concerns of serious post-injection reactions observed with testosterone undecanoate (NDA 22-219) under development for marketing in the United States as an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The Division of Reproductive and Urologic Products (DRUP) requested this consult to help identify and adjudicate reported cases of anaphylaxis and pulmonary oil microembolism [(POME), an adverse respiratory and systemic reaction to the embolization of the oil used in the drug product into the pulmonary microcirculation] events associated with this product's use in the post-marketing setting. The following review covers a brief regulatory history of testosterone undecanoate (also known by tradenames Aveed, Nebido, and Reandron), a discussion of anaphylaxis and POME with case examples of each, and results from the review of spontaneous post-marketing reports for testosterone undecanoate outside of the U.S. For consistency, unless specifically identified otherwise, such as in case reports, the testosterone drug product will be referred by its chemical name, testosterone undecanoate (TU).

Background

TU is an androgen for IM injection indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone such as congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism. The TU drug product contains testosterone undecanoate, 250 mg/mL, in a solution of castor oil and benzyl benzoate. The proposed dose is 750 mg (3 mL) by intramuscular injection (IM) at initiation, 4 weeks, and every 10 weeks thereafter. TU has been approved and marketed in Europe under the trade names Nebido and Reandron since market authorization was granted in November 2003, albeit at a higher recommended dose of 1000 mg (4 mL IM). Its proposed tradename for the US market is Aveed.

The original NDA was submitted on August 24, 2007 by Indevus Pharmaceuticals, Inc. Although TU demonstrated adequate efficacy in terms of serum testosterone parameters, post-marketing reports of medically significant post-injection "coughing fits" and allergic reactions in countries where TU had been approved raised concern. Adverse events characterized by sudden onset of cough, dyspnea, and respiratory distress occurring shortly after injection were also noted in clinical trials. In the total clinical trial population at that time used to support US approval (approximately 600 subjects and 4,000 injections), there were 2 acute post-injection reactions reported. The Applicant had also submitted 66 post-marketing adverse event reports from outside the US of which 28 were categorized as serious adverse events, 12 required emergency medical care (treated with epinephrine, antihistamines, steroids), and 6 required hospitalization. DRUP consulted the Division of Pulmonary and Allergy Products [now the Division of Pulmonary, Allergy and Rheumatology Products, (DPARP)] in April 2008 to review these post-marketing reports identified by the Applicant as POME events to determine if any of the cases might actually be allergic reactions. That review as well as an independent review by FDA-commissioned outside experts determined that 2 of the 66 adverse reactions reported definitely met the clinical criteria for anaphylaxis (further described in a subsequent section of this consultation). Because of the uncertainty surrounding the incidence and etiology of these post-injection reactions, the original NDA application received an "approvable" letter with clinical deficiencies in June 2008. DRUP has maintained that the primary reason for lack of approval was and continues to be the failure to demonstrate that benefits of TU, taken in light of the availability of alternative products for the indication, outweigh the potential risks, namely the serious post-injection reactions due to either anaphylaxis or POME events. Alternatively, the Applicant, while acknowledging that anaphylaxis can and does occur, contends that immediate post-injection reactions are rare and have yet to result in death or permanent disability. In addition, they assert that careful and slow IM injection, as well as a lower injection volume (3 mL compared to the 4 mL dose approved in the rest of the world) are adequate measures to mitigate these reactions. In order to attempt to resolve what was felt to be an impasse between DRUP and the Applicant regarding the risk/benefit profile for TU, DRUP recommended resubmission of the NDA with additional safety data in order to bring the risk/benefit discussion to an Advisory Committee.

For the current NDA submission, the Applicant searched their database of spontaneous post-marketing reports over an 8 year period (November 25, 2003 to November 24, 2011) using agreed-upon search terms for anaphylaxis (Appendix 1) and POME (Appendix 2). The search resulted in the identification of 330 potential anaphylaxis events and 533 potential POME events.

Because the search terms for anaphylaxis were a subset of the search terms for POME, virtually all potential anaphylaxis reports are contained within the 533 potential POME population.

Following is DPARPs evaluation of the post-marketing reports of potential anaphylaxis and POME submitted by the Applicant with a focus on evaluating serious and/or medically important adverse reactions consistent with anaphylaxis or POME. While in most cases, a reasonable determination can be made as to whether an adverse reaction is due to anaphylaxis or severe POME, it should be noted that the similarity of the clinical presentation makes it difficult to distinguish between an allergic or hypersensitivity reaction versus a pulmonary oil embolism in some cases. However, the severity or seriousness of the adverse reaction is not diminished by the lack of an exact etiology.

Anaphylaxis – definition/case identification

Although anaphylaxis has always been regarded as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, there has been no universal agreement on the clinical definition of anaphylaxis or the criteria for diagnosis. Because the lack of specific diagnostic criteria hampered research, created confusion among health care providers, and led to inconsistent diagnosis and treatment of patients, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened meetings in 2004 and 2005 to address this need. The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the US Food and Drug Administration; the European Academy of Allergy and Clinical Immunology; the Australasian Society of Clinical Immunology and Allergy. The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems.[1] It is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening.

The three recommended diagnostic criteria are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c) Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to review all adverse reaction case reports to identify cases consistent with anaphylaxis. DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling criterion 1 above in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. However, based on the knowledge that the components of TU have already been associated with anaphylaxis and/or allergic reactions, one could potentially justify using both criteria 1 and 2 to identify cases of anaphylaxis.

To identify cases of anaphylaxis culled from spontaneous post-marketing reports over an 8 year period (2003-2011) by the use of the agreed-upon anaphylaxis search terms, DPARP reviewed the case narratives of the 330 potential cases of anaphylaxis that resulted from the Applicant's search. When we used the most conservative method for identifying anaphylaxis cases by using only NIAID/FAAN criterion #1 and including cases that reported the adverse reaction as either "anaphylaxis" or "anaphylactoid reaction", we identified 47 cases of anaphylaxis. This number increased to 68 when less restrictive criteria (NIAID/FAAN criteria 1 and 2) were used to identify anaphylaxis. While use of criteria 1 and 2 was more inclusive, a risk is the inclusion of severe adverse reactions that failed to have skin manifestations, which could also represent severe POME as well as anaphylaxis. However, whether these severe adverse reactions are categorized as anaphylaxis or POME does not make them any less severe. The overall number of anaphylaxis cases identified by DPARP is less than the 79 cases of anaphylaxis identified during the Applicant's internal review and reported in the NDA Complete Response submission. There could be several reasons for the discrepancy. The most apparent appears to be our conservative approach in defining anaphylaxis using NIAID/FAAN criterion 1 only while the Applicant seems to have been more liberal in applying the criteria. Additionally, in reaching their overall number, the Applicant appears to have accepted reports of adverse reactions that were broader in nature and included terms such as "hypersensitivity" or "allergic reaction" as reports of anaphylaxis. The interpretation of clinical symptoms in light of NIAID/FAAN criteria can also be somewhat subjective. For example, the presence of throat tightening could be interpreted as a mucocutaneous symptom indicative of edema or, alternatively, as a respiratory symptom. Again, as mentioned above, whether categorized as anaphylaxis or POME does not make the adverse reactions any less severe.

In addition to the post-marketing reports from 2003 through 2011 that were reviewed for anaphylaxis, additional safety data were submitted to the TU NDA in a periodic safety update report covering the time period from November 25, 2011 through April 30, 2012. This report contained adverse reactions reported after the Applicant's data lock and thus were not included

in the post-marketing surveillance database search. Review of adverse reaction case reports in this submission identified an additional 6 (NIAID/FAAN criterion 1) or 8 (NIAID/FAAN criteria 1+2) cases of anaphylaxis bringing the total number of anaphylaxis cases to 53 and 76, respectively.

For the cases of anaphylaxis DPARP identified, 9-14 of the reactions (depending on the criteria used) occurred upon the first exposure to TU. The mechanism for reaction with first exposure is unclear, but might be explained by nonspecific histamine release from drug, complement activation from the drug, or prior sensitization to a component of the TU drug product or another cross-reactive agent. It should be noted that drugs may cause anaphylaxis due to both IgE-mediated and non-IgE mediated etiologies. An example is vancomycin, which may produce both IgE-mediated and non-specific mast cell degranulation and anaphylaxis. Whether IgE-mediated or not, the underlying mechanism does not alter the clinical diagnosis of anaphylaxis and the risk for serious injury or even death.

Following are several representative case narratives for anaphylaxis.

Case 200815625LA (Brazil): After his fifth injection of Nebido (1000 mg/4 mL), this 60 year old male instantaneously experienced an anaphylactic reaction (considered life-threatening) involving throat itching, cough, glottis spasm, and edema. He was treated with serum physiological, adrenalin, Solu-cortef intravenously, and oxygen supplementation for 2 hours and oral Talerc (antihistamine). He was hospitalized under observation and discharged home after 12 hours fully recovered. After the reaction, he discontinued Nebido and started treatment with testosterone dipropionate gel.

Case 200910048BNE (Great Britain): Approximately 1 year and 4 months after initiating treatment with Nebido (1000 mg/4 mL), this 39 year old male experienced anaphylactic shock (considered life-threatening) during Nebido injection. After 2 mL from a 4 mL vial of Nebido had been administered intramuscularly, the patient suddenly complained of throat closing, coughing, and difficulty breathing as well as facial and tongue swelling. The injection was stopped and 0.5 mcg adrenalin was given along with oxygen. Upon arrival to the hospital, adrenalin was repeated (20 minutes following the first dose). He was admitted for further observation and discharged 24 hours later fully recovered. Following this reaction, he discontinued treatment with Nebido.

Case 2011-016767 (Great Britain): Immediately after the second Nebido injection (1000 mg/4 mL), this 42 year old male experienced anaphylactic shock (considered life-threatening). Symptoms included throat tightness, difficulty breathing, cough, and erythematous rash. He received adrenalin, oxygen, Piriton, Efcortesol, and prednisolone. He fully recovered during hospitalization and was discharged home on prednisolone and Piriton.

Case GB-2007-000740 (Great Britain): During the second dose of Nebido (1000 mg/4 mL), this 54 year old male experienced an anaphylactic reaction (considered life-threatening). Halfway through the injection, he developed cough which worsened as the injection continued. Although he was given water, his symptoms progressed to involve difficulty breathing, laryngeal edema, diaphoresis, and near respiratory arrest. His pulse was 48 bpm during the episode. He was given two 0.5 mL doses of adrenalin 1:1000 and oxygen via a re-breathing bag before hospital transfer. He recovered the same day and received no further doses of Nebido.

Potential Anaphylaxis-inciting Agents

When a safety signal for anaphylaxis or hypersensitivity to a drug becomes apparent, one must consider the allergenicity of the individual components of the drug product. As such, DPARP examined the potential for each of the individual components of TU to trigger clinical symptoms consistent with anaphylaxis. TU contains one active ingredient, testosterone undecanoate, and two excipients, castor oil and benzyl benzoate. While no studies have been undertaken to attempt to systematically differentiate the potential cause(s) of anaphylaxis for the specific TU product, both evidence from the literature and individual adverse reaction case reports support the notion that several of the components of TU, including excipients, may be responsible for the cases of anaphylaxis observed.

Testosterone undecanoate

Testosterone undecanoate, the drug substance and active ingredient, is a testosterone ester which forms active testosterone by cleavage of the ester side chain. From review of the literature, we are not aware of reports that the specific testosterone ester, testosterone undecanoate, is associated with immediate hypersensitivity reactions. However, the case report below suggests that testosterone itself (the only common ingredient between the TU injectable product and the Testogel and Andropatch topical testosterone products) may be capable of eliciting an anaphylactic reaction.

Case GB-2007-023826 (Great Britian)

Immediately after TU injection, a 46 year old male experienced anaphylaxis (considered life-threatening) with cough, inspiratory wheeze, tightening of throat, rash on abdomen, and closing of airways. The patient was treated with adrenalin and oral antihistamine. He had no history of asthma, eczema, or atopy, but reported past allergic skin reactions to Testogel and Andropatch requiring discontinuation of both.

Castor oil

Castor oil is derived from the castor seed *(Ricinus communis*). The castor seeds are cold pressed to extract the oil which is then clarified by heat. Although castor seed contains the toxic protein ricin, this protein is denatured and removed during the oil extraction process. The oil itself is a triglyceride composed primarily of ricinoleic acid and is frequently used as a skin-conditioning agent, emulsion stabilizer, and surfactant in cosmetics. In the food industry, food grade castor oil is used in food additives, flavorings, and in packaging. The FDA considers castor oil as "generally recognized as safe and effective" when administered enterally as a laxative. As with the TU product, depot formulations of IM injectable drugs sometimes use vegetable oil vehicles, such as castor oil, to increase storage in fatty tissues of the body and thus prolong drug half-life.

With regard to allergenicity and the potential to cause anaphylaxis, the ricinoleic acid of which castor oil is composed has been implicated as the causative allergen in allergic contact dermatitis case reports.[2-5] Three proteins known to be potent allergens have also been identified as well from the castor seed: Ric c 1, Ric c 2, and allergen 3.[6] The presence of castor seed allergen in castor oil depends upon the purity of the oil and thus the extraction process. A castor oil derivative, polyethoxylated castor oil is also an excipient in many drugs and has been implicated in anaphylactic reactions following cyclosporin and paclitaxel administration.[7-10]

In addition to the allergens noted above, the ricinoleic acid component of castor oil shares similarity in structure with salicylic acid (both are hydroxy acids) and ricinoleic acid has been demonstrated to act on the prostanoid system as well, which suggests the possibility of cross-reaction in persons who are salicylate allergic/sensitive[11]. Following is a case report of a severe adverse reaction and subsequent evaluation in a subject who was later discovered to have aspirin hypersensitivity that may support the concept of such a cross-reaction.

Case DE-2004-037302 and 201040508GPV (Germany): During injection of the first dose of Nebido (1000 mg/4 mL), a 38 year old male developed hyperventilation, hypertension, and pronounced facial erythema without urticaria. In addition, he complained of malaise and shivers. He was treated with prednisolone and cetirizine. He gradually recovered and was discharged home. The following day he continued to feel a sensation of heat in his extremities, malaise, and "fevers", but no rash or urticaria.

As a result of the reaction, he was enrolled in an Applicant-sponsored clinical trial (study IP157-003) designed to assess immediate hypersensitivity reactions in a controlled manner. On evaluation, he had no reaction to skin prick testing with either diluted or undiluted TU (Nebido). He received blinded intramuscular injections of saline placebo and Nebido. He had no reaction to placebo, but upon re-exposure to 0.4 mL of Nebido (1/10th dose), he developed reddening of the skin, hypertension, dyspnea, and flushed feeling. He received corticosteroids and antihistamines according to protocol, and his symptoms resolved within 20 minutes. The patient reported similar hypersensitivity reactions to aspirin in the past leading the allergist involved in the case to believe the reaction was neither IgE-mediated anaphylaxis nor POME, but rather a non-allergic hypersensitivity reaction.

Benzyl benzoate

Benzyl benzoate is a colorless, oily liquid that is rapidly metabolized to benzoic acid and benzyl alcohol. It is widely used as a preservative, a solvent in perfumes, and a component of insecticides and insect repellents in topically applied products and as a flavoring agent in foods and medications. In oil-based vehicles meant for IM depot steroid preparations, it lowers viscosity to improve ease of administration and prevents crystallization of steroids during storage. As a class (benzyl alcohol, benzoic acid, and sodium benzoate), benzoates are recognized to produce "nonimmunologic" contact urticaria and immediate reactions.[12] Following is a well-described published case report of an anaphylactic reaction in an adolescent patient who received the TU product (Reandron) and subsequent evaluation that directly implicates benzyl benzoate as the cause.[13]

Case 200932012GPV (Australia)

A 16-year-old boy with primary hypogonadism due to bilaterally absent testes, but otherwise unremarkable medical history, was converted from monthly intramuscular injections of testosterone esters (Sustanon, Schering-Plough) to depot testosterone undecanoate (Reandron 1000, Bayer). He had significant improvement in his mood fluctuations and energy levels on the depot preparation.

Less than 3 minutes after the third dose administration, he experienced a life-threatening anaphylactic reaction involving generalized urticaria and pruritus, tightening in the throat,

angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough, and dizziness. He was treated with adrenalin, intravenous promethazine, prednisolone, oxygen, and intravenous fluids. He was taken to an emergency department, but was not hospitalized overnight.

Upon further evaluation, skin prick testing revealed a 10x8 mm wheal to Reandron and no reaction to testosterone esters gel, or saline solution control. Skin prick testing to the Reandron components revealed a 10x10 mm wheal to benzyl benzoate and no reaction to either castor oil or testosterone undecanoate alone.

Pulmonary oil microembolism (POME) – definition/case identification

POME is an adverse reaction as a result of direct vascular or lymphovascular delivery of oil-based preparations to the pulmonary microvasculature. It was initially described coincident with procedures which involved large injection volumes of oil such as during lymphangiography, and hysterosalpingography but has also been noted to occur during or immediately after IM injections of oil-based depot injections including other oil-based testosterone preparations (testosterone enanthate).[14-15]

Both the presenting symptoms and severity can be variable, but cough and some degree of dyspnea seem to virtually always be present. POME can be severe; in these cases symptoms such as chest pain, dizziness, profuse sweating, paresthesias, syncope, and circulatory collapse have been noted.

The pathophysiology underlying this phenomenon is postulated to be similar to that observed with the more widely-recognized fat embolism syndrome. Pulmonary oil microembolization leads to transient acute pulmonary hypertension related to mechanical vascular occlusion and immediate respiratory symptoms such as cough and dyspnea. More severe microembolism is likely to result in decreased cardiac output with syncope and collapse. As with fat embolism, release of free fatty acids by the action of pulmonary lipases may also cause an inflammatory reaction and result in lung injury. This may explain why symptoms with severe oil/fat microembolism may be biphasic, initial acute symptoms such as cough dyspnea which resolve relatively quickly followed by return of symptoms later due to the inflammatory effect of free fatty acids to lung microvasculature.[16-18] Although not extensively studied, the management of POME would be the same as that for fat embolism, supportive care until symptoms resolve.

As with the evaluation of anaphylaxis adverse reactions, to identify cases of POME culled from spontaneous post-marketing reports over the 8 year period (2003-2011) by the use of the agreed-upon POME search terms, DPARP and DRUP together reviewed the case narratives of the 533 potential cases of POME that resulted from the Applicant's search. During the review we noted overlap of potential POME with potential anaphylaxis cases. This was likely due to the fact the anaphylaxis search terms were also included in the larger group of search terms used for POME.

The criteria used to identify POME cases were very similar to those of the Applicant except that POME cases were also reviewed for severity. To be categorized as severe, the reaction must have been identified as POME and must have met at least one of the following criteria:

- reported as an serious adverse event

- required hospitalization or emergency department care
- required medical treatment
- involved syncope or decreased blood pressure
- labeled medically important, serious, or life-threatening by the reporter or Sponsor

Using the POME identification and severity grading criteria, of the 533 potential case of POME from the data-base search, we identified 170-191 cases of POME (the range is due to whether the severe reactions meeting NIAID criteria 1 and 2 are classified as anaphylaxis or POME) of which 55-76 met the criteria for being severe. As with the anaphylaxis reports, an additional 6-8 adverse reaction reports of severe POME were identified in the periodic safety update report covering the time period from November 25, 2011 through April 30, 2012, that wasnot included in the Applicant's post-marketing surveillance database search.

