



NDA 022-219: testosterone undecanoate (proposed tradename Aveed) for intramuscular injection

**Joint Meeting of the Advisory Committee for
Reproductive Health Drugs and the Drug Safety
and Risk Management Advisory Committee**

April 18, 2013

Audrey Gassman, M.D.

Deputy Director

Division of Reproductive and Urologic Products

U.S. Food and Drug Administration

Overview

- Why bring testosterone undecanoate injection to the Advisory Committees?
- Questions to the Committees

Why Discuss testosterone undecanoate?

- Efficacy of the proposed 750 mg (3 mL) dosing regimen for testosterone undecanoate was established
- Severe post-injection reactions (anaphylaxis and POME) were identified
- Important to assess risk-benefit for this injectable testosterone replacement therapy

Objective of Today's Meeting

The Agency is soliciting the Committee members' views on the risk-benefit profile for testosterone undecanoate injection intended for use in adult men for conditions associated with a deficiency or absence of endogenous testosterone

Question 1 for the Committees

VOTE: Given the severe post-injection reactions that were reported with testosterone undecanoate (TU) in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?

- a. If you voted “**Yes**”, please provide your rationale.
- b. If you voted “**No**”, please provide your rationale

Question 2 for the Committees

VOTE: Whether you voted “Yes or No” to Question 1, please vote whether the Applicant’s proposed instructions for use in product labeling that testosterone undecanoate be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.

- a. If you voted “**Yes**”, please provide your rationale.
- b. If you voted “**No**”, please provide other measures you would recommend to the Agency



Regulatory History and Major Clinical Issue

Mark Hirsch, M.D.

Medical Team Leader

Division of Reproductive and Urologic Products

U.S. Food and Drug Administration

Regulatory History

Original NDA

August 2007

Approvable Action

- *Reports of immediate post-injection adverse events pose a safety concern....*
- *Although their exact etiology has yet to be determined, these reports are consistent with POME and anaphylaxis.*

Regulatory History

Concern:

- 8 total clinical trial cases
 - 2 cases of post-injection sudden urge to cough and dyspnea in U.S. clinical trials
 - 6 other cases in ex-U.S. trials (convulsions, syncope, cardiovascular collapse, etc)
- 66 post-injection reaction cases from 33 months of ex-U.S. post-marketing
 - 28 *serious (42%), 12 hospitalized (18%)*
 - Pulmonary/Allergy consult: 2 cases reflect anaphylaxis and 2 others possible anaphylaxis

Regulatory History

FDA Request:

- Characterize the etiology of the post-injection reactions
- Determine the incidence of the post-injection reactions

Regulatory History

Complete Response

March 2009

Complete Response Action

- *Post-injection reactions continue to pose a safety concern.*
- *The proposed Risk Evaluation and Mitigation Strategy (REMS) does not assure that the benefits outweigh the risks of the product.*

Regulatory History

Concern:

- 5 POME reactions in clinical trials (5 of 2834 subjects)
 - *1 serious event*
- 0 anaphylaxis
- 3 additional clinical trial cases (*convulsions, syncope, circulatory collapse*)
- 116 post-injection reaction cases from 54 months of ex-U.S. post-marketing
- On final review - 106 post-marketing cases
 - 68 POME, 38 anaphylaxis

Regulatory History

FDA Request:

- Identify component(s) that are contributing to the post-injection reactions and re-formulate
- Identify a population in whom the identified risks would be acceptable

Regulatory History

Type A Meeting

May 2010

Sponsor proposed:

- *A narrowed target population*
- *A restricted distribution program*

Division responded:

- *The proposed target population is not viable*
- *The proposed restricted distribution proposal requires clarification*

Regulatory History

Type C Meeting

June 2011

Sponsor proposed:

- *A standard hypogonadal population*
- *REMS with Element to Assure Safe Use (ETASU) - a restricted distribution program*

Division responded:

- *After further consideration, a REMS with ETASU is not appropriate in this situation*

Regulatory History

Final Pre-Submission Communication November 2011

Sponsor:

- *400 post-injection reaction post-marketing cases*
 - *160 POME and 240 anaphylaxis*
 - *All POME cases will be counted*
 - *Only 23 anaphylaxis cases will be counted*

Division:

- *MedDRA search terms are reasonable*
- *FDA will continue to use the NIH (clinical) definition of anaphylaxis during evaluation*
- *Provide detailed reports for all cases of POME and anaphylaxis irrespective of adjudication*

Regulatory History

Most Recent Submission

November 2012

- Focus = Severe post-injection reactions in clinical trials and ex-U.S. post-marketing experience
- In clinical trials – few cases; to be discussed by Dr. Kornegay
- Postmarketing experience
 - Sponsor identified 228 cases of POME and 45 cases of anaphylaxis
 - FDA identified **137 severe post-injection reaction cases**
 - Any anaphylaxis
 - Any SAE
 - Any case requiring treatment
 - Any case involving syncope or sudden lowering of BP
 - Any case reported as serious or medically important