Following are several case narratives of what DPARP believes are of severe POME.

Case 201018709GPV (Austria): This 40 year old male experienced circulatory collapse with a fall in blood pressure, cough, and dyspnea (considered serious) immediately after Nebido injection (1000 mg/4 mL). Onset of symptoms occurred 20 seconds after injection and lasted for 30 minutes. He did not suffer from urticaria. He recovered and did not receive medical treatment. The patient started Nebido one year prior to the reaction and had never experienced similar signs or symptoms previously. The treating physician stated that the injection was applied intramuscularly while the patient was in a horizontal position.

Case DE-2005-004016 (Germany): A male patient of unknown age experienced circulatory collapse with several minutes of unconsciousness, nausea, cough, and encopresis (defecation) (considered serious) 15 seconds following Nebido injection (1000 mg/4 mL). The patient had been treated with Nebido once previously but it is unknown if it was tolerated. He recovered but it is unknown over what time frame or if treatment was given. Attempts to contact the involved practice to obtain additional information were unsuccessful.

Case 2011-040546 (Brazil): Approximately 1-2 minutes after Nebido injection (1000 mg/4 mL), this male patient of unknown age experienced adverse reactions considered serious consisting of reduced breathing capacity and increased difficulty breathing, dizziness, vertigo, darkened vision, joint pain, weakness, pallor, profuse sweating, decreased body temperature, and total absence of autonomy (he remained sitting for 15-20 minutes as a result). During the episode the patient thought that he would die as a result of these events. It is not known if any treatment was given. The patient recovered after an unspecified duration. It was not reported if Nebido was used previously.

Case 200919765LA (Honduras): While his first dose of Nebido (1000 mg/4 mL) was still being administered intramuscularly, this 33 year old male started to complain of difficulty breathing which progressed to cyanosis (considered serious). The treating physician stopped the injection and immediately administered intravenous hydrocortisone and chlorpheniramine. Within minutes, the patient improved then began to cry as well as cough and vomit. That evening the patient called the physician and informed him that he was having fever to 40°C which was treated with unspecified NSAIDs and resolved. The treating physician reported that the injection

had been applied slowly and intramuscularly following aspiration. The patient received an additional two doses without problems.

Case 200815181GPV (Germany): Following Nebido injection (1000 mg/4 mL), this 52 year old male developed a heat sensation in his neck, tickle in his throat, severe dyspnea, headache, muscle twitching, and 20 second loss of consciousness (considered serious). He was placed in shock positioning and given normal saline intravenous fluid resuscitation. The patient was hospitalized and underwent intensive care therapy without artificial ventilation. A CCT did not reveal pathological findings. Infarction was excluded and no bleeding was detectable. The next day, about 28 hours later, the patient was discharged. A physician assumed micro fat embolism retrospectively and stated a possible relation to Nebido. He had been on Nebido for 4 years prior to this reaction and has received it subsequently without problem.

Summary

In summary, the potential safety signals (anaphylaxis and severe POME) identified in the original NDA submission and early post-marketing experience of TU are confirmed upon review of additional post-marketing reports.

Review of potential anaphylaxis cases culled from the Applicant's set of search criteria and submitted with the NDA has resulted in the identification of from 47 to 68 cases of anaphylaxis as defined by the NIAID/FAAN criteria, a clinical definition of anaphylaxis that FDA has adopted to assess for anaphylaxis in clinical trials and post-marketing reports since their publication in 2006. The range in the number of cases identified is the result of using the most conservative application of the NIAID/FAAN definition (criterion1 only) or a more inclusive estimate that employs both criteria 1 and 2 to define anaphylaxis, but since there is overlap in the signs and symptoms of anaphylaxis and POME, likely includes a substantial number of severe cases that represent POME. An additional 6-8 cases of anaphylaxis were identified in a periodic safety update report covering the time period from November 25, 2011 through April 30, 2012 that occurred after the Applicant's data lock bringing the total number of anaphylaxis cases to 53 to 76 using NIAID/FAAN 1 or NIAID/FAAN 1+2 criteria, respectively.

In addition to the cases defined as anaphylaxis, there may be additional cases consistent with hypersensitivity reactions that do not meet the anaphylaxis criteria and cannot be distinguished from POME and are classified as such.

Review of potential cases of POME has resulted in the identification of 170-191 total cases of which we consider 55-76 cases to be severe adverse reactions as a result of pulmonary oil embolism. As with anaphylaxis reports, an additional 6-8 adverse reaction reports of severe POME were identified in the periodic safety update report covering the time period from November 25, 2011 through April 30, 2012, that occurred after the Applicant's data lock, which further increases the number of POME cases reported.

The severity of the episodes is, at least in part, due to decreased cardiac output as a result of acute pulmonary hypertension resulting in dizziness, dyspnea and collapse. Because the symptoms associated with POME observed in the TU post-marketing reports have lasted up to

several days and the protracted clinical course reported in patients who have been inadvertently been administered testosterone products intravascularly, it is likely that POME also results in pulmonary inflammatory changes with a similar pathology to that observed in patients with and animal models of fat embolism.

The occurrence of POME events may be dependent on the overall volume of the oil-based injection received. The Applicant has proposed a lower volume (3mL) and therefore, lower dose (750 mg) of TU in the US NDA application than the dose approved elsewhere in the world (4 mL/1000 mg), at least in part, as an attempt to reduce the incidence of and alleviate concern over POME events. However, because only the 4 mL dose is used around the world where TU is approved, there is not enough clinical information to be able to discern if the 3 mL dose may be associated with reduced POME events.

Because the reports of POME events in the literature are sparse and only describe the acute event, the long-term consequences are largely unknown. POME events encompass a wide range of severity from mild cough to severe dyspnea, cyanosis, and loss of consciousness. As mentioned above, pulmonary oil microembolization leads to transient acute pulmonary hypertension related to mechanical pulmonary vascular occlusion and immediate symptoms. More severe microembolism is likely to result in decreased cardiac output with syncope and collapse. Subsequent release of fatty acids in the lung by the action of pulmonary lipases may result in pulmonary inflammation and injury which becomes apparent hours after the initial insult. In cases of a severe POME event, many patients might choose to discontinue treatment. However, many POME events may be less severe in nature and, because they are not severe enough to cause drug discontinuation, might occur repeatedly over time with subsequent exposures. The “harmless” nature of these milder cases of POME is largely speculative since there is no data in the literature to suggest what the long-term cardiopulmonary consequences might be of repeated POME over time. The effects of POME, whether severe acute episodes or mild repeated ones, in patients with concomitant cardiac disease or risk factors are also unknown.

The decision to approve or not approve TU is a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data. The identification of cases of anaphylaxis and POME from post-marketing reports is, by definition, a qualitative analysis since anaphylaxis and severe POME do undoubtedly occur. If a quantitative determination is necessary in order to inform the risk-benefit decision for TU, a large safety study, specifically designed to assess the incidence of anaphylaxis and POME would need to be conducted.

References

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006; 117:391-7
2. Sasseville D, Desjardins M, Almutawa F. Allergic contact dermatitis caused by glycyrrhetinic acid and castor oil. Contact Dermatitis. 2011; 64:168-9.
3. Di Berardino L, Della Torre F. Side effects to castor oil. Allergy. 2003; 58:826.
4. Le Coz CJ, Ball C. Recurrent allergic contact dermatitis and cheilitis due to castor oil. Contact Dermatitis. 2000; 42:114-5.
5. Magerl A, Heiss R, Frosch PJ. Allergic contact dermatitis from zinc ricinoleate in a deodorant and glyceryl ricinoleate in a lipstick. Contact Dermatitis. 2001; 44:119-21.
6. Thorpe SC, Kemeny DM, Panzani RC, McGurl B, Lord M. Allergy to castor bean II. Indentification of the major allergens to castor bean seeds. J Allergy Clin Immunol. 1988;82:67–72.
7. Takamatsu Y, Ishizu M, Ichinose I, Ogata K, Onoue M, Kumagawa M, et al. Intravenous cyclosporing and tacrolimus caused anaphylaxis but oral cyclosporin capsules were tolerated in allogeneic bone marrow transplant recipient. Bone Marrow Transplantation. 2001;28:421-3.
8. Ebo DG, Piel GC, Conraads V, Stevens WJ. IgE-mediated anaphylaxis after first intravenous infusion of cyclosporin. Ann Allergy Asthma Immunol. 2001; 87:243-5.
9. Kuiper RA, Malingre MM, Beijnen JH, Schellens JH. Cyclosporin-induced anaphylaxis. Ann Pharmacother. 2000; 34:858-61.
10. Price KS, Castells MC. Taxol reactions. Allergy Asthma Proc. 2002; 23:205-8.
11. Tunarua S, Althoffa TF, Nüsingb RM, Dienerc M, and Offermannsa S. Castor oil induces laxation and uterus contraction via ricinoleic acid activating prostaglandin EP3 receptors. PNAS 2012; 109:9179–9184.
12. Nair B. Final Report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. Int J Tox. 2001; 20:23-50.
13. Ong GS, Somerville CP, Jones TW, Walsh JP. Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. Case Rep Med. 2012; 2012:384054.
14. Uzun O, Findik S, Danaci M, Katar D, Erkan L. Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. Respirology 2004; 9:34-6.
15. Delatestryl (testosterone enanthate for injection) package insert. Approved December 24, 1953. Accessed at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
16. Textbook of Respiratory Medicine. John Murray and Jay Nadel eds. WB Saunders Co 1988; Chapter 55, Pulmonary Embolism, p. 1322.
17. Peltier LF. Fat embolism, a perspective. Clinical Orthopedics and Related Research July 1988; No. 232:263-270.
18. Russell M, Storck A, Ainslie M. Acute respiratory distress following intravenous injection of an oil-steroid solution. Can Respir J 2011;18:e59-e61.

APPENDIX 1

MedDRA Preferred Terms included in Anaphylaxis Reaction search by category

Anaphylactic/anaphylactoid shock conditions (SMQ)
Acute prerenal failure
Acute respiratory failure
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anuria
Blood pressure immeasurable
Cerebral hypoperfusion
Circulatory collapse
Distributive shock
Grey syndrome neonatal
Hepatic congestion
Hepatojugular reflux
Hepatorenal failure
Hypoperfusion
Jugular vein distension
Multi-organ failure
Myocardial depression
Neonatal anuria
Neonatal multi-organ failure
Neonatal respiratory failure
Organ failure
Propofol infusion syndrome
Renal failure
Renal failure acute
Renal failure neonatal
Respiratory failure
Shock

Anaphylactic reaction (SMQ)
Acute respiratory failure
Allergic oedema
Anaphylactic reaction

Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Asthma
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Bronchial oedema
Bronchospasm
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Chest discomfort
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Cough
Diastolic hypotension
Dyspnoea
Erythema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
First use syndrome
Fixed eruption
Flushing
Generalised erythema
Hyperventilation
Hypotension
Kounis syndrome
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Lip oedema

Lip swelling
Nasal obstruction
Oedema
Oedema mouth
Oropharyngeal spasm
Oropharyngeal swelling
Periorbital oedema
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous
Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Shock
Skin swelling
Sneezing
Stridor
Swelling
Swelling face
Swollen tongue
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria papular
Wheezing

APPENDIX 2

MedDRA Preferred Terms included in POME search by category

Arrhythmia related investigations, signs and symptoms (SMQ)
Bradycardia
Cardiac arrest
Cardiac death
Cardiac telemetry abnormal
Cardio-respiratory arrest
Chronotropic incompetence
Electrocardiogram abnormal
Electrocardiogram ambulatory abnormal
Electrocardiogram change
Electrocardiogram repolarisation abnormality
Electrocardiogram RR interval prolonged
Electrocardiogram U-wave abnormality
Electrocardiogram U-wave biphasic
Gallop rhythm present
Heart rate abnormal
Heart rate decreased
Heart rate increased
Loss of consciousness
Palpitations
Rebound tachycardia
Sudden cardiac death
Sudden death
Syncope
Tachycardia
Tachycardia paroxysmal

Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)
Accelerated idioventricular rhythm
Accessory cardiac pathway
Adams-Stokes syndrome
Agonal rhythm
Anomalous atrioventricular excitation
Arrhythmia
Arrhythmia supraventricular
Atrial conduction time prolongation

Atrial fibrillation
Atrial flutter
Atrial tachycardia
Atrioventricular block
Atrioventricular block complete
Atrioventricular block first degree
Atrioventricular block second degree
Atrioventricular conduction time shortened
Atrioventricular dissociation
Atrioventricular extrasystoles
Bifascicular block
Bradyarrhythmia
Brugada syndrome
Bundle branch block
Bundle branch block bilateral
Bundle branch block left
Bundle branch block right
Cardiac fibrillation
Cardiac flutter
Conduction disorder
ECG P wave inverted
Electrocardiogram delta waves abnormal
Electrocardiogram P wave abnormal
Electrocardiogram PQ interval prolonged
Electrocardiogram PR prolongation
Electrocardiogram PR shortened
Electrocardiogram QRS complex prolonged
Electrocardiogram QT prolonged
Electrocardiogram repolarisation abnormality
Extrasystoles
Heart alternation
Heart rate irregular
Long QT syndrome
Nodal arrhythmia
Nodal rhythm
Pacemaker generated arrhythmia
Pacemaker syndrome
Parasystole
Paroxysmal arrhythmia
Pulseless electrical activity

Reperfusion arrhythmia
Retrograde p-waves
Rhythm idioventricular
Sick sinus syndrome
Sinoatrial block
Sinus arrest
Sinus arrhythmia
Sinus bradycardia
Sinus tachycardia
Supraventricular extrasystoles
Supraventricular tachyarrhythmia
Supraventricular tachycardia
Tachyarrhythmia
Torsade de pointes
Trifascicular block
Ventricular arrhythmia
Ventricular asystole
Ventricular dyssynchrony
Ventricular extrasystoles
Ventricular fibrillation
Ventricular flutter
Ventricular pre-excitation
Ventricular tachyarrhythmia
Ventricular tachycardia
Wandering pacemaker
Withdrawal arrhythmia
Wolff-Parkinson-White syndrome

Ischaemic cerebrovascular conditions (SMQ)
Basal ganglia infarction
Basal ganglia stroke
Basilar artery occlusion
Basilar artery stenosis
Basilar artery thrombosis
Brachiocephalic artery occlusion
Brain stem infarction
Brain stem ischaemia
Brain stem stroke
Brain stem thrombosis
Capsular warning syndrome

Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery bypass
Carotid artery disease
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism
Cerebellar infarction
Cerebellar ischaemia
Cerebral arteriosclerosis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery stenosis
Cerebral artery thrombosis
Cerebral gas embolism
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral revascularisation synangiosis
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vasoconstriction
Cerebral venous thrombosis
Cerebrovascular accident
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular spasm
Cerebrovascular stenosis
Embolic cerebral infarction
Embolic stroke
Inner ear infarction
Ischaemic cerebral infarction

Ischaemic stroke
Lacunar infarction
Lateral medullary syndrome
Millard-Gubler syndrome
Moyamoya disease
Post procedural stroke
Precerebral artery occlusion
Reversible ischaemic neurological deficit
Spinal artery embolism
Stroke in evolution
Thalamic infarction
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Vascular encephalopathy
Vertebral artery occlusion
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Wallenberg syndrome

Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)
Agnosia
Amaurosis fugax
Angiogram cerebral abnormal
Aphasia
Balint's syndrome
Carotid artery aneurysm
Carotid artery dissection
Central pain syndrome
Cerebral aneurysm ruptured syphilitic
Cerebral haemosiderin deposition
Cerebrovascular accident prophylaxis
Charcot-Bouchard microaneurysms
Diplegia
Dysarthria
Hemiparesis
Hemiplegia
Intra-cerebral aneurysm operation

Intracranial aneurysm
Monoparesis
Monoplegia
Paralysis
Paralysis flaccid
Paraparesis
Paraplegia
Paresis
Post stroke depression
Quadriparesis
Quadriplegia
Red blood cells CSF positive
Spastic paralysis
Spastic paraplegia
Superficial siderosis of central nervous system
Visual midline shift syndrome

Asthma/bronchospasm (SMQ)
Allergic bronchitis
Allergic cough
Allergic respiratory disease
Allergic respiratory symptom
Alveolitis allergic
Analgesic asthma syndrome
Asthma
Asthma exercise induced
Asthma late onset
Asthmatic crisis
Bronchial hyperreactivity
Bronchial obstruction
Bronchospasm
Bronchospasm paradoxical
Charcot-Leyden crystals
Forced expiratory volume decreased
Functional residual capacity increased
Hyperventilation
Hypocapnia
Hypoxia
Infantile asthma
Lung hyperinflation

Obstructive airways disorder
Occupational asthma
PCO2 decreased
Peak expiratory flow rate abnormal
Peak expiratory flow rate decreased
PO2 decreased
Prolonged expiration
Pulmonary sensitisation
Reactive airways dysfunction syndrome
Respiratory alkalosis
Reversible airways obstruction
Status asthmaticus
Tachypnoea
Wheezing

Cardiac failure (SMQ)
Acute left ventricular failure
Acute pulmonary oedema
Acute right ventricular failure
Atrial natriuretic peptide abnormal
Atrial natriuretic peptide increased
Brain natriuretic peptide abnormal
Brain natriuretic peptide increased
Cardiac asthma
Cardiac cirrhosis
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiac index decreased
Cardiac output decreased
Cardiac resynchronisation therapy
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac ventriculogram right abnormal
Cardio-respiratory distress
Cardiogenic shock
Cardiomegaly
Cardiopulmonary failure

Cardiorenal syndrome
Cardiothoracic ratio increased
Central venous pressure increased
Chronic left ventricular failure
Chronic right ventricular failure
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Dilatation ventricular
Dyspnoea paroxysmal nocturnal
Ejection fraction decreased
Heart transplant
Hepatic congestion
Hepatic vein dilatation
Hepatojugular reflux
Jugular vein distension
Left ventricular dysfunction
Left ventricular failure
Low cardiac output syndrome
Myocardial depression
Neonatal cardiac failure
Nocturnal dyspnoea
Oedema
Oedema due to cardiac disease
Oedema neonatal
Oedema peripheral
Orthopnoea
Peripheral oedema neonatal
Pulmonary congestion
Pulmonary oedema
Pulmonary oedema neonatal
Right ventricular dysfunction
Right ventricular failure
Scan myocardial perfusion abnormal
Venous pressure increased
Venous pressure jugular abnormal
Venous pressure jugular increased
Ventricular dysfunction
Ventricular dyssynchrony
Ventricular failure

Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
Acute left ventricular failure
Acute prerenal failure
Acute respiratory failure
Adams-Stokes syndrome
Anuria
Blood pressure immeasurable
Cardiac arrest
Cardiac arrest neonatal
Cardiac death
Cardiac fibrillation
Cardiac flutter
Cardio-respiratory arrest
Cardio-respiratory arrest neonatal
Cardiogenic shock
Cardiovascular insufficiency
Cerebral hypoperfusion
Circulatory collapse
Grey syndrome neonatal
Hepatic congestion
Hepatojugular reflux
Hepatorenal failure
Hypoperfusion
Jugular vein distension
Multi-organ failure
Myocardial depression
Neonatal anuria
Neonatal multi-organ failure
Neonatal respiratory failure
Organ failure
Propofol infusion syndrome
Pulse absent
Pulseless electrical activity
Renal failure
Renal failure acute
Renal failure neonatal
Respiratory failure
Shock
Sudden cardiac death

Ventricular asystole
Ventricular fibrillation
Ventricular flutter

Anaphylactic/anaphylactoid shock conditions (SMQ)
Acute prerenal failure
Acute respiratory failure
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anuria
Blood pressure immeasurable
Cerebral hypoperfusion
Circulatory collapse
Distributive shock
Grey syndrome neonatal
Hepatic congestion
Hepatojugular reflux
Hepatorenal failure
Hypoperfusion
Jugular vein distension
Multi-organ failure
Myocardial depression
Neonatal anuria
Neonatal multi-organ failure
Neonatal respiratory failure
Organ failure
Propofol infusion syndrome
Renal failure
Renal failure acute
Renal failure neonatal
Respiratory failure
Shock

Angioedema (SMQ)
Allergic oedema
Angioedema
Auricular swelling

Breast oedema
Breast swelling
Choking
Choking sensation
Circumoral oedema
Conjunctival oedema
Corneal oedema
Drug hypersensitivity
Endotracheal intubation
Epiglottic oedema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Gastrointestinal oedema
Generalised oedema
Genital swelling
Gingival oedema
Gingival swelling
Gleich's syndrome
Hereditary angioedema
Hypersensitivity
Idiopathic urticaria
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Local swelling
Localised oedema
Nasal obstruction
Nasal oedema
Nipple oedema
Nipple swelling
Obstructive airways disorder
Oculorespiratory syndrome
Oedema
Oedema genital

Oedema mouth
Oedema mucosal
Oedema neonatal
Oedema peripheral
Orbital oedema
Oropharyngeal swelling
Palatal oedema
Penile oedema
Penile swelling
Periorbital oedema
Peripheral oedema neonatal
Pharyngeal oedema
Reversible airways obstruction
Scleral oedema
Scrotal oedema
Scrotal swelling
Skin oedema
Skin swelling
Small bowel angioedema
Stridor
Suffocation feeling
Swelling
Swelling face
Swollen tongue
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Tracheostomy
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria papular
Vaginal oedema
Visceral oedema
Vulval oedema
Wheezing

Anaphylactic reaction (SMQ)
Acute respiratory failure
Allergic oedema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Asthma
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Bronchial oedema
Bronchospasm
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Chest discomfort
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Cough
Diastolic hypotension
Dyspnoea
Erythema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
First use syndrome
Fixed eruption
Flushing
Generalised erythema
Hyperventilation
Hypotension
Kounis syndrome
Laryngeal dyspnoea

Laryngospasm
Laryngotracheal oedema
Lip oedema
Lip swelling
Nasal obstruction
Oedema
Oedema mouth
Oropharyngeal spasm
Oropharyngeal swelling
Periorbital oedema
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous
Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Shock
Skin swelling
Sneezing
Stridor
Swelling
Swelling face
Swollen tongue
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria papular
Wheezing

Acute central respiratory depression (SMQ)
Acute respiratory distress syndrome
Acute respiratory failure
Alveolar oxygen partial pressure abnormal
Alveolar oxygen partial pressure decreased
Anoxia
Apnoea
Apnoeic attack
Asphyxia
Blood gases abnormal
Blood pH abnormal
Blood pH decreased
Bradypnoea
Breath holding
Breath sounds abnormal
Breath sounds absent
Capnogram abnormal
Cardiac arrest
Cardiac arrest neonatal
Cardio-respiratory arrest
Cardio-respiratory arrest neonatal
Cardio-respiratory distress
Cardiopulmonary failure
Central-alveolar hypoventilation
Cheyne-Stokes respiration
Cyanosis
Cyanosis central
Death neonatal
Dyspnoea
End-tidal CO2 abnormal
End-tidal CO2 decreased
Hypercapnia
Hypopnoea
Hypoventilation
Hypoxia
Infantile apnoeic attack
Neonatal anoxia
Neonatal asphyxia
Neonatal hypoxia
Neonatal respiratory acidosis

Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory distress syndrome
Neonatal respiratory distress syndrome prophylaxis
Orthopnoea
Oxygen saturation abnormal
Oxygen saturation decreased
Oxygen supplementation
PCO2 abnormal
PCO2 decreased
PO2 abnormal
PO2 decreased
Respiration abnormal
Respiratory acidosis
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory disorder
Respiratory disorder neonatal
Respiratory distress
Respiratory failure
Respiratory fume inhalation disorder
Respiratory gas exchange disorder
Respiratory paralysis
Respiratory rate decreased
Severe acute respiratory syndrome
Sleep apnoea syndrome
Venous oxygen partial pressure abnormal
Venous oxygen partial pressure decreased
Venous oxygen saturation abnormal
Venous oxygen saturation decreased

Immediate type hypersensitivity reactions (BMQ)
Acute respiratory failure
Allergic bronchitis
Allergic cough
Allergic cystitis
Allergic keratitis
Allergic oedema
Allergic pharyngitis

Allergic respiratory symptom
Allergic transfusion reaction
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Application site hypersensitivity
Arthritis allergic
Asthma
Asthmatic crisis
Auricular swelling
Blepharitis allergic
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Bronchial oedema
Bronchospasm
Capillary leak syndrome
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Conjunctival oedema
Conjunctivitis allergic
Corneal oedema
Cough
Diastolic hypotension
Distributive shock
Documented hypersensitivity to administered drug
Drug eruption
Drug hypersensitivity
Drug rash with eosinophilia and systemic symptoms
Dyspnoea
Epiglottic oedema

Erythema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
First use syndrome
Flushing
Generalised erythema
Gingival oedema
Gingival swelling
Hypersensitivity
Hypotension
Infusion site hypersensitivity
Injection site hypersensitivity
Kounis syndrome
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Loss of consciousness
Nasal congestion
Nasal obstruction
Nasal oedema
Neonatal hypotension
Occupational asthma
Oedema
Oedema genital
Oedema mouth
Oedema mucosal
Oedema peripheral
Oral allergy syndrome
Oropharyngeal discomfort
Oropharyngeal spasm
Oropharyngeal swelling
Orthopnoea

Palatal oedema
Periorbital oedema
Peripheral circulatory failure
Pharyngeal oedema
Pruritus
Pruritus allergic
Pruritus generalised
Pulse absent
Pulse volume decreased
Rash
Rash erythematous
Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Reversible airways obstruction
Scleral oedema
Scleritis allergic
Sensation of foreign body
Shock
Skin oedema
Skin swelling
Small bowel angioedema
Sneezing
Stridor
Suffocation feeling
Swelling
Swelling face
Swollen tongue
Syncope
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria papular

Wheezing

Paresthesia and dysesthesia (ME)
Burning sensation
Burning sensation mucosal
Dysaesthesia
Dysaesthesia pharynx
Formication
Hand-arm vibration syndrome
Intranasal paraesthesia
Lhermitte's sign
Oral dysaesthesia
Paraesthesia
Paraesthesia mucosal
Paraesthesia of genital female
Paraesthesia of genital male
Paraesthesia oral
Skin burning sensation
Tinel's sign
Additional preferred terms
Angina pectoris
Atrial parasystole
Blood pressure management
Blood pressure orthostatic decreased
Carotid angioplasty
Cerebral revascularisation
Chest pain
Chills
Cold sweat
Congenital hemiparesis
Cough decreased
CSF bilirubin positive
Diastolic dysfunction
Discomfort
Dizziness
Dizziness exertional
Dizziness postural
Drug administered at inappropriate site
Drug administration error
Dyspnoea at rest

Dyspnoea exertional
Embolism
Embolism arterial
Exertional headache
Eye pruritus
Fat embolism
Fatigue
Feeling abnormal
Feeling cold
Feeling hot
Feeling of body temperature change
Flushing
Head discomfort
Headache
Hot flush
Hyperhidrosis
Immediate post-injection reaction
Incorrect route of drug administration
Injection site urticaria
Internal carotid artery kinking
Lenegre's disease
Malaise
Medication error
N-terminal prohormone brain natriuretic peptide abnormal
N-terminal prohormone brain natriuretic peptide increased
Nausea
Non-cardiac chest pain
Non-cardiogenic pulmonary oedema
Ocular hyperaemia
Oral discomfort
Orthostatic hypotension
Orthostatic intolerance
Painful respiration
Paradoxical embolism
Platypnoea
Pleuritic pain
Post procedural complication
Post procedural discomfort
Post procedural pulmonary embolism
Post-tussive vomiting

Presyncope
Procedural complication
Procedural dizziness
Procedural headache
Procedural hypotension
Procedural nausea
Procedural pain
Procedural vomiting
Pseudoangina
Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Respiratory fatigue
Respiratory rate increased
SI QIII TIII pattern
Spinal artery thrombosis
Systolic dysfunction
Tension headache
Throat irritation
Trepopnoea
Type II hypersensitivity
Type IV hypersensitivity reaction
Unevaluable event
Vasopressive therapy
Ventricular parasystole
Vertebral artery dissection
Vomiting
Vulvovaginal swelling
Wrong technique in drug usage process

MedDRA Preferred Terms included in POME search (alphabetical listing)

Accelerated idioventricular rhythm
Accessory cardiac pathway
Acute left ventricular failure
Acute prerenal failure
Acute pulmonary oedema
Acute respiratory distress syndrome
Acute respiratory failure
Acute right ventricular failure
Adams-Stokes syndrome
Agnosia
Agonal rhythm
Allergic bronchitis
Allergic cough
Allergic cystitis
Allergic keratitis
Allergic oedema
Allergic pharyngitis
Allergic respiratory disease
Allergic respiratory symptom
Allergic transfusion reaction
Alveolar oxygen partial pressure abnormal
Alveolar oxygen partial pressure decreased
Alveolitis allergic
Amaurosis fugax
Analgesic asthma syndrome
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angina pectoris
Angioedema
Angiogram cerebral abnormal
Anomalous atrioventricular excitation
Anoxia
Anuria
Aphasia
Apnoea
Apnoeic attack

Application site hypersensitivity
Arrhythmia
Arrhythmia supraventricular
Arthritis allergic
Asphyxia
Asthma
Asthma exercise induced
Asthma late onset
Asthmatic crisis
Atrial conduction time prolongation
Atrial fibrillation
Atrial flutter
Atrial natriuretic peptide abnormal
Atrial natriuretic peptide increased
Atrial parasystole
Atrial tachycardia
Atrioventricular block
Atrioventricular block complete
Atrioventricular block first degree
Atrioventricular block second degree
Atrioventricular conduction time shortened
Atrioventricular dissociation
Atrioventricular extrasystoles
Auricular swelling
Balint's syndrome
Basal ganglia infarction
Basal ganglia stroke
Basilar artery occlusion
Basilar artery stenosis
Basilar artery thrombosis
Bifascicular block
Blepharitis allergic
Blood gases abnormal
Blood pH abnormal
Blood pH decreased
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure immeasurable
Blood pressure management
Blood pressure orthostatic decreased

Blood pressure systolic decreased
Brachiocephalic artery occlusion
Bradyarrhythmia
Bradycardia
Bradypnoea
Brain natriuretic peptide abnormal
Brain natriuretic peptide increased
Brain stem infarction
Brain stem ischaemia
Brain stem stroke
Brain stem thrombosis
Breast oedema
Breast swelling
Breath holding
Breath sounds abnormal
Breath sounds absent
Bronchial hyperreactivity
Bronchial obstruction
Bronchial oedema
Bronchospasm
Bronchospasm paradoxical
Brugada syndrome
Bundle branch block
Bundle branch block bilateral
Bundle branch block left
Bundle branch block right
Burning sensation
Burning sensation mucosal
Capillary leak syndrome
Capnogram abnormal
Capsular warning syndrome
Cardiac arrest
Cardiac arrest neonatal
Cardiac asthma
Cardiac cirrhosis
Cardiac death
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive

Cardiac failure high output
Cardiac fibrillation
Cardiac flutter
Cardiac index decreased
Cardiac output decreased
Cardiac resynchronisation therapy
Cardiac telemetry abnormal
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac ventriculogram right abnormal
Cardio-respiratory arrest
Cardio-respiratory arrest neonatal
Cardio-respiratory distress
Cardiogenic shock
Cardiomegaly
Cardiopulmonary failure
Cardiorenal syndrome
Cardiothoracic ratio increased
Cardiovascular insufficiency
Carotid angioplasty
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery bypass
Carotid artery disease
Carotid artery dissection
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Central pain syndrome
Central venous pressure increased
Central-alveolar hypoventilation
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism
Cerebellar infarction

Cerebellar ischaemia
Cerebral aneurysm ruptured syphilitic
Cerebral arteriosclerosis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery stenosis
Cerebral artery thrombosis
Cerebral gas embolism
Cerebral haemosiderin deposition
Cerebral hypoperfusion
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral revascularisation
Cerebral revascularisation synangiosis
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vasoconstriction
Cerebral venous thrombosis
Cerebrovascular accident
Cerebrovascular accident prophylaxis
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular spasm
Cerebrovascular stenosis
Charcot-Bouchard microaneurysms
Charcot-Leyden crystals
Chest discomfort
Chest pain
Cheyne-Stokes respiration
Chills
Choking
Choking sensation
Chronic left ventricular failure
Chronic right ventricular failure
Chronotropic incompetence
Circulatory collapse
Circumoral oedema
Cold sweat

Conduction disorder
Congenital hemiparesis
Conjunctival oedema
Conjunctivitis allergic
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Corneal oedema
Cough
Cough decreased
CSF bilirubin positive
Cyanosis
Cyanosis central
Death neonatal
Diastolic dysfunction
Diastolic hypotension
Dilatation ventricular
Diplegia
Discomfort
Distributive shock
Dizziness
Dizziness exertional
Dizziness postural
Documented hypersensitivity to administered drug
Drug administered at inappropriate site
Drug administration error
Drug eruption
Drug hypersensitivity
Drug rash with eosinophilia and systemic symptoms
Dysaesthesia
Dysaesthesia pharynx
Dysarthria
Dyspnoea
Dyspnoea at rest
Dyspnoea exertional
Dyspnoea paroxysmal nocturnal
ECG P wave inverted
Ejection fraction decreased
Electrocardiogram abnormal
Electrocardiogram ambulatory abnormal

Electrocardiogram change
Electrocardiogram delta waves abnormal
Electrocardiogram P wave abnormal
Electrocardiogram PQ interval prolonged
Electrocardiogram PR prolongation
Electrocardiogram PR shortened
Electrocardiogram QRS complex prolonged
Electrocardiogram QT prolonged
Electrocardiogram repolarisation abnormality
Electrocardiogram RR interval prolonged
Electrocardiogram U-wave abnormality
Electrocardiogram U-wave biphasic
Embolic cerebral infarction
Embolic stroke
Embolism
Embolism arterial
End-tidal CO2 abnormal
End-tidal CO2 decreased
Endotracheal intubation
Epiglottic oedema
Erythema
Exertional headache
Extrasystoles
Eye oedema
Eye pruritus
Eye swelling
Eyelid oedema
Face oedema
Fat embolism
Fatigue
Feeling abnormal
Feeling cold
Feeling hot
Feeling of body temperature change
First use syndrome
Fixed eruption
Flushing
Forced expiratory volume decreased
Formication
Functional residual capacity increased

Gallop rhythm present
Gastrointestinal oedema
Generalised erythema
Generalised oedema
Genital swelling
Gingival oedema
Gingival swelling
Gleich's syndrome
Grey syndrome neonatal
Hand-arm vibration syndrome
Head discomfort
Headache
Heart alternation
Heart rate abnormal
Heart rate decreased
Heart rate increased
Heart rate irregular
Heart transplant
Hemiparesis
Hemiplegia
Hepatic congestion
Hepatic vein dilatation
Hepatojugular reflux
Hepatorenal failure
Hereditary angioedema
Hot flush
Hypercapnia
Hyperhidrosis
Hypersensitivity
Hyperventilation
Hypocapnia
Hypoperfusion
Hypopnoea
Hypotension
Hypoventilation
Hypoxia
Idiopathic urticaria
Immediate post-injection reaction
Incorrect route of drug administration
Infantile apnoeic attack

Infantile asthma
Infusion site hypersensitivity
Injection site hypersensitivity
Injection site urticaria
Inner ear infarction
Internal carotid artery kinking
Intra-cerebral aneurysm operation
Intracranial aneurysm
Intranasal paraesthesia
Ischaemic cerebral infarction
Ischaemic stroke
Jugular vein distension
Kounis syndrome
Lacunar infarction
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Lateral medullary syndrome
Left ventricular dysfunction
Left ventricular failure
Lenegre's disease
Lhermitte's sign
Limbal swelling
Lip oedema
Lip swelling
Local swelling
Localised oedema
Long QT syndrome
Loss of consciousness
Low cardiac output syndrome
Lung hyperinflation
Malaise
Medication error
Millard-Gubler syndrome
Monoparesis
Monoplegia
Moyamoya disease

Multi-organ failure
Myocardial depression
N-terminal prohormone brain natriuretic peptide abnormal
N-terminal prohormone brain natriuretic peptide increased
Nasal congestion
Nasal obstruction
Nasal oedema
Nausea
Neonatal anoxia
Neonatal anuria
Neonatal asphyxia
Neonatal cardiac failure
Neonatal hypotension
Neonatal hypoxia
Neonatal multi-organ failure
Neonatal respiratory acidosis
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory distress syndrome
Neonatal respiratory distress syndrome prophylaxis
Neonatal respiratory failure
Nipple oedema
Nipple swelling
Nocturnal dyspnoea
Nodal arrhythmia
Nodal rhythm
Non-cardiac chest pain
Non-cardiogenic pulmonary oedema
Obstructive airways disorder
Occupational asthma
Ocular hyperaemia
Oculorespiratory syndrome
Oedema
Oedema due to cardiac disease
Oedema genital
Oedema mouth
Oedema mucosal
Oedema neonatal
Oedema peripheral
Oral allergy syndrome