Major Clinical Issue

Severe Post-Injection Reactions (n=137)

- Impaired breathing, coughing fits, choking
 - Cyanosis
 - Loss of consciousness
- Throat swelling, throat tightness
- Nausea and vomiting
- Sweating, dizziness, anxiety, muscular weakness
- Cardiovascular changes
 - Hypotension
 - Hypertension / increased BP
 - Chest discomfort / EKG change
- Urticaria / rash / face edema / itching

Major Clinical Issue

Severe Post-Injection Reactions (n=137)

Temporal Relationship between Reactions and Injection of TU						
During Injection	Immediate After	2'-10'* After	Within 60 Min	1-8 hr After	Not Specified	Within 24 hrs
43	51	9	3	1	25	5
94 (68.6%)		12 (8.8%)		31 (22.6%)		

* ' = minute(s)

Major Clinical Issue

Severe Post-Injection Reactions (n=137)

Hospitalized /ER	Life- Threatening	Medically Significant*	Syncope /BP Dropped
32 (23%)	9 (7%)	128 (93%)	19 (14%)

* “Medically significant” indicated by the reporters.

Major Clinical Issue

Severe Post-Injection Reactions (n=137)

Subjects Who Underwent Treatments (n=60, 44%)

Epinephrine	Cortico- Steroids	Anti- Histamines	Other Therapies
13 (10%)	38 (28%)	30 (22%)	18 (13%)

Major Clinical Issue

Severe Post-Injection Reactions with Other Injectable Testosterone Products (n=33)

- FAERS search using same criteria as for testosterone undecanoate injection
- 44 years experience (January 1969 – January 2013)
- 33 severe post-injection reaction cases identified
 - 14 cases - severe POME
 - 19 cases - anaphylaxis

Testosterone Undecanoate Severe Post-Injection Reactions in the Post-Marketing Setting

Joint Meeting of the Advisory Committee for
Reproductive Health Drugs and Drug Safety and Risk
Management Advisory Committee

April 18, 2013

Stacy Chin, MD

Clinical Reviewer

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

ODE II, OND, CDER, FDA

Overview

- Background
- Anaphylaxis
 - Diagnostic criteria
 - Results of case review
 - Examples of anaphylaxis cases
 - Potential etiologies
- Pulmonary oil microembolism (POME)
 - Definition/Pathophysiology
 - Results of case review
 - Examples of POME cases
- Conclusions

Background

- DPARP initially consulted to review post-marketing reports from the original NDA submitted August 24, 2007
- Involved since then to review additional reports of post-injection reactions on several occasions
- For current NDA submission, consulted to review cases of potential anaphylaxis and pulmonary oil microembolism (POME) culled from Applicant's spontaneous post-marketing surveillance database spanning an 8 year period

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Anaphylaxis Determination

2006 NIAID/FAAN anaphylaxis diagnostic criteria

1. Acute onset of an illness 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:
 - a. *Involvement of the skin-mucosal tissue*
 - b. *Respiratory compromise*
 - c. *Reduced BP or associated symptoms*
 - d. *Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)*

3. Reduced BP after exposure to known allergen for that patient:
 - a. *Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. *Adults: systolic BP <90 mm Hg or >30% decrease from baseline*

Anaphylaxis – Results of Case Review

- Post-marketing reports searched over 8 yr period (2003-11)
- Revealed 330 potential anaphylaxis reports

Anaphylaxis Cases	NIAID Definition (Criterion 1 only)
Ex-US Post-Marketing Reports November 2003 - November 2011	47
Periodic Safety Update Report November 2011- April 2012	6
Total Anaphylaxis Cases	53

Anaphylaxis – Case Examples

- Patient 1
 - 39 year old male: “Anaphylactic shock” occurred during Nebido injection with symptoms of throat closing, coughing, difficulty breathing, facial and tongue swelling. Treated with epinephrine twice and oxygen, hospitalized.
- Patient 2
 - 54 year old male: “Anaphylactic reaction” with onset halfway through injection of 2nd dose with symptoms of cough, progressing to difficulty breathing, laryngeal edema, diaphoresis, and near respiratory arrest. Treated with epinephrine twice and oxygen, transferred to hospital.

Anaphylaxis – Assessment for Potential Etiologies

1. Clinical history
2. Laboratory testing (acute episode)
 - Histamine, total tryptase
 - Serum 24 hour urine histamine and N-methylhistamine
3. Confirmation of trigger
 - Skin testing, allergen-specific IgE
 - Incremental challenge/provocation tests

No substantial studies have been conducted to investigate the underlying cause

- Study IP157-003

Anaphylaxis – Assessment for Potential Etiologies

- 3 components in the TU drug product
 - Testosterone undecanoate (750 mg/3 mL)
 - Castor oil (885 mg/3 mL)
 - Benzyl benzoate (1500 mg/ 3mL)

Evidence from literature, case reports, or from substance chemistry/biologic action that any of the drug product components could potentially cause anaphylaxis

Anaphylaxis – Testosterone Undecanoate

- Testosterone ester; forms active testosterone by cleavage of ester side chain
 - No literature reports of immediate hypersensitivity reactions with testosterone undecanoate
- Case report suggests testosterone may be capable of eliciting anaphylaxis
 - 46 year old male with “Anaphylaxis” (cough, rash, closing of airways) immediately after Nebido injection
 - Previously discontinued both Testogel and Andropatch due to allergic skin reactions
 - Testosterone only common ingredient

Anaphylaxis – Castor Oil

- Castor oil derived from castor seed (*Ricinus communis*)
 - Frequently used as a skin-conditioning agent, emulsion stabilizer, surfactant in cosmetics, food additive, and laxative
 - Potent allergens: Ric c 1, Ric c 2, and allergen 3
 - Prolongs half-life of depot formulation drugs
- Ricinoleic acid – primary component of castor oil
 - Implicated in allergic contact dermatitis
 - Hydroxy acid similar to salicylic acid
 - Interacts with prostanoids
- Polyethoxylated castor oil implicated in anaphylactic reactions
 - Cyclosporin and paclitaxel

Anaphylaxis – Castor Oil

- Case report supports concept of castor oil and salicylate cross-reactivity
 - 38 year old male: immediate adverse reaction during 1st Nebido injection; treated with prednisolone and cetirizine
- Subsequently enrolled in Study IP157-003
 - Skin prick testing to Nebido negative
 - Symptoms after 1/10th dose (0.4 mL) Nebido: flushing, hypertension, and dyspnea; treated with prednisolone, Fenistil (topical antihistamine), and loratadine
 - Reported similar hypersensitivity reactions to aspirin (salicylic acid)

Anaphylaxis – Benzyl Benzoate

- Colorless liquid widely used as a preservative and flavoring agent
 - Lowers viscosity in TU
- Known to produce contact urticaria and immediate reactions
 - Case report implicates benzyl benzoate as cause of anaphylaxis
 - 16 year old boy: “Anaphylactic reaction” < 3 minutes after 3rd dose of Reandron
 - Generalized urticaria, throat tightening, angioedema of the lips and face, dyspnea, and hypotension among others. Treated with epinephrine, promethazine, prednisolone, oxygen, and IV fluids
 - Skin prick testing: 10x8 mm wheal to Reandron, 10x10 mm wheal to benzyl benzoate; no reaction to castor oil or testosterone undecanoate alone

Summary – Anaphylaxis

- Anaphylaxis identified using NIAID Criterion 1
 - Most stringent (conservative estimate)
 - Potential for under-reporting cases
- Case review
 - 47 cases of anaphylaxis over 8 year period (2003 – 2011)
 - 6 additional cases from safety update report (11/2011 – 4/2012)
- TU product components
 - Testosterone undecanoate
 - Castor oil
 - Benzyl benzoate
- Literature and case reports suggest any component may cause anaphylaxis