Oral discomfort
Oral dysaesthesia
Orbital oedema
Organ failure
Oropharyngeal discomfort
Oropharyngeal spasm
Oropharyngeal swelling
Orthopnoea
Orthostatic hypotension
Orthostatic intolerance
Oxygen saturation abnormal
Oxygen saturation decreased
Oxygen supplementation
Pacemaker generated arrhythmia
Pacemaker syndrome
Painful respiration
Palatal oedema
Palpitations
Paradoxical embolism
Paraesthesia
Paraesthesia mucosal
Paraesthesia of genital female
Paraesthesia of genital male
Paraesthesia oral
Paralysis
Paralysis flaccid
Paraparesis
Paraplegia
Parasystole
Paresis
Paroxysmal arrhythmia
PCO2 abnormal
PCO2 decreased
Peak expiratory flow rate abnormal
Peak expiratory flow rate decreased
Penile oedema
Penile swelling
Periorbital oedema
Peripheral circulatory failure
Peripheral oedema neonatal

Pharyngeal oedema
Platypnoea
Pleuritic pain
PO2 abnormal
PO2 decreased
Post procedural complication
Post procedural discomfort
Post procedural pulmonary embolism
Post procedural stroke
Post stroke depression
Post-tussive vomiting
Precerebral artery occlusion
Presyncope
Procedural complication
Procedural dizziness
Procedural headache
Procedural hypotension
Procedural nausea
Procedural pain
Procedural vomiting
Prolonged expiration
Propofol infusion syndrome
Pruritus
Pruritus allergic
Pruritus generalised
Pseudoangina
Pulmonary congestion
Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Pulmonary oedema
Pulmonary oedema neonatal
Pulmonary sensitisation
Pulse absent
Pulse volume decreased
Pulseless electrical activity
Quadriparesis
Quadriplegia
Rash
Rash erythematous

Rash generalised
Rash pruritic
Reactive airways dysfunction syndrome
Rebound tachycardia
Red blood cells CSF positive
Renal failure
Renal failure acute
Renal failure neonatal
Reperfusion arrhythmia
Respiration abnormal
Respiratory acidosis
Respiratory alkalosis
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory disorder
Respiratory disorder neonatal
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Respiratory fatigue
Respiratory fume inhalation disorder
Respiratory gas exchange disorder
Respiratory paralysis
Respiratory rate decreased
Respiratory rate increased
Retrograde p-waves
Reversible airways obstruction
Reversible ischaemic neurological deficit
Rhythm idioventricular
Right ventricular dysfunction
Right ventricular failure
Scan myocardial perfusion abnormal
Scleral oedema
Scleritis allergic
Scrotal oedema
Scrotal swelling
Sensation of foreign body
Severe acute respiratory syndrome
Shock

SI QIII TIII pattern
Sick sinus syndrome
Sinoatrial block
Sinus arrest
Sinus arrhythmia
Sinus bradycardia
Sinus tachycardia
Skin burning sensation
Skin oedema
Skin swelling
Sleep apnoea syndrome
Small bowel angioedema
Sneezing
Spastic paralysis
Spastic paraplegia
Spinal artery embolism
Spinal artery thrombosis
Status asthmaticus
Stridor
Stroke in evolution
Sudden cardiac death
Sudden death
Suffocation feeling
Superficial siderosis of central nervous system
Supraventricular extrasystoles
Supraventricular tachyarrhythmia
Supraventricular tachycardia
Swelling
Swelling face
Swollen tongue
Syncope
Systolic dysfunction
Tachyarrhythmia
Tachycardia
Tachycardia paroxysmal
Tachypnoea
Tension headache
Thalamic infarction
Throat irritation
Throat tightness

Thrombotic cerebral infarction
Thrombotic stroke
Tinel's sign
Tongue oedema
Torsade de pointes
Tracheal obstruction
Tracheal oedema
Tracheostomy
Transient ischaemic attack
Trepopnoea
Trifascicular block
Type I hypersensitivity
Type II hypersensitivity
Type IV hypersensitivity reaction
Unevaluable event
Upper airway obstruction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria papular
Vaginal oedema
Vascular encephalopathy
Vasopressive therapy
Venous oxygen partial pressure abnormal
Venous oxygen partial pressure decreased
Venous oxygen saturation abnormal
Venous oxygen saturation decreased
Venous pressure increased
Venous pressure jugular abnormal
Venous pressure jugular increased
Ventricular arrhythmia
Ventricular asystole
Ventricular dysfunction
Ventricular dyssynchrony
Ventricular extrasystoles
Ventricular failure
Ventricular fibrillation
Ventricular flutter
Ventricular parasystole
Ventricular pre-excitation

Ventricular tachyarrhythmia
Ventricular tachycardia
Vertebral artery dissection
Vertebral artery occlusion
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Visceral oedema
Visual midline shift syndrome
Vomiting
Vulval oedema
Vulvovaginal swelling
Wallenberg syndrome
Wandering pacemaker
Wheezing
Withdrawal arrhythmia
Wolff-Parkinson-White syndrome
Wrong technique in drug usage process

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date: March 22, 2013

To: Members of Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees

From: Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology (OSE)

Subject: **Briefing Document-Risk Management Considerations**

Product: Aveed (testosterone undecanoate injection)

1 INTRODUCTION

This memorandum summarizes Endo Pharmaceutical Solutions Inc.'s proposed risk evaluation and mitigation strategy (REMS) and provides an analysis of the risk management options to address the risk of serious post-injection reactions with Aveed (testosterone undecanoate) injection.

2 BACKGROUND

2.1 PRODUCT INFORMATION[1]

Aveed is under review for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

The proposed dosing of Aveed consists of an initial intramuscular injection of 3 mL (750 mg), a second 3 mL dose injected 4 weeks later, and then 3 mL injected every 10 weeks thereafter. The sponsor recommends a healthcare provider inject Aveed slowly over 30 to

[1]Endo Pharmaceutical Solutions Inc.'s proposed package insert. Submitted November 29, 2012 to NDA 022219.

60 seconds into the gluteus medius muscle, avoid intravascular injection, and that the patient be observed for 30 minutes after the injection.

Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of refined castor oil (885 mg) and benzyl benzoate (1,500 mg).

The product has been approved outside of the United States since 2003. In Europe, it is available as a 1000 mg/4mL solution for injection.

2.2 RISK EVALUATION AND MITIGATION STRATEGIES[2]

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide (MG) or patient package insert (PPI), a communication plan (CP) to healthcare providers, elements to assure safe use (ETASU), and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.

---

[2] FDA Draft Guidance for Industry – *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, dated September 2009. Available at: http://www fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 BENEFIT/RISK CHARACTERIZATION

3.1 HYPOGONADISM AND TREATMENT OPTIONS

Hypogonadism in men results from a lack of endogenous testosterone. The aim of testosterone replacement therapy (TRT) in men with hypogonadism is to restore or normalize male secondary sexual characteristics (such as beard, body hair, voice) and male sexual behavior, and to promote normal male somatic development (muscle mass, bone). The consequences of long-term testosterone deficiency in hypogonadal men may include decreased muscle mass and strength, decreased sexual function, and osteoporosis.

Primary and secondary hypogonadism are chronic conditions. Patients are treated indefinitely (years to decades) with TRT. Patients can be maintained on the same product throughout treatment. Some men using transdermal testosterone may be switched to parenteral testosterone if their testosterone concentrations are not adequately replaced.

There are a variety of TRT products approved including intramuscular agents (testosterone enanthate, testosterone cypionate),[3] subcutaneous pellets (Testopel), transdermal film (AndroDerm, Testoderm), topical gels (AndroGel, Fortesta, Testim), topical solutions (Axiron), oral medications (methyltestosterone), and mucoadhesive agents (Striant).

3.2 EXPECTED BENEFIT

Aveed confers the expected clinical benefits for a TRT product but requires fewer injections per year compared to other injectable testosterone products. Patients receive an injection every 10 weeks compared to every 2 to 4 weeks.

3.3 SEVERITY OF RISK

Aveed is associated with pulmonary oil microembolism (POME) and anaphylaxis.

- **POME** is thought to be due to lymphovascular microembolization of oil (castor oil component in the injection solution) to the lung causing short-duration reactions characterized by the need to cough, coughing, dyspnea, and/or respiratory distress.[4] These can be mild to severe. The long-term consequences of repeated POME events are unknown. They may be observed more often with Aveed due to the relatively greater injection volume relative to other products that

[3] Testosterone propionate is not currently marketed. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=TESTOSTERONE%20PROPIONATE. Accessed February 26, 2013.

[4] Lee C. Division of Pulmonary and Allergy Drug Products medical officer consultation response. Signed April 21, 2008 by Lee C and Chowdhury B.

contain castor oil.[5] POME may be less likely when oil-based products are injected carefully and slowly and when smaller volumes are injected.[4] However, case reports describe events occurring during the injection using proper injection technique.

- **Anaphylaxis**: Any component of the formulation may cause anaphylaxis. In particular, benzoates as a class are recognized to produce immediate reactions that are either anaphylactoid or anaphylactic.[5] Rate or volume of intramuscular injection would not be expected to influence the rate of anaphylaxis.[4]

Cases of both anaphylaxis and POME also occurred in the clinical trials. Case narratives are not available.

FDA analyzed post-marketing cases occurring outside the US that were reported to Endo. Endo submitted the narratives of these cases as part of their new drug application. All of the cases reported post-marketing generally occurred during or shortly after the injection and occurred after any dose. Clinical differentiation of these events is difficult. No deaths were reported however, some cases required hospitalization and/or emergency department visit. Details regarding the FDA case adjudication and analysis can be found in the Division of Pulmonary, Allergy, and Rheumatology Products clinical review which is included in this background packet.[6]

3.4 RISK IN CONTEXT OF DRUGS IN CLASS

POME and Anaphylaxis

The two approved and available intramuscular testosterone injection products contain oil and one also includes benzyl benzoate. Testosterone enanthate contains sesame oil.[7] The recommended dose of testosterone cypionate (50 – 400 mg testosterone) contains cotton seed oil and 58-460 mg benzyl benzoate. [8] The recommended dose of Aveed (750 mg testosterone) contains 1,500 mg benzyl benzoate.[1]

Testosterone enanthate and testosterone cypionate are labeled (Adverse Reactions section) for hypersensitivity and anaphylactoid reactions. Testosterone enanthate also includes a Precaution to avoid intravascular injection because of "rare post-marketing reports of transient reactions involving urge to cough, coughing fits, and respiratory distress immediately after the injection."[8]

Other serious risks with testosterone products

Topical TRT products are not associated with POME but are associated with the risk of virilization in children resulting from secondary exposure to testosterone. In 2009, FDA

[5] Durmowicz A. Division of Pulmonary and Allergy Drug Products medical officer consultation response. Signed June 13, 2011 by Durmowicz A and Chowdhury B.

[6] Chen S. Division of Pulmonary, Allergy, and Rheumatology Products medical officer consultation.

[7] Delatestryl (testosterone enanthate) injection package insert. www.dailymed nlm.nih.gov accessed February 26, 2013.

[8] Depotestosterone (testosterone cypionate) injection package insert. www.dailymed nlm.nih.gov accessed February 26, 2013.

required a Boxed Warning in the package insert to address this risk and a REMS consisting of a Medication Guide (MG) for distribution to patients. Virilization through secondary exposure is not a concern with intramuscular testosterone products. A 2009 FDA search of the Adverse Event Reporting System (AERS) found no indirect exposure case reports for the intramuscular injection products. Product labeling for the topical testosterone products does not warn about this risk.

4 RISK MANAGEMENT OPTIONS

4.1 ENDO'S PROPOSED REMS

To address the risk of serious post-injection reactions, Endo proposes a REMS consisting of a MG and CP. The CP includes a single Dear Healthcare provider letter. The letter is to be distributed to the following:

- urologists, endocrinologists, and designated primary care physicians, nurses, and physician assistants who prescribe or who are likely to prescriber/administer Aveed
- members of the following professional societies
    - The American Urological Association
    - The Endocrine Society
    - The Sexual Medicine Society of North America

Endo proposes to distribute the letter via US mail or electronically at the time of product approval and 6 months post-approval to the above audiences. In addition, sales representatives will provide it during their first sales call. Endo proposes to review order records and distribute the letter to any identified healthcare provider who has not received the communication for the first 12 months post-approval.

4.2 ADDITIONAL RISK MANAGEMENT OPTIONS

a) Reformulation

If these reactions are due to the excipients, the most effective mechanism to *prevent* the resulting serious adverse reactions is product reformulation. However, this would require the Sponsor to redevelop the product beginning with Phase 1 trials.

Without reformulation, the risk does not lend itself to a definitive plan to *prevent* these adverse events, so the focus of any risk management plan must be on minimizing the severity and sequelae of the event.

b) Communication Efforts or Prescribing Restrictions

- Efforts to inform patients and prescribers about the risk of life-threatening post-injection reactions associated with Aveed, the need for access to resuscitation equipment, the need to observe of patients for a period of time following the injection, and proper administration technique could be required. There is often

little incentive for prescribers to review materials that are not required within a REMS, given the demands on their time and competing priorities.

- Active strategies to better ensure these safe use measures are followed can be required and could include:
    - Limiting prescribing to those prescribers who are enrolled and certified in a REMS program. The prescriber would confirm understanding of the risk and attest that they can manage the resulting adverse events. Distributors and/or pharmacies would need to be enrolled/certified to ensure that Aveed was only dispensed to those certified prescribers.
    - Enrolling patients to ensure that they understand the risk before beginning treatment. Patient enrollment would be cumbersome for Aveed because the product will be distributed directly to prescribers, not by pharmacies to patients.

5 FACTORS CONSIDERED IN DETERMINING THE RISK MANAGEMENT APPROACH

The frequency of occurrence and severity of an identified serious adverse event are two factors that are considered when making decisions about the need for and rigor of a risk management strategy to be implemented for products. Due to a variety of limitations on the data provided by Endo, FDA is not able to determine the incidence of serious post-injection reactions definitively. The reported post-injection reactions are serious and life-threatening in some cases.

The drug's benefit and available therapies are also factors to consider. Aveed does not address an unmet medical need or provide substantial benefit over existing, available treatment options. Rather, there are a variety of other TRT options and dosage forms available.

The disease and patient population must also be considered, as well as what is considered acceptable treatment risks for a disease or condition. Hypogonadism and its complications are important but are generally not considered life-threatening conditions. Depending on the underlying cause, patients may be relatively healthy, making it less acceptable to expose them to serious medication risks.

Because it is not possible to predict who or when patients will experience a serious post-injection adverse event, the risk management approaches are limited to *informing* prescribers and patients about the risk or *restricting distribution* of Aveed to prescribers who attest to understanding the risk, practice in healthcare settings with proper medical equipment to manage the event, and are capable (or have staff/colleagues capable and immediately accessible) of managing the event, and only administer Aveed to patients who are counseled about the risks/benefits and agree to treatment.

Finally, the impact of additional safe use measures on the healthcare system must be considered. A REMS cannot *prevent* post-injection reactions associated with the use of Aveed (although it could mitigate serious outcomes associated with the event through education coupled with access to appropriate supportive measures and treatment). A

strategy that restricts access by requiring enrollment of prescribers, distributors/ pharmacies, and potentially patients imposes substantial burden to these stakeholders.

The Agency discussed these factors and evaluated the merits of restricting distribution; carefully considering the burdens to prescribers, pharmacists, and patients, in light of Aveed's benefits and risks. The Agency is concerned that implementing any one of these restrictive measures or some combination of them for Aveed imposes excessive burden for stakeholders for a drug with limited additional benefit compared to the other treatment options.

6 SUMMARY

FDA has the authority to require a REMS if additional measures beyond labeling are necessary to ensure that the benefits of a drug outweigh the risks. In considering a REMS for Aveed, the primary benefit of Aveed is fewer injections in a patient population who has a variety of other treatment options available. A REMS cannot prevent these potentially life-threatening reactions and safe use restrictions pose substantial burden on stakeholders.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Briefing Document - Epidemiology: Evaluation of Anaphylaxis and Pulmonary Oil Microembolism Reporting Rates

Date:	15 March, 2013
Reviewer(s):	Cynthia Kornegay, Ph.D. Patty Greene, Pharm.D. Division of Epidemiology II
Team Leaders	David Moeny, M.P.H., R. Ph. Grace Chai, Pharm.D. Division of Epidemiology II
Associate Director	Rita Ouellet-Hellstrom, Ph.D., M.P.H. Division of Epidemiology II
Deputy Director:	Laura A. Governale, Pharm.D., MBA Division of Epidemiology II
Subject	Evaluation of reporting rates for pulmonary oil microembolism and anaphylaxis related to administration of intramuscular testosterone undecanoate
Drug Name(s):	Aveed® (testosterone undecanoate)
Application Type/Number:	NDA 022-219
Applicant/sponsor:	Endo Pharmaceuticals Solutions, Inc.
OSE RCM #:	2013-252

TABLE OF CONTENTS

EXECUTIVE SUMMARY 2
1 INTRODUCTION 4
2 REVIEW METHODS AND MATERIALS 6
2.1 Reporting Rates and Incidence Rates 6
2.2 FDA Drug Use Data Sources 6
3 REVIEW RESULTS 6
3.1 US Sales Data- IMS Health, IMS National Sales Perspective™ 6
3.2 US Patient-based Data 7
3.3 Worldwide Drug Use Information - Endo Pharmaceuticals Solutions, Inc. ... 9
3.3.1 Off-label Use 10
3.3.2 OSE/DEPI Comments on Drug Utilization 11
3.4 Reporting Rates 11
3.4.1 Endo Pharmaceutical-Supplied POME and Anaphylaxis Reporting Rates 11
3.4.2 OSE/DEPI Comments on Reporting Rate Calculations 12
3.5 Incidence Rates 14
3.5.1 Sponsor Reported POME Incidence Rates 16
3.5.2 Reported Anaphylaxis Incidence Rates - Endo Pharmaceuticals 18
3.5.3 OSE/DEPI Comment on Reported Incidence Rates 19
4 DISCUSSION OF REPORTING AND INCIDENCE RATES 20
5 CONCLUSIONS 21
6 REFERENCES 22
APPENDIX 1 - CHARACTERISTICS OF INJECTABLE TESTOSTERONE PREPARATIONS 24
Appendix 2: - Drug Use Database Descriptions 26
Appendix 3 – Summary of Studies 27

EXECUTIVE SUMMARY

Aveed® (testosterone undecanoate, TU) is a testosterone replacement product intended for use as a 750 mg/3 ml injection in adult males for conditions associated with testosterone deficiency. TU has been available worldwide since November 2003 as a 1000 mg / 4ml injection product (Nebido) with an indication of confirmed male hypogonadism, but is not approved in the U.S. On April 18th, 2013, an advisory committee meeting will discuss issues related to the U.S. approval of Aveed. Currently, there are two other injectable testosterone products approved in the U.S.; testosterone enanthate (approved in 1953) and testosterone cypionate (approved in 1979). If approved, Aveed will allow for a longer time between injections.

In 2009, FDA issued a "Complete Response" to Endo Pharmaceuticals Solutions (Endo) for Aveed due to cases of anaphylaxis or pulmonary oil microembolism (POME) that occurred worldwide in the postmarketing period for Nebido. There were between five and eight potential cases in the TU clinical trials, and an additional 66 potential cases reported in the postmarketing period. In response, , Endo provided POME and anaphylaxis reporting rates based on worldwide sales of TU. OSE/DEPI was asked to evaluate the validity of these reporting rates, to put these rates into context, and provide an estimate of the use of injectable testosterone in the U.S..