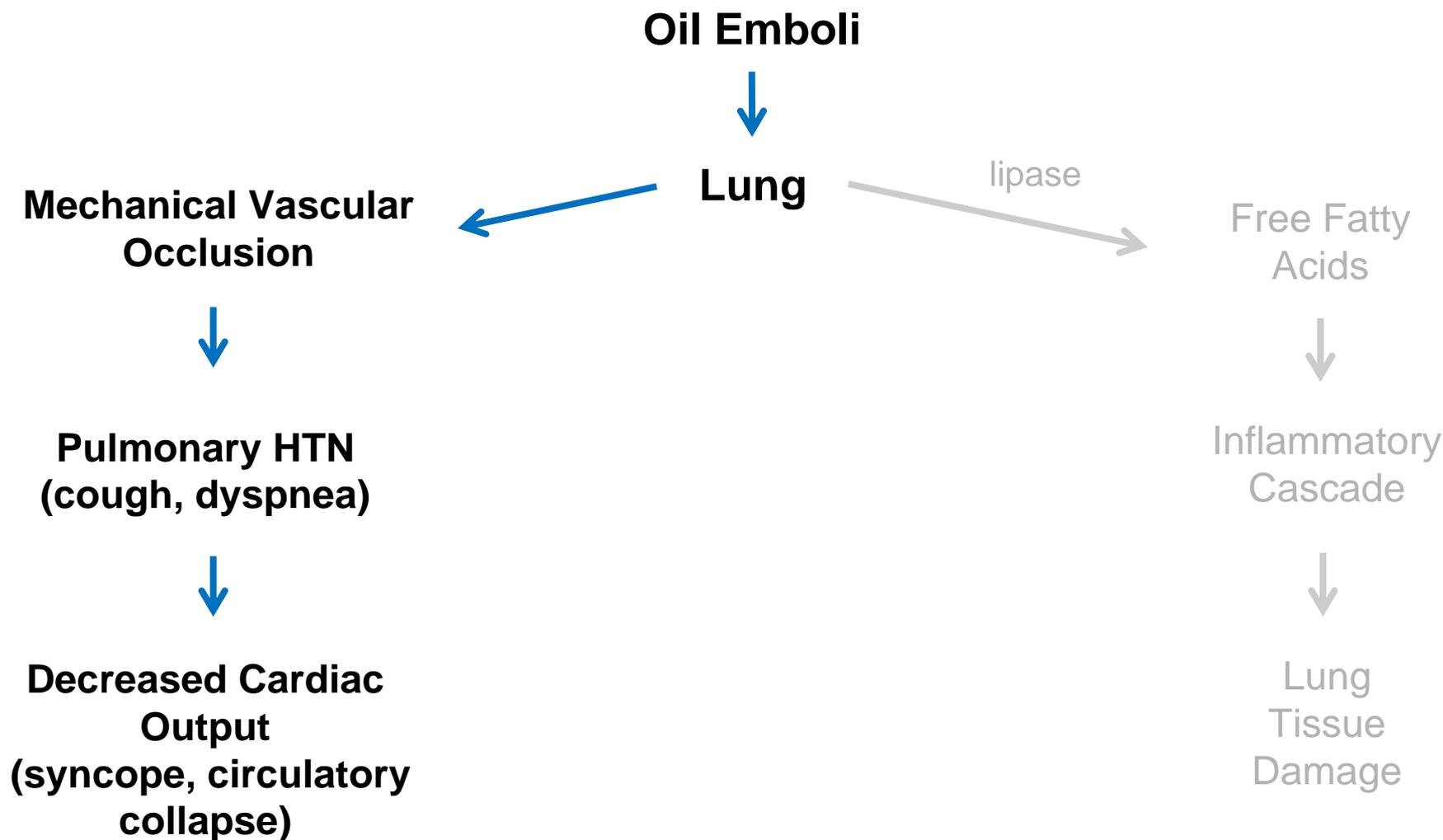
Overview

- Background
- Anaphylaxis
 - Diagnostic criteria
 - Results of case review
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- **Pulmonary oil microembolism (POME)**
 - Definition/Pathophysiology
 - Results of case review
 - Examples of POME cases
- Conclusions

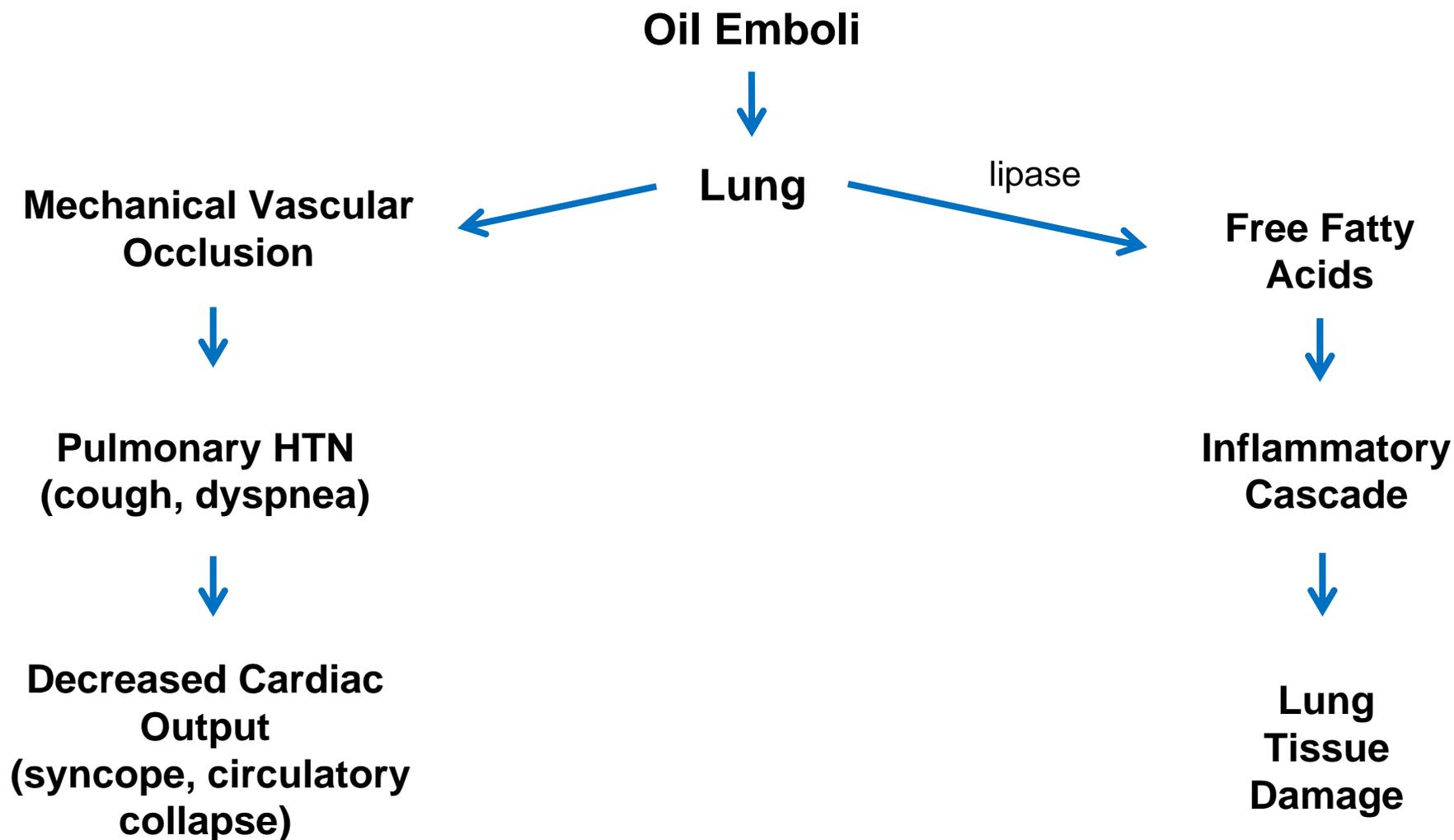
Pulmonary oil microembolism (POME)

- Adverse reaction as a result of direct vascular or lymphovascular delivery of oil-based preparations to the pulmonary microvasculature
- Volume of oil hypothesized to play a role
- Symptoms and severity are variable
 - Cough
 - Dyspnea
 - Chest pain
 - Dizziness
 - Profuse sweating
 - Paresthesia
 - Syncope
 - Circulatory collapse

POME - Pathophysiology



POME - Pathophysiology



POME - Case Definition

- Reported event occurred within 24 hours of injection
- Symptoms involved
 - Cough or dyspnea (with or without other symptoms)
 - 2 or more symptoms suggestive of POME: throat irritation, malaise, profuse sweating, chest pain, dizziness, paresthesia, or syncope
- Cases severe if any of the following criteria were met:
 - Reported as a serious adverse event
 - Required hospitalization or emergency department care
 - Required medical treatment
 - Involved syncope or decrease in blood pressure
 - Labeled medically important, serious, or life-threatening by the reporter or Applicant

POME – Results of Case Review

- Post-marketing reports searched over 8 yr period (2003-11)
- Revealed 533 potential POME reports

Post-marketing Reports (Ex-US)	Cases of POME
POME cases November 2003 – November 2011	191
Periodic Safety Update Report November 2011 – April 2012	8
Total POME cases November 2003 – April 2012	199
Severe POME cases November 2003 – April 2012	84

POME – Case Examples

Patient 3

- 52 year old male: Heat sensation in neck, tickle in throat, severe dyspnea, headache, muscle twitching, and 20 second loss of consciousness following Nebido injection. Shock positioning and IV fluid resuscitation. ICU hospitalization; Head CT without pathological findings. Retrospective diagnosis of “micro fat embolism”.

Patient 4

- Male of unknown age: Circulatory collapse with several minutes of unconsciousness, nausea, cough, and encopresis (defecation) 15 seconds following 2nd Nebido injection. Unclear if treatment given. Recovered over unknown period of time.

POME – Case Example

Patient 5

- Male of unknown age: Difficulty breathing, dizziness, vertigo, darkened vision, weakness, pallor, profuse sweating, and total absence of autonomy with onset 1-2 minutes after Nebido injection. “Thought he would die as a result of these events”. Unclear if treatment was given. Recovered after unspecified duration.

POME - Summary

- Total of 199 cases of POME identified
 - 84 severe cases
 - Severe dyspnea, loss of consciousness, circulatory collapse, loss of bowel function
- Relationship to volume
 - Approved dose utilizes 4 mL (1000 mg)
 - Insufficient clinical information with 3 mL (750 mg)
 - Many reactions reported to occur mid-injection
- Long-term cardiopulmonary consequences
 - Unknown chronic effects of repeated less severe POME events over time

Conclusions

- Anaphylaxis and POME reported in the post-marketing setting
 - 53 cases anaphylaxis (most conservative definition)
 - 199 cases of POME, 84 severe
 - 137 total severe post-injection reactions (anaphylaxis + severe POME)
- Concern for long-term consequences of POME
 - TU drug product intended for chronic use
 - Unknown effects of both severe and repeated mild events on future cardiopulmonary function

Reporting and Incidence Rates for Pulmonary Oil Microembolism (POME) and Anaphylaxis

**Joint Meeting of the Advisory Committee for Reproductive Health Drugs
and Drug Safety and Risk Management Advisory Committee**

April 18, 2013

Cynthia Kornegay, Ph.D.
Epidemiologist
Division of Epidemiology II
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