While reporting rates are simple to construct and seemingly intuitive to understand, there are several underlying conditions for both the numerator and denominator that must be met for a valid and interpretable metric. The biggest concern is identifying the appropriate population at risk. To construct a rate, both the cases and the population at risk must be from the same population. This is not the case with TU reporting rates; the cases are from a spontaneous reporting system and the population at risk is represented by sales information. The reporting rates submitted by Endo are actually measuring an association, which does <u>not</u> translate necessarily to a direct relationship between the event and the drug. In summary, there is no way to validate, interpret, or place Endo's reporting rates into context.

In addition to reporting rates, Endo, provided incidence rates for POME and anaphylaxis based on clinical and postmarketing studies of TU. There was one POME case in the study group that received a dose of 750 mg TU (a 3 ml injection), and 8 cases in the group of patients who received a dose of 1000 mg TU (a 4 ml injection). This translates to incidence rates of 3.2 and 4.7 POME cases per 10,000 injections, respectively. There were two cases of anaphylaxis in the in the 1000 mg dose group, for a rate of 1.2 cases per 10,000 TU injections (or 32.4 cases per 10,000 treatment-years of exposure).

When the POME incidence rates were compared to two postmarketing TU studies, the rates remained consistent (4.8 and 5.1 POME cases per 10,000 injections. Although a definitive rate of drug-related anaphylaxis is difficult to establish, the rate seen in the TU clinical and postmarketing trials is significantly higher than published rates of 0.8 to 5 cases per 10,000 treatment-years (15). While Endo is aware of these rates, none of the reviewed documents indicate that a serious

attempt was made to reduce or eliminate either POME or anaphylaxis beyond reducing the proposed dose for the U.S. market.

In summary, Endo's failure to characterize TU use accurately especially for the 750 mg product, the consistent high POME and anaphylaxis incidence rates reported in the clinical and postmarketing databases, and Endo's unwillingness to acknowledge or effectively address possible increased rates is concerning. It is unlikely that the incidence of either POME or anaphylaxis associated with TU has decreased in the postmarketing period. The risk of serious and life-threatening events should be carefully weighed against the benefit of a potentially longer injection-free period, particularly given the availability of multiple alternatives to TU, including other injectable testosterone preparations and other dose forms.

1 INTRODUCTION

Aveed® (testosterone undecanoate, TU) is a testosterone replacement product intended for use as a 750 mg/3 ml injection in adult males for conditions associated with testosterone deficiency. TU is authorized to be marketed in 90 countries and is available in 72 countries worldwide as a 1000 mg / 4ml injection product marketed as Nebido. It is not approved for use in the U.S. An upcoming advisory committee meeting, on April 18th, 2013, will discuss issues related to the U.S. approval of Aveed.

Nebido is given as an intramuscular injection approximately every 12-14 weeks. In the European Union (EU), the dose is 1000 mg or 4 ml per injection. The proposed dose in the U.S. is 750 mg or 3 mg per injection, given at the start of therapy, 4 weeks later, and approximately every 10 weeks thereafter. There are currently two other injectable testosterone products approved for use in the U.S., Delatestryl® (testosterone enanthate) and Depo Testosterone® (testosterone cypionate). The dose regimen for testosterone replacement for both of these drugs is 50 mg – 400 mg per injection (every two to four weeks).

Male testosterone deficiency is commonly a symptom of a condition called hypogonadism, which can be either primary or secondary. Primary hypogonadism (PH) is caused by testicular disease, and can be caused by congenital disorders, testicular cancer (or its treatment), infection, or high doses of certain antibiotics (4, 8). The estimated prevalence of primary hypogonadism is one in 10,000 men (8).

Secondary hypogonadism, or hypogonadotropic hypogonadism (HH), is a more common disorder. In contrast to PH, it stems from a congenital or acquired impairment of the pituitary gland (8). Causes of acquired HH include age, obesity, type II diabetes, strenuous exercise, eating disorders, malnutrition, traumatic brain injury, chronic diseases, and cancer(8). As testosterone levels decrease with age, the prevalence of HH increases(12). Morley et al compared three studies of hypogonadism, and found that in men aged 40 to 59 years, the prevalence was between 2% and 30%(12). However, in men aged 70 to 79 years, the prevalence ranged from 34% to 70%. Giagulli et al estimated that while 30% of men between the ages of 40 and 60 have HH, only 6% to 12% are symptomatic. In addition, approximately 5% of all men with some form of hypogonadism are treated(4).

Symptoms of hypogonadism (either primary or secondary) vary widely in type and severity depending on the age at which the condition manifests. Prenatal hypogonadism can result in micropenis, hypospadias, or cryptorchidism. If the condition strikes in the early teens, it may manifest as delayed puberty, eunochoidal body type, scant body hair, a high-pitched voice, or small testicles, penis, and prostate. Adult-onset hypogonadal symptoms include loss of libido, body hair, energy, muscle mass, and strength, low sperm count and shrinking testes, gynecomastia, weight gain, depression, sleep disturbance, hot flushes, osteoporosis and low-trauma fractures, and an inability to concentrate. The standard treatment for both primary and secondary hypogonadism is testosterone replacement therapy (4, 8, 12).

Worldwide, injectable TU marketed as Nebido was approved in 2003 for the treatment of testosterone therapy in confirmed male hypogonadism. (Oral TU has been available worldwide since the mid-1970's (6). Each single-dose vial of Nebido contains 1000 mg of TU in a 4 ml dose. The other ingredients are castor oil and benzyl benzoate, a preservative. Long-term, Nebido is administered as a gluteal injection every 10-14 weeks after the initial doses, while the proposed dose schedule is every 10 weeks for Aveed. TU is not intended for use in children, adolescents, or womens, and should only be used after the patient's hypogonadism has been confirmed with laboratory tests(1).

For reference, in the US, two other injectable testosterone products, Delastryl® (testosterone enanthalate or TE), and Depo-Testosterone® (testosterone cypionate or TC), are currently available. TE was approved in the US in 1953. A 5 ml, multi-dose vial holds up to 5 doses of TE at 200 mg/ml. Other ingredients are sesame oil and chlorobutanol, a preservative. TE indicated for hypogonadism and delayed puberty in males, and inoperable metastatic mammary breast cancer in females. TE is administered every two to four weeks, depending on dosage and indication, into the gluteal muscle. TE is a pregnancy category X and a schedule III controlled substance. It carries warnings for hypercalcemia, hepatic conditions (including cancer), prostate hyperplasia and cancer, edema, gynecomastia, and compromised adult stature when used for delayed puberty(3) .

TC was approved in the US in 1979. TC is available in 10 ml, multi-dose vials with 200 mg of TC per ml. Additional ingredients are cottonseed oil, benzyl benzoate, and benzyl alcohol as a preservative. The only indications for TC are the treatment of primary or hypogonadal (i.e., secondary) hypogonadism in men. TC carries the same warnings and classifications as TE as well as an additional warning against the use to enhance athletic performance(14).

The primary safety concerns associated with injectable TU, TE, and TC are the acceleration of sub-clinical prostate cancer and benign prostatic hyperplasia.

Appendix 1 provides a table that summarizes the characteristics of all three injectable testosterone preparations.

If approved, Aveed will allow for longer periods between injections compared to the two currently available testosterone products although shorter than Nebido. FDA issued a "Complete Response" to Endo in 2009 due to cases of anaphylaxis or pulmonary oil microembolism (POME) that occurred worldwide in the postmarketing period for Nebido. There were between five and eight potential cases in the TU clinical trials, and an additional 66 potential cases reported to Endo in the postmarketing period(7). Endo has provided reporting rates for both POME and anaphylaxis based on estimated sales of TU in the documents reviewed for this assessment. OSE/DEPI was asked to evaluate the validity of these reporting rates and provide an estimate of the use of injectable testosterone in the U.S. to put these rates into context.

2 REVIEW METHODS AND MATERIALS

2.1 REPORTING RATES AND INCIDENCE RATES

The following sponsor documents were reviewed for this report:

- Periodic Safety Update Report 9, Nov. 25th 2009 – Nov. 24th 2010 (PSUR 9, dated Jan 2011)
- PSUR 10, Nov. 25th 2010 – Nov. 24th 2011, dated Jan 2012
- PSUR Addendum Report, Nov. 25th 2011 – April 30th 2012, dated Jun 2012
- Aveed Summary of Clinical Safety (Section 2.7.4), dated Oct 2012
- Aveed Clinical Overview (Section 2.5), dated Nov 2012

FDA background information was obtained from:

- Cross-Discipline Team Leader Memo, NDA 22-219, signed Nov. 30, 2009
- REMS Review, Aveed®, NDA 22-219, OSE RCM #2011-1429, signed Sep. 30, 2011
- Nebido® EU-Safety Risk Management Plan, dated Jan 2013

In addition, PubMed was searched for articles describing TU studies, as well as case reports involving injectable TU use.

2.2 FDA DRUG USE DATA SOURCES

To assess the feasibility of determining use for the older testosterone products as potential comparators to the TU, the IMS Health, IMS National Sales Perspective™ database was searched. National estimates of the number of packages (eaches) sold for testosterone products by dosage formulation from manufacturers into retail and non-retail markets were retrieved for the years 2008 through 2012. Sales data represent the amount of product sold from manufacturers to the "back door" of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; sales data do not reflect what is being sold or administered to patients directly.

The Source Healthcare Analytics' ProMetis Lx® database was also searched to determine the nationally estimated number of patients with a prescription claim for testosterone cypionate (TC) and testosterone enanthate (TE) injection by patient age and sex in the outpatient retail pharmacy setting for the years 2009 through 2012.

3 REVIEW RESULTS

3.1 US SALES DATA- IMS HEALTH, IMS NATIONAL SALES PERSPECTIVE™

US sales data were not available as far back as 1953 so comparisons of the older products with TU cannot be made. Nonetheless, current information on sales and patient use in the US is provided for context.

Table 1 displays the nationally estimated number of packages (bottles, cartons or vials) sold for testosterone products by dosage formulation from manufacturers to U.S. retail and non-retail channels of distribution between 2008 through 2012.

Although sales of all testosterone products increased by 27% from year 2008 to 2011, there was a decrease (-9%) from year 2011 to 2012, primarily due to a decrease in sales of topical testosterone products. Approximately 88 million packages were distributed nationwide for testosterone products in year 2012, a net increase of 16% since year 2008. Sales of testosterone injection products accounted for 6% of total sales in year 2012.

Sales of testosterone injection products increased 3-fold from 1.6 million vials sold in 2008 to approximately 5.2 million vials sold in year 2012. The average percent change in sales by year of testosterone injectable products was approximately 35% during each year between 2008 and 2012 (data not shown). Sales data during year 2012 indicated that approximately 55% of testosterone vials (Eaches) were distributed to outpatient retail pharmacies; 24% were to non-retail settings; and 21% were to mail-order/specialty pharmacies.[1] Since the injectable testosterone is distributed primarily to outpatient pharmacies, outpatient retail pharmacy utilization patterns were used to obtain national patient estimates. Non-retail and mail-order pharmacy data were not included in this analysis.

Table 1: Sales of testosterone products in packages sold (bottles, cartons, or vials), by dosage form, to all U.S. channels of distribution, Y2008-2012

	Year 2008		Year 2009		Year 2010		Year 2011		Year 2012		Y2008-2012	
	Packages (N)	*Share %*	Packages (N)	*Share %*	Packages (N)	*Share %*	Packages (N)	*Share %*	Packages (N)	*Share %*	Packages (N)	*Share %*
TESTOSTERONE TOTAL	76,277,658	*100.00%*	84,764,839	*100.00%*	94,047,326	*100.00%*	97,002,698	*100.00%*	88,276,674	*100.00%*	440,369,195	*100.0%*
T TOPICALS	74,323,170	*97.4%*	82,231,924	*97.%*	90,797,950	*96.5%*	92,684,114	*95.6%*	82,662,859	*93.6%*	422,700,017	*96.0%*
I INJECTABLES	1,551,293	*2.0%*	2,090,855	*2.5%*	2,768,703	*2.9%*	3,833,685	*4.0%*	5,160,618	*5.9%*	15,405,154	*3.6%*
J INSERTS/IMPLANTS	374,219	*0.5%*	413,659	*0.5%*	451,540	*0.5%*	454,663	*0.5%*	426,153	*0.5%*	2,120,234	*0.5%*
D DERMATOLOGICALS	9,747	*0.0%*	12,303	*0.0%*	13,849	*0.0%*	12,597	*0.0%*	12,657	*0.0%*	61,153	*0.0%*
O ORALS	9,513	*0.0%*	8,042	*0.0%*	7,697	*0.0%*	7,691	*0.0%*	7,422	*0.0%*	40,365	*0.0%*
Y ALL OTHERS	9,716	*0.0%*	8,056	*0.0%*	7,587	*0.0%*	9,948	*0.0%*	6,965	*0.0%*	42,272	*0.0%*

Source: IMS Health, IMS National Sales Perspectives™, Year 2008-2012, extracted January 2013 File: NSPC 2012-2713 Testosterone by form 3-8-13.xls

3.2 US PATIENT-BASED DATA

Table 2 and Figure 1 provide the nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate (TC) and testosterone enanthate (TE), stratified by patient age, from U.S. outpatient retail pharmacies for years 2009 through 2012. Overall, the number of patients with at least one prescription claim for injectable testosterone product more than doubled from approximately 328,000 patients in year 2009 to 796,000 patients in year 2012. Throughout this time period, patients 50+ years of age accounted for slightly more than half of patients using testosterone injections

[1] IMS Health, IMS National Sales Perspectives™. Year 2012. Extracted March 2013. File: NSPC 2013-252 Inj Test by channel 3-4-13.xls

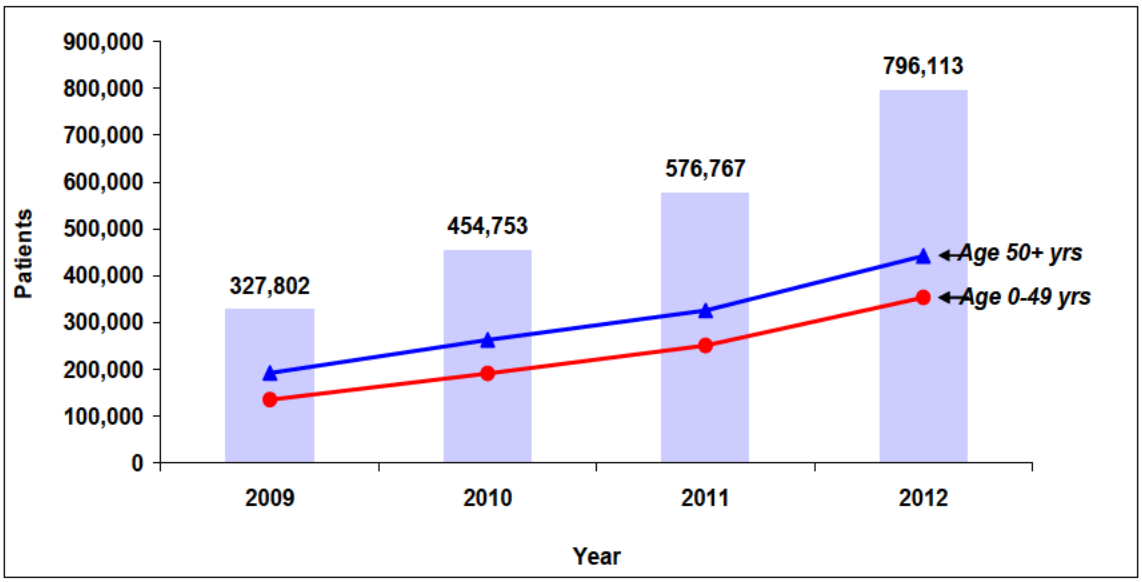
compared to patients 0-49 years of age. Between both age groups, the absolute number of patients, 0-49 years and 50+ years, more than doubled from year 2009 to year 2012.

Table 2: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, by patient age, in U.S. outpatient retail pharmacies, years 2009-2012

	2009		2010		2011		2012	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
Injectable Testosterone	**327,802**	***100.0%***	**454,753**	***100.0%***	**576,767**	***100.0%***	**796,113**	***100.0%***
Age 0-49 yrs	**135,394**	***41.3%***	**191,556**	***42.1%***	**250,965**	***43.5%***	**353,703**	***44.4%***
<30 yrs	18,520	*13.7%*	24,758	*12.9%*	30,198	*12.0%*	38,262	*10.8%*
30-39 yrs	38,123	*28.2%*	54,906	*28.7%*	73,472	*29.3%*	105,501	*29.8%*
40-49 yrs	78,751	*58.2%*	111,892	*58.4%*	147,295	*58.7%*	209,940	*59.4%*
Age 50+ yrs	**192,393**	***58.7%***	**263,177**	***57.9%***	**325,783**	***56.5%***	**442,382**	***55.6%***
50-59 yrs	90,403	*47.0%*	126,617	*48.1%*	160,898	*49.4%*	222,626	*50.3%*
60-69 yrs	64,401	*33.5%*	87,790	*33.4%*	108,241	*33.2%*	146,108	*33.0%*
70+ yrs	37,590	*19.5%*	48,770	*18.5%*	56,645	*17.4%*	73,648	*16.6%*
Unspecified Age	15	0.0%	20	0.0%	19	0.0%	29	0.0%

Source Healthcare Analytics' ProMetis Lx®. Years 2009-2012. Extracted March 2013.File Name: SHALX 2013-252 Testosterone Inj 3-6-13.xls

Figure 1: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, in U.S. outpatient retail pharmacies, years 2009-2012



Source Healthcare Analytics' ProMetis Lx®. Years 2009-2012. Extracted March 2013.

Table 3 provides the nationally estimated number of patients with at least one prescription claim for injectable testosterone products, stratified by patient age and sex, aggregated for years 2009 through 2012. Patients 50-59 years of age accounted for slightly more than a quarter of patients (28% of patients), followed by patients 40-49 years (25% of patients), and 60-69 years (19% of patients). Throughout this time period, male patients accounted for the majority of patients (96% of patients) with at least one prescription claim for testosterone injection. Among patients younger than 30 years old, there was a slightly higher proportion of female patients (13%) compared to all other age groups. Females accounted for 5% or less of patients overall.

Table 3: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, by patient age and sex in U.S. outpatient retail pharmacies, years 2009-2012 aggregated

	2009-2012							
	Total		Males			Females		
	Patient Count	*Share*	Patient Count	*Vert. Share*	*Horiz. Share*	Patient Count	*Vert. Share*	*Horiz. Share*
	N	%	N	%	%	N	%	%
Injectable Testosterone	1,222,040	*100.0%*	1,166,933	*100.0%*	95.5%	55,107	*100.0%*	*4.5%*
Age <30 yrs	68,537	*5.6%*	59,688	*5.1%*	87.1%	8,849	*16.1%*	*12.9%*
30-39 yrs	158,382	*13.0%*	150,392	*12.9%*	95.0%	7,990	*14.5%*	*5.0%*
40-49 yrs	310,715	*25.4%*	297,195	*25.5%*	95.6%	13,520	*24.5%*	*4.4%*
50-59 yrs	335,458	*27.5%*	320,832	*27.5%*	95.6%	14,626	*26.5%*	*4.4%*
60-69 yrs	226,258	*18.5%*	219,342	*18.8%*	96.9%	6,916	*12.6%*	*3.1%*
70+ yrs	122,650	*10.0%*	119,443	*10.2%*	97.4%	3,207	*5.8%*	*2.6%*
Unspecified Age	41	*0.0%*	41	*0.0%*	100.0%	0	*0.0%*	*0.0%*

Source Healthcare Analytics' ProMetis Lx®. Years 2009-2012. Extracted March 2013.File Name: SHALX 2013-252 Testosterone Inj 3-6-13.xls

3.3 WORLDWIDE DRUG USE INFORMATION - ENDO PHARMACEUTICALS SOLUTIONS, INC.

Information on the total sales of TU by vial is provided in the Endo's Summary of Clinical Safety and the EU Safety Risk Management Plan documents. Table 4 shows the total and the percent change in sales by year for 2003 through 2012. In the Summary of Clinical Safety, Endo reported total sales of 3,107,652 vials from November 25, 2003 to November 24, 2011. The EU Risk Management Plan states that 4,121,809 vials were sold between November 2003 and November 2012. This indicates an increase of 32% between 2011 and 2012, which is substantially larger than the increases seen from previous years. Endo does not note nor explain this sudden increase.

Table 4: Worldwide TU Sales by ampule, November 2003 – 2012*

Year	Total Ampules	Change from Prior Year
2003-2008	1,014,992	
2008-2009	587,474	14%
2009-2010	671,668	14%
2010-2011	767,505	14%
2011-2012**	1,007,405	31%
Total 2003-2011	3,114,404	
Total 2003-2012**	4,121,809	

*Adapted from Endo's Summary of Clinical Safety, pp161-182
** Adapted from Endo's EU Safety Risk Management Plan, pp 15-16

In addition, Endo supplied IMS Health prescription information between June 2007 and July 2008 for a selected number of countries in the EU Safety Risk Management plan (page 17). **The following data should be interpreted with caution, as the use profile in the 5 countries was not verified in any way with the use profile in the other countries, and may not be representative of Nebido use in the other countries where it is approved.** Germany, France, Italy, Spain, and the UK combined had 147,403 Nebido prescriptions during this time. Ninety-six percent of these prescriptions were for men whereas 4% (N=5702) prescriptions were for women. All of the female and 85% of the male prescriptions were for patients aged 21 to 64 years old. Among men, about 2% of prescriptions (N=2492) were for patients aged 16 to 20 years old, and the remaining 13% were for men over the age of 65 years.

3.3.1 Off-label Use

The EU Safety Risk Management Plan presented by Endo briefly discusses abuse and off-label use of TU (pages 43-46). The biggest potential source of abuse is use as a performance-enhancing drug among body builders and athletes. Although it is difficult to assess the level of anabolic steroid use as abuse, estimates range from 6% in high school athletes to almost 100% in body builders(13, 16). Endo believes that both the intramuscular administration and the length of time TU stays in the body, however, serve to discourage would-be abusers. In addition, the Endo states that additional measures designed to minimize theft and diversion of TU are in place, but do not describe these measures further.

According to the IMS Health data supplied by Endo, approximately 75% of TU prescriptions were for approved indications, while the intended indication could not be determined for 15%. Based on the available data, IMS concluded that 10% of the undetermined prescriptions were for off-label indications for Nebido, the majority of which were for unspecified ovarian and pituitary disorders in women, gender-identity disorder in men, and prostate hyperplasia. There was no evidence of use in children under the age of 16 years in the IMS indication data provided.

3.3.2 OSE/DEPI Comments on Drug Utilization

Endo's primary source of drug utilization data is worldwide wholesale sales of Nebido. Presumably, this method of estimating patient exposure was chosen to capture use information from the large number of countries in which Nebido is marketed and to compensate for the inability to obtain actual exposed patient counts. Obtaining estimates for the number of patients exposed to a drug administered in physician offices is difficult in many countries due to the varying reimbursement methods, and the inability to collect information on physician activities. Furthermore, in certain populations such as athletes, use of anabolic steroids such as Nebido for performance enhancement has been documented. It is plausible that a substantial proportion of anabolic steroids used for performance enhancement are obtained without prescriptions or a doctor's order, but that adverse events may be reported if the patient seeks medical attention. Therefore, while imprecise, Endo's method of estimating patient exposure is likely the best that can be accomplished to assess postmarketing risks.

The FDA has provided U.S. data for the other products in the testosterone market to provide trends in the market and to gain insight into the potential patient exposure that would be expected if marketing approval for Aveed is granted. An increase was seen in each database. U.S. sales (IMS) and patient utilization (ProMetis Lx) of TE and TC has increased approximately 35% between 2011 and 2012, and a similar increase (32%) in the worldwide sales of Nebido (IMS) was seen in the data reported by Endo. The reason for both increase in use of TE and TC in the U.S. and the large worldwide increase for Nebido is unknown but is likely due to increased marketing.

3.4 REPORTING RATES

3.4.1 Endo Pharmaceutical-Supplied POME and Anaphylaxis Reporting Rates

To support their application, the Endo provided reporting rates for anaphylaxis and POME for 2008 through 2012. Endo calculated the denominator for the reporting rate using the total number of 1000mg/4ml Nebido vials sold worldwide for the year in question. Endo assumed that each injection lasted an average of 12 weeks, and that patients received 4.3 injections per year. Years were measured from November 25th to November 24th of the next year, coinciding with the date of approval for the drug. Reporting rates were obtained by dividing the confirmed number of cases by the calculated total of person- (or treatment-) years of exposure for each year.

Tables 5 and 6 show the reporting rates for confirmed POME and anaphylaxis between 2004 and 2011. The reporting rate remained constant between 2008 and 2011, although sales of Nebido increased each year. A partial report, covering November 24th 2011 through April 30th, 2012 found five new POME cases and three cases of anaphylaxis (not included in the reporting rate calculations). In addition, in 2010, Endo reported 21 confirmed cases total of POME and anaphylaxis combined, resulting in a reporting rate of 0.4 per 10,000 treatment-years.

Table 5: Sponsor-reported TU POME reporting rates per 10,000 treatment-years

Year(s)	Number of POME Cases	Total Vials Sold	Total Patient-Years	Reporting Rate per 10,000 Treatment-Years	Reporting Rate per 10,000 injections
2004-10*	138	1,953,902	454,396	3.0	7.1
2008-9	45	587,474	136,622	3.3	
2009-10	189 suspected				
	34 confirmed	671,668	156,202	2.2	0.5
2010-11	63 suspected				
	57 confirmed	767,505	178,489	3.2	0.7

Adapted from PSUR 9, pp 33-44 and PSUR 10, pp 30-33
*Time period Jan 1 2004 through March 30 2010 and Table 9-1

Table 6: Sponsor-reported TU anaphylaxis reporting rates per 10,000 treatment-years

Year(s)	Number of Anaphylaxis Cases	Total Vials Sold	Total Treatment-Years	Reporting Rate per 10,000 Treatment-Years	Reporting Rate per 10,000 injections
2003-8	4	1,014,992	336,045*	0.1	0.04
2008-9	9	587,474	136,621	0.7	0.20
2009-10	23 suspected				
	12 included**	671,668	156,202	0.7	
2010-11	7	767,505	178,489	0.4	0.10

Adapted from PSUR 9, pp 49-62 and PSUR 10, pp 33-41
**This changed to 11 cases in the 2010-11 PSUR, although the rate did not change

3.4.2 OSE/DEPI Comments on Reporting Rate Calculations

Endo provided reporting rates for both POME and anaphylaxis covering the entire marketing period, most likely for Nebido. For POME, the reporting rate has remained relatively stable since marketing; between 3.0 and 3.3 cases per 10,000 treatment-years for each calendar year, (2004-2010 are condensed). Reporting rates per injections follow a similar trend although the rates are generally lower.

The reporting rates for anaphylaxis show a little more variation. For the first four years of marketing, the rate is 0.1 cases per 10,000 treatment-years. The rate increased to 0.7 cases per 10,000 treatment years in 2008, and dropped to 0.4 cases per 10,000 treatment years in 2011. Reporting rates per injection follow a similar trend although the rates are generally lower. Endo does not attempt to provide an explanation for changes in reporting rates over time. Instead, Endo merely points out that the prescribing information describes both conditions, notes the difficulty of distinguishing POME from anaphylaxis in this particular setting and questions whether they occur separately or in combination. The absolute rate of change for vials sold is consistent until 2011-12 (a 31% increase), however, the same is not observed for reports of both POME and anaphylaxis. Moreover, no information is available specifically for Aveed.

In general, reporting rates are simple to construct and seemingly intuitive to understand. Endo provided reporting rates for other injectable products (Mesigyna, Androcur Depot, Testoviron Depot), however, they do not address several underlying conditions necessary for a valid and interpretable metric. The biggest concern is identifying the appropriate population at risk. To construct a rate, both the cases (i.e., the numerator) and the population at risk (i.e., the denominator) must be from the same population. If this is not the case, for example, if the cases are from a spontaneous reporting system and the population at risk is drug prescribing or sales information, the resulting ratio does <u>not</u> necessarily translate to a direct relationship between the event and the drug. This can be a challenge, except for rare cases when drugs are limited in distribution or use. For oral solid drug formulation, often the best available estimate is national-level prescription drug dispensing data. However, this may be insufficient for drugs with significant off-label use or abuse potential, such as opioids and anabolic androgen steroids (including TU). In these cases, it cannot be assumed that all vials sold were for a prescribed drug injection in a patient for an approved indication, especially when diversion might be a significant factor influencing those sales.

Another important consideration is accurately identifying cases of interest. For a suspected case to be reported to the manufacturer, a medical professional or patient must recognize it as such, determine that Nebido could be associated with the event, and take the time to report it to the manufacturer. Once there, the manufacturer then has to have enough information to determine what happened and if it could be causally related to the drug. Considering the process required for a suspected event to be counted, there is considerable potential for underascertainment of events for a wide variety of reasons, including failure to consider that a drug could have caused an event, not reporting the event, reporting it with insufficient information or not reporting an event when the initial symptoms were judged non-serious, which can be a subjective assessment. Further, as Endo notes in PSUR-10, there is no universally agreed-upon definition for anaphylaxis. This may increase the potential for subjective ascertainment of anaphylaxis cases and the possibility of overly stringent evaluation, especially for events not occurring immediately post injection. For these reasons, the numerator of a reporting rate is usually assumed to be an underestimation of actual cases.

In addition to an accurate evaluation of the population at risk, an assessment of postmarketing POME and anaphylaxis risk associated with Nebido would also need to consider the following:

- That sufficient information be available to definitively classify suspected cases. For example, although injectable TE was approved in the U.S. in 1953, FDA's Adverse Event Reporting System was not created until 1969.
- Unless Nebido is specifically identified in the report, the denominator will need to include all patients who were dispensed any testosterone-product instead of just those who received Nebido. This will inflate the denominator and may falsely minimize the risk.
- Since there are multiple settings of care where injectable testosterone may be administered, there is no way to obtain national patient counts for the use of these products in the US.
- A particular concern for injectable drugs is that the actual dose may be significantly different from what is recommended in the label, so it is not clear how much product a patient receives. For example, Gu et al administered 500 ml of TU per month, as did many of the contraceptive clinical studies described in the reports reviewed (5). These doses routinely exceeded the recommended dose of 1000 ml for Nebido in a 10-14 week period.

Once a reporting rate has been calculated, it may be tempting to compare it to an incidence rate as a way of providing context for a reporting rate. However, given the limitations of most reporting rates, particularly those that include sales information in the denominator, comparing it to an incidence rate can be misleading. Incidence rates are constructed in closed populations, so the numerator (cases) and denominator (actual exposed individuals) come from the same group of patients. Events of interest are generally serious enough for patients to seek medical attention and recorded in a standardized manner, although under-ascertainment may still occur if the event is not one of the outcomes of interest or if it is not readily recognized. Sometimes, use of reporting rates is the only information available to estimate a potential risk. Given the limitations of reporting rates in general, however, and for injectable drug products in particular due to the potential for self-injections and off-label use, reporting rates are considered a crude measure of risk at best, and should not be relied upon if any other measures, especially actual incidence rates, are available.

3.5 INCIDENCE RATES

In addition to reporting rates, Endo also provided incidence rates for TU studies in their clinical safety dataset as well as several postmarketing investigations. Eighteen clinical and postmarketing studies were included for TU: sixteen in Europe, one in the U.S., and a global study. An additional, ongoing study was not included in Endo's analysis. Thirteen of these studies (including the U.S. investigation) were in hypogonadal men; the remaining five were investigations of contraception in men. Appendix 3 provides a summary of the studies discussed.

Three thousand five hundred fifty-six men (3,556) participated in these studies, including 524 men (15%) from the U.S. Overall, 407 men were included in male contraception studies, while the rest were in clinical hypogonadal studies. Table 7 presents demographic information; all study patients were men. Participants in hypogonadal clinical studies had an average age between 50 and 54 years, and between 11.5% and 17.3% of men were over 65 years. The majority of patients were white, although 11% of patients in the 750 mg clinical hypogonadal studies and 12% in the postmarketing hypogonadal studies were black and Asian, respectively. The racial distribution likely reflects the US setting for the 750 mg clinical hypogonadal study and the fact that several of the postmarketing studies were conducted in China and Korea. Mean BMI for the hypogonadal studies ranged from 28 kg/m^2 to 32 kg/m^2. About 26% of men in the postmarketing hypogonadal studies had a BMI ≥ 30 kg/m^2 compared to 45% and 60% for the 1000 mg and 750 mg clinical studies, respectively.

In contrast, the participants in the contraceptive studies were much younger, with an average age of about 30 years. No men over the age of 65 participated in these studies. The study population was mostly white, and the average BMI was approximately 24 kg/m^2 for both the 750 mg and 1000 mg study groups. A small percentage of each group, 2.6% in the 750 mg group and 2.8% in the 1000 mg group, had BMIs over 30 kg/m^2.

Table 7: Patient Demographic Data for Hypogonadal and Contraceptive Clinical and Postmarketing Studies

	Hypogonadal Studies			**Contraceptive Studies**	
	750 mg N=272	**1000 mg N=453**	**1000 mg N=2424***	**750 mg TU N=195**	**1000 mg TU N=212**
Mean Age (years)	54.4	50.4	51.1	30.3	30.7
% ≥ 65 years	17.3	11.5	14.6	N/A	N/A
% White	79	91.8	44.1	97.4	99.1
% Black	11.4	5.5	0.2	1.0	0
% Asian	0.7	0.7	11.9	0.5	0
Mean BMI (kg/m^2)	32	30.3	28	24.2	24.1
% BMI ≥ 30 kg/m^2	59.6	44.8	26.6	2.6	2.8

Adapted from Endo Summary of Clinical Safety, Tables 6 and 7 (pp 39-43)
*Postmarketing studies

Table 8 shows the median duration of exposure, number of ampules, and person-years of exposure in patients who received 750 mg and 1000 mg doses of TU, respectively. Placebo groups were not included in these studies. Patients in the 750 mg dose group received a maximum of 13 injections, while those in the 1000 mg dose group received a maximum of 22 injections. These injections occurred over a 3.2-year period for those in 750 mg study arms (median 5 to 11 months) and 5

years in the 1000 mg study arm (median 11 months to 1.4 years). There were a total of 618.2 person-years of exposure for patients who received 750 mg injections and 3603.7 person-years of exposure for patients who received 1000 mg injections. A variety of dosing regimens were used in these investigations. A summary of these regimens can be found in Appendix 3. **Of note, most of the studies did not use the regimen under consideration for Aveed in the U.S**. The maximum number of injections and median weeks of exposure, therefore, reflect the experience of men who received 1000 mg TU injections.

Table 8: Dose and Duration Totals Stratified by 750 mg vs. 1000 mg TU injections

	750 mg dose (N=467)	1000 mg dose (N=3,089)	Overall (N=3,556)
Max Injections Received	13	22	22
Total Ampules	3,149	17,068	20,217
Median (range) weeks of exposure	24 to 48 (0 to 168)	48 to 72 (0 to 264)	48 to 72 (0 to 264)
Person-Years of Exposure	618.2	3603.7	4221.9

Adapted from sponsor's Summary of Clinical Safety, section 2.2.2 (pp 36-38)

Endo identified potential POME and anaphylaxis cases using similar approaches. First, records on all 3,556 study patients were searched using standardized queries for POME or anaphylaxis. Endo developed a standard terminology for POME, and used Standardized MedDRA Queries for anaphylaxis. Endo stratified cases by 1) events that occurred on the same day of the injection and 2) those that occurred more than one day afterwards. For POME, potential cases that did not occur on the same day of the injection were eliminated. All potential anaphylaxis cases underwent a clinical review regardless of the time elapsed since the TU injection. Since there is no universally accepted standard to determine anaphylaxis, those cases were reviewed using a variety of criteria.

3.5.1 Sponsor Reported POME Incidence Rates

Table 9 shows the results for POME. Four hundred sixteen potential cases were found when searching the database. Endo excluded 321 potential cases because they occurred more than one day after the injection, leaving 95 potential cases for adjudication. After review, there were nine POME confirmed cases in eight patients. This translates to an overall rate of 4.6 cases per 10,000 injections or 21.3 cases per 10,000 person-years. There were more POME cases at the higher dose level, suggesting a possible dose response.

Table 9: Incidence of POME in clinical and postmarketing studies

	750 mg dose (N=467)	1000 mg dose (N=3089)	Overall (N=3556)

Potential cases from Query	162	254	416
Adjudicated Cases	1	8	9
Cases per 10,000 injections	3.2	4.7	4.5
Cases per 10,000 person-years	16.2	19.4	21.3

Adapted from sponsor's Summary of Clinical Safety, page 36, table 22 (page 75), table 24 (page 79)

To provide a comparison for these rates, POME rates are included from two postmarketing TU studies referenced by Endo. The first estimate is from a large observational study by Zitzmann et al. The purpose of this study was to assess the safety and tolerability of TU in hypogonadal men (17). It included a population of 1,438 men in 23 countries worldwide who received injections every 8 to 12 weeks for an average of 10 months. Over the four-year course of the study, 6,333 injections were administered. The second estimate is from Gu et al., who performed a long-term study of TU as a contraceptive in a group of Chinese men. For this study, 1,045 men were given 500 mg TU injections monthly over a two-year period. Unlike the current version of TU, the drug used in the Gu study contained tea seed oil instead of castor oil, although the preservative was not specified (5).