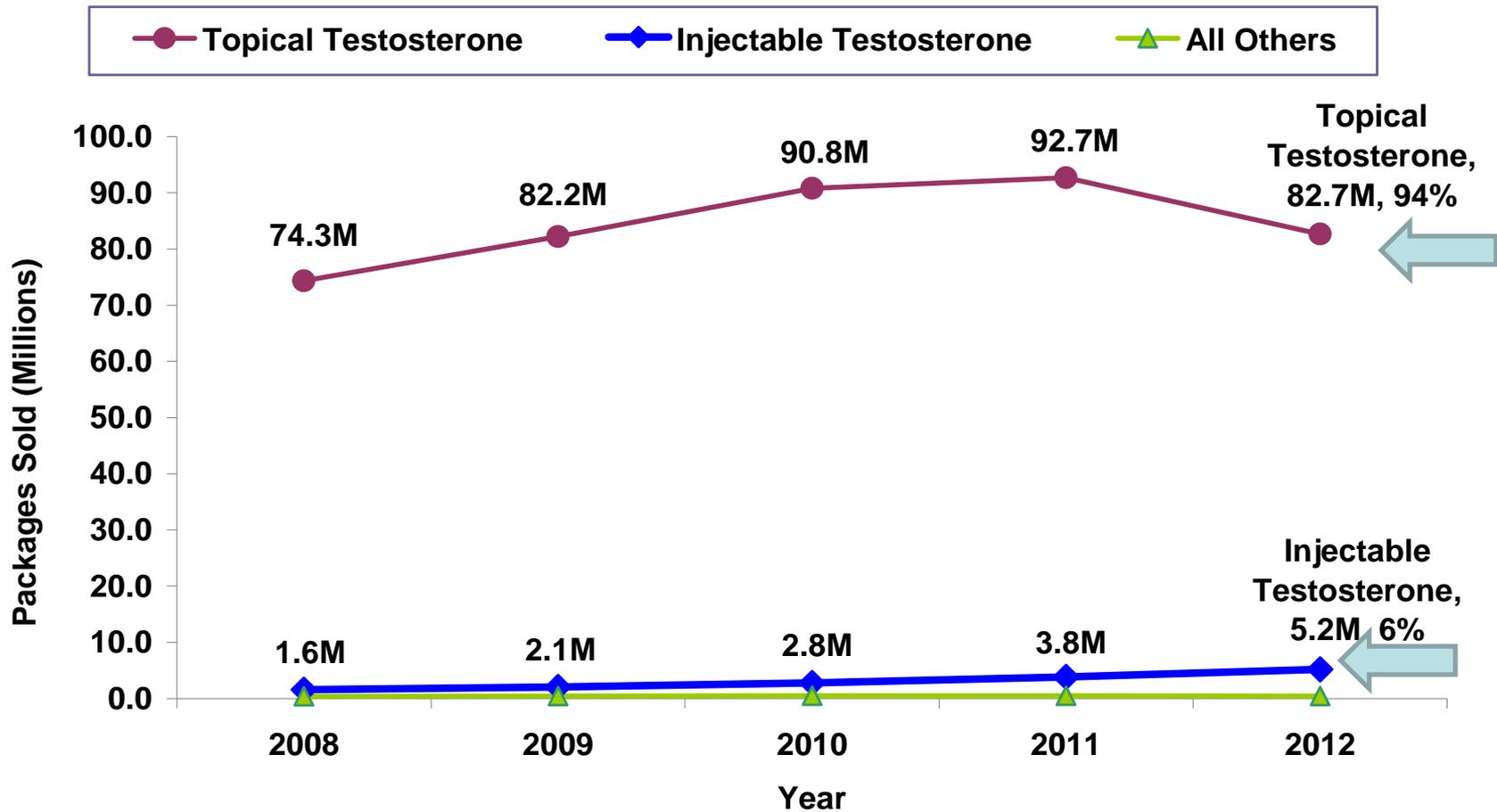
Outline

- Prevalence of hypogonadism
- U.S. Testosterone Use
- Reporting Rates
- Applicant Incidence Rates
 - POME and Anaphylaxis Incidence Rates
 - Incidence Rate Observations
- Conclusions