Table 10 shows the POME rates for each of these studies as presented by Endo. Note that the dosing regimens differed in these two studies from those for the approved product; participants in the Zitzmann study received a TU dose of between 1500 mg and 2000 mg every 12 weeks, while those in the Gu study received 1500 mg TU over the same time period(5, 17). In addition, the study populations were markedly different. The Gu study participants were between 20 and 45 years old and had an average body weight of 65 kg. Men in the Zitzmann study averaged 49.5 years of age, with 13% being above 65 years of age. The average weight for the Zitzmann study group was 87 kg. Despite these differences, both studies show POME incidence rates similar or higher to the ones seen for 1000 mg Nebido patients in the clinical trials.

Table 10: POME Incidence rates from selected TU studies

	POME per Patient (%)	POME per 10,000 Patients	POME per Injection (%)	POME per 10,000 Injections
Zitzmann (2013) (1000 mg every 8 to 12 weeks)	3/1438 (0.2%)	20.1	3/6333 (0.05%)	4.8
Gu (2009) (500 mg monthly)**	22/1054 (2.1%)	208.1	22/42,876 (<0.01%)	5.1

Adapted from PSUR 10, table 9-7 (page 43)
**Total number of injections not published. Range of total injections estimated based on dosing regimen and number of patients completing the study treatment phase in the published article.

3.5.2 Reported Anaphylaxis Incidence Rates - Endo Pharmaceuticals

Table 11 displays the results for the drug-related anaphylaxis analysis. The standardized query identified 90 potential cases. Twenty-three cases occurred on the day of the event, while 67 happened more than one day after the injection. All potential cases were sent for adjudication, and there were two cases in the final count. This translates to an overall rate of 4.7 cases per 10,000 injections or 32.4 cases per 10,000 treatment-years in men using the 1,000 mg Nebido dose.

Table 11: Incidence of anaphylaxis in clinical and postmarketing studies

	750 mg dose (N=467)	1000 mg dose (N=3089)	Overall (N=3556)
Potential cases from Query	35	55	90
Adjudicated Cases	0	2	2
Cases per 10,000 injections	0	1.2	0.9
Cases per 10,000 person-years	0	32.4	4.7

Adapted from sponsor's Summary of Clinical Safety, page 36, table 32 (page 85), table 33 (page 86)

The incidence rates for anaphylaxis vary widely in other studies that attempted to characterize it. In addition to lacking a standard definition for the condition, many studies that have attempted to quantify the incidence of anaphylaxis were limited to small or selective populations, or were not able to include likely points of contact of an anaphylaxis patient and the healthcare system, such as emergency medical technicians or emergency department visits(11). Flabbee et al reviewed several studies and found that in general, the rate for severe anaphylaxis ranged from 0.5 to 3 cases per 10,000 patients. For less severe disease, the rates ranged from 4 to 101 cases per 10,000 emergency department visits. Note that these rates did not discern the source of the reaction. Published drug-related anaphylaxis rates range from a

low of 0.99 cases per 10,000 patient-years for anaphylaxis to highs of 0.8 to 5 cases per 10,000 person-years (2, 15). Thong et al point out that while penicillin was once thought to be the main cause of drug-induced anaphylaxis, subsequent investigations have not supported that theory(15).

3.5.3 OSE/DEPI Comment on Reported Incidence Rates

In addition to attempting to calculate reporting rates, Endo also provided incidence rates for the EU and US clinical trials as well as several postmarketing TU studies. To enable comparison across all of the studies, incidence rates per 10,000 injections were calculated by OSE/DEPI from available information when not provided by Endo. For POME, the rates were 3.2 cases and 4.7 cases per 10,000 injections for the750 mg and 1000 mg TU injections, respectively. In the case of anaphylaxis, there were no cases in the 750 mg TU dose group, and the rate for the 1000 mg TU dose group was 1.2 cases per 10,000 injections. Of note, only the U.S. clinical trial used the proposed dosing regimen of 750 mg TU over a 10-12 week period; the remaining studies used different doses and schedules (see Appendix 3).

Endo selected two postmarketing TU studies to compare POME incidence; a study conducted in hypogonadal men and a contraceptive study (5, 17). Both studies had POME rates similar or slightly higher to those seen in the TU clinical trials, albeit the doses were higher than what is currently being recommended for the U.S. patients. An important consideration is that the Zitzmann study is included in both Endo's clinical trial POME calculation and as a comparator study. However, the incidence rate in the clinical trial patients when excluding this study is 4.6 cases per 10,000 injections. So, while large (this study contributed 1,438 of the 2,404 total 1000 mg TU patients), this study did not significantly alter the POME incidence rate.

Reliable estimates of anaphylaxis incidence are very difficult to obtain. This is primarily because there is no standardized definition for anaphylaxis. In addition, studies in single populations, such as hospitalized patients or registries, might miss more likely sources of anaphylaxis cases such as those seen only in emergency departments (9). In addition, the incidence rates appear to vary over time, and both within and across countries and populations (2, 9, 11, 15). Nevertheless, the rate of anaphylaxis seen in the clinical and postmarketing TU studies of 4.7 cases per 10,000 injections (or 32.4 cases per 10,000 person-years) is significantly higher than the estimated range for drug-induced anaphylaxis of between 0.8 and 5 per 10,000 person-years(15) reported in the literature.

The POME and anaphylaxis incidence rates in the clinical and postmarketing databases each indicate a consistent trend. The incidence of POME was constant in the clinical and postmarketing studies, under presumably ideal administration conditions. In addition, the POME rate has persisted over time despite increased publicity on the part of Endo and increased awareness by healthcare practitioners. Endo does not provide any additional suggestions for addressing this continuing risk; instead, they merely note that it seems to be a transient condition although they do propose a lower dose for U.S. patients. Concerning anaphylaxis, despite the difficulty of obtaining reliable incidence rates in the general population, the rate in

the TU studies is higher than other published rates. Endo does not comment on this fact either, other than to describe the difficulty of definitively adjudicating suspected anaphylaxis events. In summary, Endo does not acknowledge either of these trends and does not present any alternatives for tracking or reducing their occurrence in the general population of users.

4 DISCUSSION OF REPORTING AND INCIDENCE RATES

OSE/DEPI was asked to evaluate the reporting rates for POME and anaphylaxis submitted by Endo in support of the approval of Aveed. Calculating reporting rates for injectable drug products in general is not ideal for a number of reasons, chiefly, the inability to specify the appropriate population at risk. In addition, given the multiple dosing regimens used in worldwide TU studies and its possible abuse as an anabolic steroid, make it difficult to know how much of the product was actually administered to hypogonadal men based solely on sales data. OSE/DEPI does note some potential issues with Endo's submission. Whereas sales increase over time, particularly from November 2011 to November 2012, reports of POME and anaphylaxis cases do not increase at the same rate. The fact that the POME and anaphylaxis reporting rates remain consistent is likely an artifact of the large denominator used rather than a stable or decreasing number of events.

Endo also attempts to provide some insight into actual TU prescribing using a single year of information from five EU countries. Considering that TU is approved in 94 countries, and that Nebido has been widely available since 2003, this is likely not an accurate portrayal of TU use worldwide. Further evidence of this is provided by several clinical and postmarketing contraceptive studies that typically used doses of 1500 mg every 10 – 12 weeks (5, 10).

Endo's use of total exposed time resulted in an underestimation of the magnitude of the events in question. While the number of cases is unchanged, the time at risk should only encompass the first 24 hours of exposure, not the entire period between injections. For the reporting and incidence rates, the events per number of injections may be the more appropriate metric to use.

In addition to reporting rates, Endo provided incidence rates for POME and anaphylaxis based on clinical and postmarketing studies of TU. The incidence rates for POME were compared to two postmarketing studies highlighted in the documents provided; a contraceptive study and one in hypogonadal men (5, 17). These studies showed a consistent rate of POME over time, even in ideal study conditions. However, subjects in both studies were exposed to higher TU doses compared to what Endo is recommending for U.S. patients. While it is more difficult to determine rates of drug-induced anaphylaxis, the rate seen in Endo's data of 4.7 cases per injection or 32.4 cases per 10,000 patient-years is higher than published rates for drug-induced anaphylaxis in general of 0.8 to 5 cases per 10,000 patient-years(2, 15). Endo does not acknowledge either the consistency of the POME rate or the comparatively high anaphylaxis rates; their response to these conflicting findings is to describe the difficulty in adjudicating cases and note that these events are in the international prescribing information.

5 CONCLUSIONS

In summary, Endo's inability to characterize TU use accurately, the consistent POME and excess anaphylaxis incidence rates seen in the clinical and postmarketing databases, and Endo's unwillingness to acknowledge or effectively address these rates is concerning. It is unlikely that the incidence of either POME or anaphylaxis associated with TU has decreased in the postmarketing period, since these events still occurred under ideal study conditions. The risk of serious and life-threatening events should be carefully weighed against the benefit of a potentially longer period between TU injections, particularly given that there are multiple alternatives to TU, including other injectable testosterone preparations and other dose forms.

6 REFERENCES

1. Bayer. Nebido prescribing information, http://www.nebido.com/en/hcp/product-information/prescribing-information/index.php, Accessed. 2013. (.

2. Clark S, Camargo CA, Jr. Epidemiology of anaphylaxis. Immunol Allergy Clin North Am 2007;27:145-63, v.

3. Endo Pharmaceuticals. Delatestryl Full Prescribing Information, http://www.endo.com/File%20Library/Products/Prescribing%20Information/Delatestryl_PI.pdf, accessed 3/2012. 2013. (.

4. Giagulli VA, Triggiani V, Corona G, et al. Evidence-based medicine update on testosterone replacement therapy (TRT) in male hypogonadism: focus on new formulations. Curr Pharm Des 2011;17:1500-11.

5. Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. J Clin Endocrinol Metab 2009;94:1910-5.

6. Hirschhauser C, Hopkinson CR, Sturm G, et al. Testosterone undecanoate: a new orally active androgen. Acta Endocrinol (Copenh) 1975;80:179-87.

7. Hirsh M **Cross-Discipline Team Leader Memo for** AVEED™ testosterone undecanoate injection NDA 22-219. Food and Drug Administration, 2009.

8. Lenzi A, Balercia G, Bellastella A, et al. Epidemiology, diagnosis, and treatment of male hypogonadotropic hypogonadism. J Endrocrinol Invest 2009;32:934-8.

9. Lieberman P. Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol 2008;8:316-20.

10. Mackey MA, Conway AJ, Handelsman DJ. Tolerability of intramuscular injections of testosterone ester in oil vehicle. Hum Reprod 1995;10:862-5.

11. Moneret-Vautrin DA, Morisset M, Flabbee J, et al. Epidemiology of life-threatening and lethal anaphylaxis: a review. Allergy 2005;60:443-51.

12. Morley JE, Perry HM. Androgen treatment of male hypogonadism in older males. J Steroid Biochem Mol Biol 2003;85:367-73.

13. Pearl JM. Severe reaction to "natural testosterone":how safe are the ergogenic aids? Am J Emerg Med 1993;11:188-9.

14. Pfizer. Depo-Testosterone U.S. physician prescribing information, http://labeling.pfizer.com/ShowLabeling.aspx?id=548, accessed. 2013. (.

15. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011;71:684-700.

16. Yesalis CE, Anderson WA, Buckley WE, et al. Incidence of the nonmedical use of anabolic-androgenic steroids. NIDA Res Monogr 1990;102:97-112.

17. Zitzmann M, Mattern A, Hanisch J, et al. IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. J Sex Med 2013;10:579-88.

APPENDICES

APPENDIX 1 - CHARACTERISTICS OF INJECTABLE TESTOSTERONE PREPARATIONS

Product	Excipients	Packaging	Dose Regimen	Indications	Warnings
Nebido® (Testosterone undecanoate) International, 2003	Castor oil, benzyl benzoate	1000 mg TU 4 ml single-dose vial	1000 mg every 10 to 14 weeks	-Confirmed Male Hypogonadism	-Use in women, children, and adolescents -Prostate diseases (incl. cancer) -Hypercalcemia -Liver tumor -Edema -Aggravation of epilepsy and migraine -Enhancing muscle development and athletic performance -POME
Depo Testosterone® (Testosterone Cypionate) U.S., 1979	Cottonseed oil, benzyl benzoate, benzyl alcohol	2000 mg TC 10 ml multi-dose vial	50 mg to 400 mg every 2 to 4 weeks	In males: -Primary Hypogonadism -Hypogonadal Hypogonadism	-Pregnancy Category X -Schedule III Controlled Substance -Hypercalcemia -Hepatic conditions (incl. cancer) -Prostate hyperplasia and cancer -Edema -Gynecomastia -Compromised adult stature
Delastryl® (Testosterone Enanthate) U.S., 1953	Sesame oil, chlorobutanol	1000 mg TE 5 ml multi-dose vial	50 mg to 400 mg every 2 to 4 weeks	In males: -Primary Hypogonadism -Hypogonadal Hypogonadism -Delayed Puberty	-Pregnancy Category X -Schedule III Controlled Substance -Hypercalcemia -Hepatic

Product	Excipients	Packaging	Dose Regimen	Indications	Warnings
				In females: -Inoperable Metastatic Mammary Cancer	conditions (incl. cancer) -Prostate hyperplasia and cancer -Edema -Gynecomastia -Enhancing athletic performance

APPENDIX 2: - DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Source Healthcare Analytics' ProMetis Lx®

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

APPENDIX 3 – SUMMARY OF STUDIES

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
US Clinical Study					
IP157-001 Completed	Hypogonadism	A 2-arm, open-label, randomized, multicenter pharmacokinetic and long-term safety study of intramuscular (IM) injections of testosterone undecanoate (TU) 750 mg and 1000 mg in hypogonadal men This is a 5-part protocol that includes 2 IM treatment arms in Part A, 2 IM treatment arms in Part B, a single IM treatment arm in Part C, a single IM treatment arm in Part C2, and 2 subcutaneous (SC) treatment arms in Part D.	Phase III	Randomized, 2-arm, active-controlled, multiple-dose	**Part A:** TU 750 mg IM TU 1000 mg IM **Part B:** All subjects received TU 1000 mg IM initial dose followed by two arms of: TU 750 mg IM TU 1000 mg IM **Part C:** TU 750 mg IM **Part C2:** TU 750 mg IM **Part D:** TU 1000 mg SC (Part A subjects)
European Clinical Studies					
JPH01495 Completed	Hypogonadism	Study to investigate the pharmacokinetics of TU after single IM injection	Phase I	Open-label, single-arm, single-dose	TU 1000 mg IM

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
JPH04995 (includes LTFU study) Completed	Hypogonadism	Study to investigate the pharmacokinetics and efficacy of TU after multiple IM injections in hypogonadal men	Phase II/III	Open-label, single-arm, multiple-dose	TU 1000 mg IM
ME98096 (includes 2 LTFU studies) Completed	Hypogonadism	Open-label study to evaluate safety and pharmacokinetic parameters of total and free testosterone after repeated IM administrations of TU 1000 mg (5 injections over	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM
ME97029 (includes 2 LTFU studies) Completed	Hypogonadism	Study to investigate the efficacy and safety of TU vs. testosterone enanthate (TE) after IM injection in hypogonadal men	Phase III	Randomized, open-label, parallel-group, 2-arm, active-	TU 1000 mg IM TE 250 mg IM

t ll d

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
306605 (includes LTFU study) Completed	Hypogonadism	Open-label, 1-arm study to investigate safety and efficacy of IM injections of TU 1000 mg in hypogonadal men at variable intervals during a 136-week to 192-week treatment including pharmacokinetics of TU during steady state in a subgroup of 30 subjects Long-term safety and efficacy of IM injections of TU including pharmacokinetics during steady	Phase III	Open-label, single-arm, multiple-dose	TU 1000 mg IM
303934 Terminated Early[a]	Male andropause	A monocenter, prospective, randomized, double-blind, parallel- group, placebo-controlled, long- term clinical trial to investigate the effects of a long-acting IM preparation of TU on andropause- related	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled,	TU 1000 mg IM Placebo 4 mL IM
European Male Contraception Studies					
97028 Completed	Male contraception in healthy males	Male contraception with TU vs. combined administration of TU and levonorgestrel (LNG) - a double- blind, randomized, single-center comparative study	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-	TU 1000 mg IM **+** oral placebo TU 1000 mg IM **+**oral LNG

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
97173 Completed	Male contraception in healthy males	Male contraception with a sequential regimen of cyproterone acetate (CPA) and TU followed by a lower dose of CPA and TU in normal men	Phase II	Randomized, single-blind, 3-arm, placebo-controlled, multiple-dose	**Induction Phase:** All subjects received TU 1000 mg IM + CPA 20 mg/day oral **Maintenance Phase:** Randomized to 1 of the following 3 regimens: TU 1000 mg IM + CPA 20 mg/day oral TU 1000 mg IM + CPA 2 mg/day oral TU 1000 mg IM + daily oral placebo
98016 Completed	Male contraception in healthy males	A single-center, prospective, 1-arm, uncontrolled study to investigate the efficacy and safety of male contraception with TU and norethisterone enanthate (NET-EN) over 24 weeks	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM + NET-EN 200 mg IM
99015 Completed	Male contraception in healthy males	Study on efficacy and safety of male contraception with TU and NET combined in different application regimens	Phase II	Randomized, open-label, parallel-group, 3-arm, active-	TU 1000 mg IM + NET-EN 200 mg IM TU 1000 mg IM + NET-EN 400 mg IM TU 1000 mg IM + NET-A 10 mg/day oral

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
42306 Completed	Male contraception in healthy males	A phase IIb, double blind, placebo-controlled, randomized, multicenter, multiple dose trial investigating the efficacy, safety and pharmacokinetics of a subcutaneous etonogestrel (ENG) rod combined with IM TU for male fertility control	Phase IIb	Randomized, double-blind, parallel-group, 7-arm, placebo-controlled, multiple-dose	TU 750 mg IM + Low Release ENG Implant every 10 weeks TU 750 mg IM + Low Release ENG Implant every 12 weeks TU 1000 mg IM + Low Release ENG Implant every 12 weeks TU 750 mg IM + High Release ENG Implant every 10 weeks TU 750 mg IM + High Release ENG Implant every 12 weeks TU 1000 mg IM + High Release ENG Implant every 12 weeks Placebo IM + Placebo Implant
Postmarketing Studies					
AWB 0105 Completed	Androgen deficiency	Efficacy and tolerability of Nebido®	Post-marketing surveillance: prospective, non-intervention	Open-label, single-arm, multiple-dose	TU 1000 mg IM
39732 (NE060 1 **IPASS)** Completed	Hypogonadism	International, multicenter post authorization surveillance study on the use of Nebido® to assess tolerability and treatment outcomes in daily clinical practice (IPASS Nebido®)	Post-marketing surveillance: non-intervention al	Open-label, single-arm, multiple-dose	TU 1000 mg IM

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	**Indication**	**Title**	**Type**	**Study Design**	**Treatments**
14329 **(Czech NEO)** Completed	Hypogonadism	NEO; Observational post-marketing study (NEbidO)	Post-marketing surveillance: Non-intervention al	Open-label, single-arm, multiple-dose	TU 1000 mg IM
NB02 Completed	Hypogonadism	NEBIDO Therapy in Hypogonadal Male Patients With Paraplegia With Osteoporosis Compared With Conventional Osteoporosis	Post-marketing surveillance: Non-intervention al	Open-label, 3-arm, multiple-dose, single center	TU 1000 mg
TG09 Completed	Hypogonadism	Efficacy and tolerability of Testogel/Nebido in combination with a standardized exercise and diet programme in hypogonadal male patients with abdominal obesity compared with exercise	Post-marketing surveillance: Non-intervention al observationa	Open-label, 2-arm, multiple-dose, single center	TU 1000 mg, Testogel
14853 Terminated Early[b]	Hypogonadism	Effect of exercise alone or in combination with testosterone replacement on muscle strength and quality of life in older men with low testosterone concentrations; a randomized double-blind, placebo controlled	Post-marketing surveillance: Intervention al	Randomized, Double blind, parallel-group, 2-arm, placebo controlled	TU 1000 mg, Placebo

Data Source: Data Integration Plan for EN3331 Integrated Summary of Safety (dated 30-May-2012) (5.3.5.3, AVEED ISS [Appendix E]).

[a] Terminated early

[b] Terminated early due to slow recruitment rate.

CPA=Cyproterone acetate; ENG=Etonogestrel; IM=Intramuscular; LNG=Levonorgestrel; LTFU=Long-term follow up; NET-A=Norethisterone acetate; NET-EN=Norethisterone enanthate; SC=Subcutaneous; TE=Testosterone enanthate; TU=Testosterone undecanoate.

Nonclinical Briefing Document

Introduction

The nonclinical program addressed the in vitro affinity of testosterone undecanoate (TU) for the human androgen receptor, ADE (absorption, distribution and elimination) in rats, potential for toxicity after repeated intramuscular dosing in rats, local toxicity after a single intramuscular injection in pigs, and genotoxicity. The applicant relied upon published literature to assess the potential for reproductive toxicity and carcinogenicity.

A. Pharmacologic Activity

Testosterone undecanoate (TU) is a fatty acid ester of testosterone. TU is an inactive pro-drug which is hydrolyzed in vivo to testosterone and undecanoic acid. TU itself has little potential for pharmacological activity since its relative binding affinity for the human androgen receptor was only 1.3% of testosterone.

B. Absorption, Distribution, and Elimination

The absorption, distribution, and elimination of radiolabeled TU were characterized in rats after intramuscular administration. The distribution of radioactivity was essentially limited to the liver, kidney, and large and small intestines and their contents. Nearly half of the administered dose, based on radiolabel, remained near the dose site eight weeks after the initial injection. Most of the radioactivity was excreted in feces and to a lesser extent in urine. The fate of undecanoic acid was not directly addressed because the radioactive label was on the steroid ring. However, undecanoic acid is not predicted to be toxic since it a fatty acid that that is readily metabolized via the fatty acid and tricarboxylic acid pathways.

C. Nonclinical Toxicology Findings

<u>Repeat Dose Toxicity</u>

A toxicology study was conducted in male rats that were dosed intramuscularly with vehicle (1:1.7 ratio of castor oil to benzylbenzoate) or TU [50, 200, or 800 mg/kg (800 reduced to 400 after 3rd dose)] every two weeks for 14 weeks. Graded doses of TU were achieved by varying the volume of dose solution administered. The vehicle control and high-dose group received the same dose volume. Testosterone cypionate (TC) (Depo®- Testosterone) was used as an active comparator. The vehicle for Depot-Testosterone (56% w/v cotton seed oil, 20% benzylbenzoate, and 1% w/v benzyl alcohol) was different from the vehicle used in the TU study. The persistence of effects was assessed 26 weeks after the last dose in the high-dose group only.

Exposure to TU in the low to highest dosed rats was roughly 2, 11, and 23 times that in humans dosed with 750 mg TU based upon either mean AUC or mean C_{max}. Maximum serum levels of testosterone increased 3, 11, and 30 times the pre-dose levels.

Exposure to TU or TC resulted in findings generally consistent with exposure to testosterone. Reduced feed intake, body weight loss, slight alterations in hematology, altered organ weights,

and thymic atrophy were observed at and above the lowest dose evaluated. These findings were generally mild and could be considered affects of exaggerated pharmacology.

Consistent with the injection of an oil vehicle, local inflammation and cystic lesions were observed in all groups. The incidence of these adverse local events increased with dose volume in the TU groups and was similar between the vehicle, high-dose TU group and the TC group. Although similar pathology was observed, the extent of the local expansion of injection site reactions beyond the immediate site of application appeared to depend upon viscosity of the dosing solution with the most to least expansion being in the vehicle control, TU groups followed by the TC group, respectively.

In the TC and all TU groups, neutrophil counts were elevated (33% to 96%) while lymphocytes were reduced (18% to 43%). As expected of an androgen, both TC and TU led to significant increases in the weight of the kidney, bulbocavernosus muscle, ventral prostate, and seminal vesicle. Adverse histopathology was not observed in these tissues with the exception of the kidney. Chronic inflammation was observed in the dorsal lateral prostate in a few rats who received the greatest dose of TU. In all TU groups, a low incidence of reversible renal pathology was observed including basophilic tubular cells and nephropathy while degeneration and necrosis of the renal proximal tubule was observed in a single rat at the highest dose. Correlating with the renal pathology was a slight increase in BUN in the high-dose group and a slight reduction in phosphorous in mid and high-dose groups. In the urinary bladder, a low incidence of transitional cell hyperplasia was observed in the high-dose group. The liver, testes, and thymus were reduced in weight after exposure to TU or TC. Animals did not recover from the reduction in testes weight after TU withdrawal. Adverse testes pathology was not observed in rats dosed with TU likely because the reduced testes weight was a compensatory response to elevated testosterone. In the liver, a slight increase in mononuclear cell infiltration and subacute inflammation was observed in the TU groups. Bilirubin was reduced in all TU groups and glucose was reduced in the highest TU dose group. Diffuse thymic atrophy was observed in all TU groups and was still observed after drug withdrawal. RBC levels were not altered by TU but hemoglobin was slightly elevated.

Early in the study, high mortality/morbidity was observed in rats injected with the largest volume of vehicle alone (3.2 mL/kg) or similarly large volumes of vehicle containing TU. This large injection volume is roughly equivalent to 200 mL in humans. Because of the high mortality/morbidity, the dose volume in these groups was reduced and morbidity and death was essentially eliminated. Death and morbidity was not reported to be immediate post-injection but occurred within four days of the first or third dose. Signs of morbidity in some of the animals that were administered large dose volumes include moderate to severe tremors, languid appearance, and lack of activity; however, no signs of respiratory distress were reported. Histopathology observed in the dead and/or moribund rats receiving large dose volumes include degeneration or necrosis of the renal tubules, myocardial degeneration, adrenal congestion, and lymphoid necrosis in the thymus, spleen, lymph nodes, lung, and bone. From the available information, it could not be determined if there were any causal relationships between the mortalities and the potential formation of pulmonary microemboli related to excessive exposure to the vehicle. The cause of morbidity and death was unclear but likely due to unintended

systemic exposure to large volumes of the vehicle resulting in cardiac, lymphatic and renal toxicities.

Genotoxicity
Testosterone undecanoate was negative in a battery of *in vitro* and *in vivo* genotoxicity assays assessing mutagenicity and clastogenicity.

Carcinogenicity and Reproductive Toxicity: The risk for reproductive toxicities and cancer is considered to be similar to other approved testosterone products based upon the established effects of testosterone.

Local Tolerance
Local tolerance was assessed in pigs after a single 0.8 mL or 3 mL intramuscular dose of vehicle (1:1.7 ratio of castor oil to benzylbenzoate) or 4 mL vehicle containing TU (1000 mg). No TU related adverse affects were observed. However, as expected of post injection trauma, injection site hemorrhaging, inflammation, presence of giant cells, and necrosis were observed four days after dosing in all groups (including vehicle). The severity increased slightly with increased dose volume. Fibrosis was observed in all groups seven days after dosing. The tissue damage essentially recovered within 42 days of dosing.

D. Nonclinical safety issues relevant to clinical use

The safety profile of testosterone is well known. Other than expected pharmacology and injection site toxicity, no significant safety concerns associated with TU were identified in the nonclinical program.

Clinical Pharmacology Briefing Document

Testosterone undecanoate (TU) is an ester prodrug of testosterone (T), with the proposed indication of Testosterone (T) replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Currently, there are various testosterone replacement products on the market with different formulations. The proposed dose in this application is 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks administered intramuscularly (IM) in the buttock.

The application is supported by 2 pivotal phase 3 safety and efficacy studies in hypogonadal men, Study IP157-001 Part C and Study IP157-001 Part C2 that have evaluated the proposed dose, and one additional supportive study, Study IP157-001 Part A has evaluated doses of 750 mg or 1000 mg given every 12 weeks. The primary endpoints in the phase 3 studies are pharmacokinetic (PK) endpoints.

In Study IP157-001 Part C, the sponsor evaluated the full pharmacokinetics (PK) of serum total T (including C_{avg} and C_{max}) following the 3rd and 4th injections and trough concentrations for up to 9 injections. In Study IP157-001 Part C2, the sponsor evaluated the full PK of serum total T following the 2nd injection and trough concentrations up to 6 injections. Study IP157-001 Part A had evaluated the serum T PK following the single dose administration, where Part C and C2 did not evaluated the first dose PK. The steady state was considered to be reached by the 3rd injection. Therefore, Study IP157-001 Part C, that has data from the 3rd injection interval, was used as the source of data to assess the primary PK and efficacy.

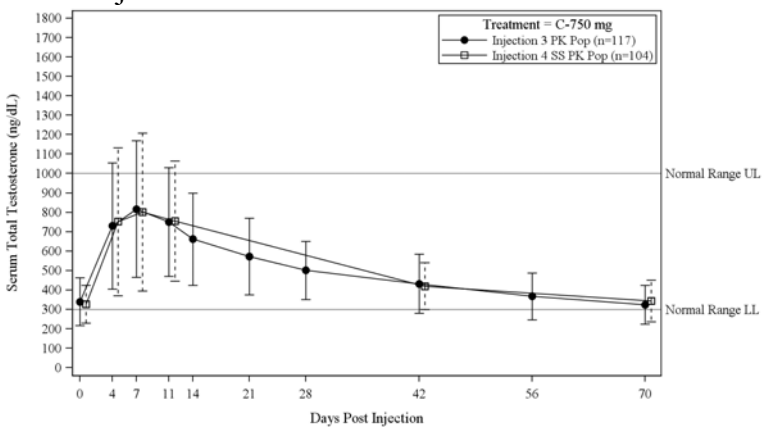
Steady State PK:
Following IM administration to the buttock, TU is slowly released from the injection site. TU is converted to T and undecanoic acid, presumably via serum esterases. For the TU 750 mg regimen, the 3rd injection interval was considered to be the first injection interval that would represent steady state conditions for serum total T concentration. Achievement of steady state was assessed based on trough serum total T concentration following the 2nd, 3rd, and 4th injections. The 3rd injection interval was used as the primary PK and efficacy assessment. The following are the total T PK parameters from the 3rd injection interval:

PK parameter	Mean	Standard deviation
C_{avg} (ng/dL)	495	141
C_{max} (ng/dL)	891	345
T_{max} (days)	7 (median)	4 – 42 (range)

Following the 3rd injection, 94% percent of patients (110 of 117) (95% confidence interval, CI, 89.6 - 98.5) had serum total T C_{avg} within the 300 – 1000 ng/dL range. Nine of 117 patients (7.7%) had C_{max} > 1500 ng/dL and no patient had $C_{max} \geq 1800$ ng/dL during the 3rd injection interval.

PK profile following the 4th injection was very similar to that of 3rd injection, with C_{avg} of 514.3 ± 163.11(ng/dL) and C_{max} of 837.6 ± 412.1. However, 4 of 104 patients (3.8%) had C_{max} > 1800 ng/dL with values of 1994, 2000, 2178, and 2201 ng/dL, respectively.

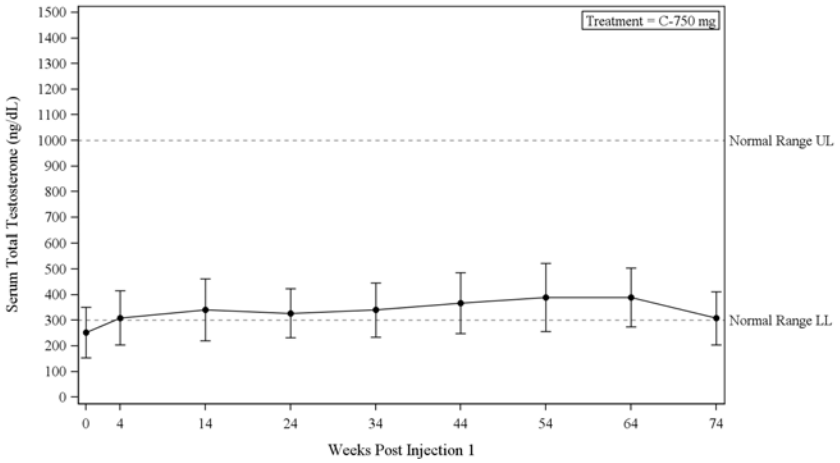
Figure 1. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) following the 3rd and 4th Injection Intervals



Single Dose PK:
The serum total T PK profile following a first injection of 750 mg TU (n=19) was similar to that at steady state but the C_{max} and C_{avg} values were lower. The mean (±SD) C_{max} and C_{avg} (over 84 days dosing interval) were 611 (224) ng/dL and 328 (96) ng/dL, respectively. The median T_{max} was 7 days.

Long Term Trough PK:
The mean tough concentration (immediately prior to injection) of serum total T levels up to 9 injections ranged from 307.8 to 389.8 ng/dL after the 1st injection and were within the normal range (300 to 1000 ng/dL).

Figure 2. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 9th Injection



Effect of body mass index (BMI) on Exposure to T:
Post hoc exploratory analyses of data from study IP157-001 Part C indicate that baseline body weight and BMI were correlated with serum total T exposure. The mean total T Ca_{vg} were 578,
567, and 445 ng/dL for patients with baseline BMI of <26, 26-30, and >30 kg/m2, respectively.
The respective mean C_{max} were 1234, 1062, and 751 ng/dL for these 3 BMI groups. There was a trend that as body weight and BMI decreased the exposure to total T from a fixed dose increased.

A similar trend was observed for both 750 mg and 1000 mg TU arms in study IP157-001 Part A following the 4th injection of the once every 12 weeks regimen. The sponsor excluded 2 patients from PK analysis of study IP157-001 Part C due to their pretreatment body weights being less than 65 kg. Only one patient (patient 031-7021) had serum T concentration available from the primary PK 3rd injection interval. He had a body weight of 59 kg and a BMI of 17.2. He exhibited high C_{max} and C_{avg} serum total T concentrations of 2888 ng/dL and 1164 ng/dL, respectively. The sponsor has proposed to include the following sentence "The use of AVEED in men below 65 kg (143 lbs.) may result in excess concentration of serum testosterone and is not recommended" under the Warnings and Precautions section of the label to address this issue.

Effects on Other Hormones:
In addition to the increase in serum total T concentration following administration of IM TU, serum Free T, dihydrotestosterone (DHT) and estradiol (E2) were increased. TU administration did not affect concentration of sex hormone binding globulin (SHBG). The increases in serum DHT and E2 were expected since they are downstream metabolites of T. Because T binds mainly to SHBG and albumin, the increase in Free T concentration was consistent with the increase in total T and lack of SHBG effect. The concentration versus time profiles for Free T, DHT and E2 generally paralleled total T profile. The group mean concentrations at measured time points during the 3rd injection interval ranged from 203 – 544 pg/mL for Free T, 244 – 451 pg/mL for DHT, 14.4 – 35.6 pg/mL for E2, and 18.9 – 20.1 nmol/L for SHBG. TU was also observed in serum, generally only at the earliest sampling times of 4 and 7 days post injection. Concentration values of DHTU were below the limit of quantification (LLOQ = 100 ng/dL) for all but a few samples.

VIII. REFERENCES

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006; 117:391-7
2. Sasseville D, Desjardins M, Almutawa F. Allergic contact dermatitis caused by glycyrrhetinic acid and castor oil. Contact Dermatitis. 2011; 64:168-9.
3. Di Berardino L, Della Torre F. Side effects to castor oil. Allergy. 2003; 58:826.
4. Le Coz CJ, Ball C. Recurrent allergic contact dermatitis and cheilitis due to castor oil. Contact Dermatitis. 2000; 42:114-5.
5. Magerl A, Heiss R, Frosch PJ. Allergic contact dermatitis from zinc ricinoleate in a deodorant and glyceryl ricinoleate in a lipstick. Contact Dermatitis. 2001; 44:119-21.
6. Thorpe SC, Kemeny DM, Panzani RC, McGurl B, Lord M. Allergy to castor bean II. Indentification of the major allergens to castor bean seeds. J Allergy Clin Immunol. 1988;82:67–72.
7. Takamatsu Y, Ishizu M, Ichinose I, Ogata K, Onoue M, Kumagawa M, et al. Intravenous cyclosporing and tacrolimus caused anaphylaxis but oral cyclosporin capsules were tolerated in allogeneic bone marrow transplant recipient. Bone Marrow Transplantation. 2001;28:421-3.
8. Ebo DG, Piel GC, Conraads V, Stevens WJ. IgE-mediated anaphylaxis after first intravenous infusion of cyclosporin. Ann Allergy Asthma Immunol. 2001; 87:243-5.
9. Kuiper RA, Malingre MM, Beijnen JH, Schellens JH. Cyclosporin-induced anaphylaxis. Ann Pharmacother. 2000; 34:858-61.
10. Price KS, Castells MC. Taxol reactions. Allergy Asthma Proc. 2002; 23:205-8.
11. Tunarua S, Althoffa TF, Nüsingb RM, Dienerc M, and Offermannsa S. Castor oil induces laxation and uterus contraction via ricinoleic acid activating prostaglandin EP3 receptors. PNAS 2012; 109:9179–9184.
12. Nair B. Final Report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. Int J Tox. 2001; 20:23-50.
13. Ong GS, Somerville CP, Jones TW, Walsh JP. Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. Case Rep Med. 2012; 2012:384054.
14. Uzun O, Findik S, Danaci M, Katar D, Erkan L. Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. Respirology 2004; 9:34-6.
15. Delatestryl (testosterone enanthate for injection) package insert. Approved December 24, 1953. Accessed at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
16. Textbook of Respiratory Medicine. John Murray and Jay Nadel eds. WB Saunders Co 1988; Chapter 55, Pulmonary Embolism, p. 1322.
17. Peltier LF. Fat embolism, a perspective. Clinical Orthopedics and Related Research July 1988; No. 232:263-270.
18. Russell M, Storck A, Ainslie M. Acute respiratory distress following intravenous injection of an oil-steroid solution. Can Respir J 2011;18:e59-e61.