Prevalence of Hypogonadism

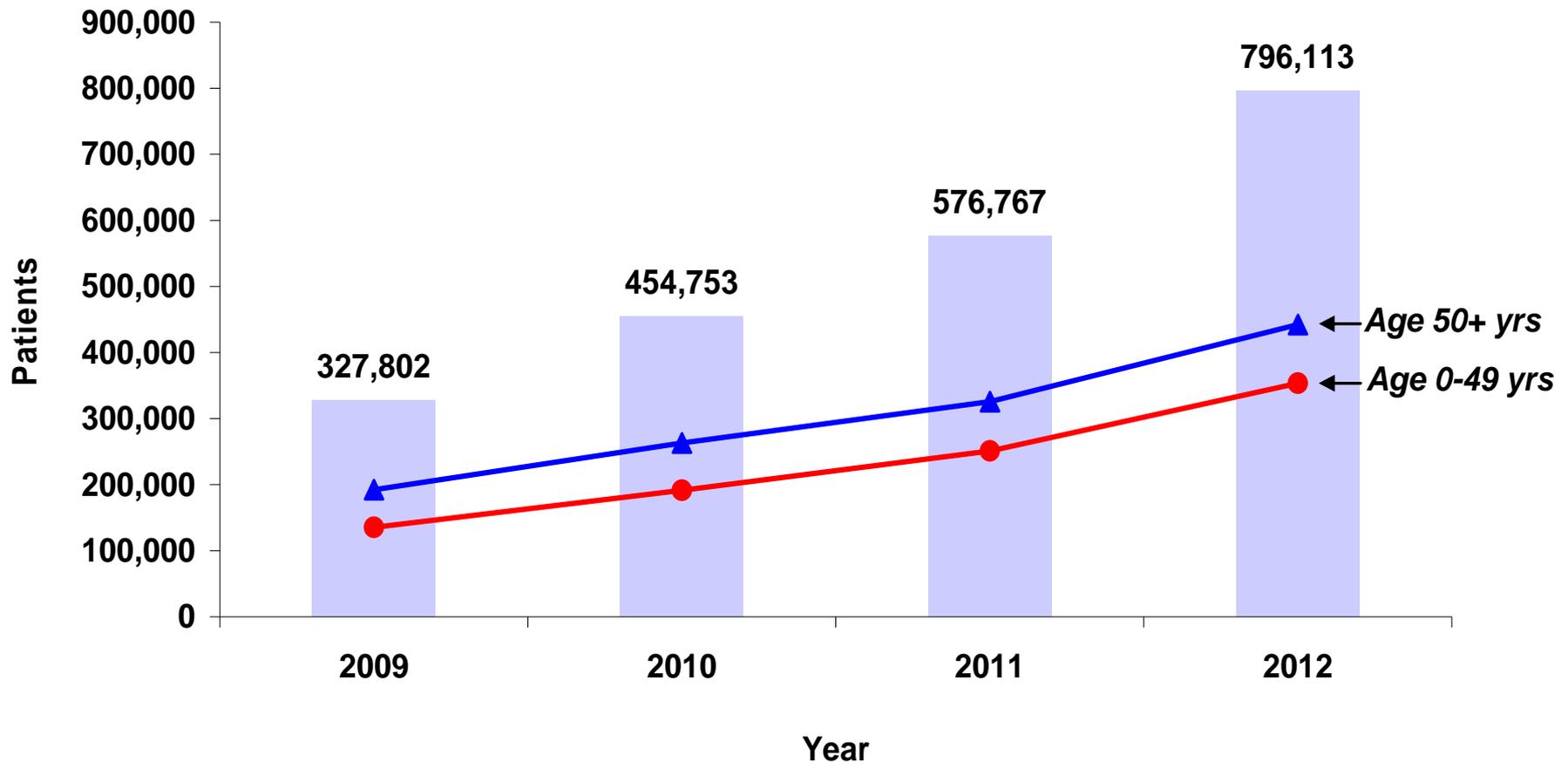
- Two types
 - Primary: disorder of testes
 - Secondary: pituitary gland conditions
- Prevalence estimates
 - 30% of men at any age
 - 4 to 5 million men in U.S.
 - 6% to 12% are symptomatic
- Approximately 5% of U.S. men and 1% of men in other countries receive treatment

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



Source: IMS Health, IMS National Sales Perspectives™, Year 2008-2012, extracted March 2013

Nationally estimated number of patients with a prescription claim for testosterone injectables* in U.S. outpatient retail pharmacies



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

*injectable testosterone products: testosterone cypionate and testosterone enanthate



Postmarketing Reporting Rate Evaluation

Reporting Rates

- FDA and Applicant had similar reporting rates
- Advantages of reporting rates
 - Simple to construct
 - Uses available information
 - Seemingly intuitive to understand
 - Comparison to incidence rates
- Several conditions must be met for reporting rates to be valid and interpretable

Reporting Rate Assumptions – Identifying Population at Risk

- To calculate a rate, both the cases (numerator) and population at risk (denominator) must be from the same base population
- Otherwise, the resulting ratio describes a correlation; a direct relationship may or may not exist
 - For example: data from a spontaneous reporting system (numerator) and sales data (denominator)
- Specific drug not always identified in report (e.g., “injectable testosterone” vs. “Nebido”)

Reporting Rate Assumptions – Identifying Cases of Interest

- Several decision points may stop a potential case from being reported
 - For example: event not recognized, association with drug not recognized, insufficient information, etc.
- Similarity of POME and anaphylaxis symptoms
- Result is underascertainment and underreporting

Reporting Rate Observations

- Cannot compare reporting and incidence rates
 - May be lower due to under-reporting
 - Particularly true if sales data is used as a denominator
 - No clear relationship between vials sold and patients
 - If substantial levels of abuse or diversion is suspected, no way to know what percentage of sales used for labeled indications
- Crude measure, should not be relied upon if any other measures, especially incidence rates, are available

Applicant Reported Incidence Rates

Applicant Incidence Rates*

- Incidence rates from clinical studies database (N=3556)
 - 725 men in clinical hypogonadal studies
 - 2424 men in postmarketing hypogonadal studies
 - 407 men in clinical contraceptive studies
- 272 men received 750 mg/3 ml injections in clinical studies; all others received 1000 mg/4 ml dose

*Adapted from Summary of Clinical Safety, pages 157-172

Applicant POME Incidence Rates*

	Clinical and postmarketing studies			Zitzmann (2013)	Gu (2009)
	750 mg/3 ml	1000 mg/4 ml	Overall	1000 mg/4ml 8-12 weeks	500 mg / month
Number of patients	467	3,089	3,556	1,438	1,054
Potential cases from Query	162	254	416	--	--
Adjudicated Cases	1	8	9	3	22
Cases/10,000 injections	3.2	4.7	4.5	4.8	5.1

*Adapted from Summary of Clinical Safety, tables 22 and 24, and PSUR 10, page 43

Applicant Anaphylaxis Incidence Rates*

Incidence of anaphylaxis in clinical and postmarketing studies			
	750 mg/3 ml dose (N=467)	1000 mg/4 ml 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	5.5	4.7

- Drug-induced anaphylaxis background rates in the published literature vary widely
 - Range from 0.8 to 5 cases per 10,000 person-years
 - Includes a wide variety of prescription drug products

*Adapted from Summary of Clinical Safety, tables 32 and 33

Applicant Reporting and Incidence Rate Evaluation Limitations

- Evolving methodology for POME classification
- Applicant used multiple definitions for anaphylaxis
- Unable to assess quality of clinical studies: protocols and final study reports not available
- Some cases were difficult to categorize
 - Minimal description of symptoms
 - Additional data not available

Conclusions

- POME incidence rates remained consistent across studies
- Anaphylaxis incidence rates at high end of generally cited range for drug-induced anaphylaxis
- Combined incidence rate of 6.4 cases per 10,000 injections
- The risk of a severe and life-threatening event should be carefully weighed against the benefits for this product, particularly since multiple alternatives are available

Risk Management Considerations

Testosterone Undecanoate (TU) Intramuscular Injection

**Joint Meeting of the Advisory Committee for Reproductive
Health Drugs and Drug Safety and Risk Management
Advisory Committee**

Suzanne Robottom, Pharm.D.

Risk Management Analyst

Division of Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Can POME and anaphylaxis associated with testosterone undecanoate (TU) be mitigated to improve the risk benefit profile, and if so, how?

Overview

- FDA's authority
- Risk/benefit considerations for TU
- Endo's risk management proposal
- Other risk management approaches

Food and Drug Administration Amendments Act (FDAAA) of 2007

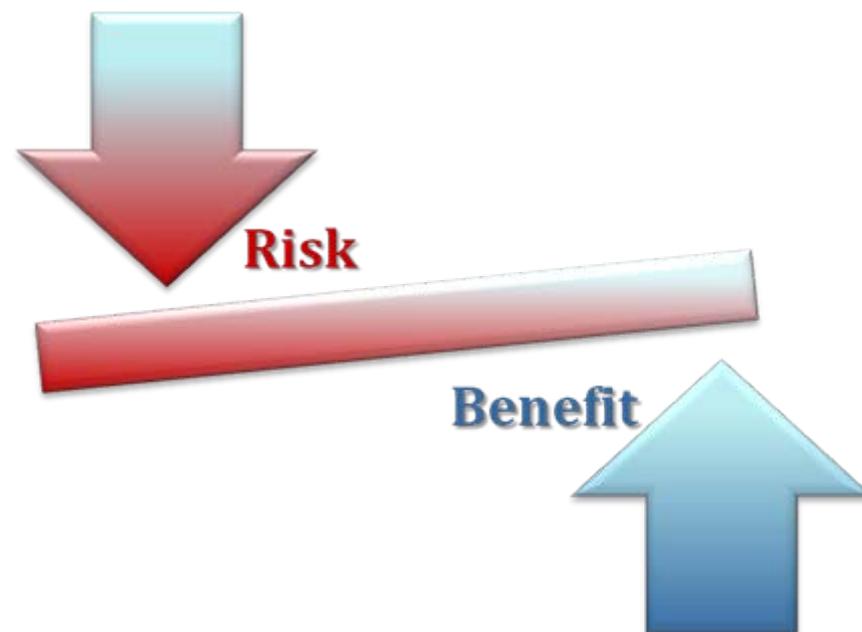
- FDAAA authorizes the FDA to require a Risk Evaluation and Mitigation Strategy (REMS)
- Risk Evaluation and Mitigation Strategy (REMS)
 - A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks
 - Designed to achieve specific goals to mitigate the serious risk(s) associated with use of a drug
 - Authority to require either pre-approval or post-approval

Elements of a REMS

- A REMS *may* include
 - Medication Guide or Patient Package Insert
 - A Medication Guide *does not* have to be part of a REMS
 - Communication Plan
 - Elements to Assure Safe Use (ETASU)
 - Implementation Plan
- A REMS *must* include
 - Timetable for Submission of Assessments

Risk/Benefit Considerations

- Analysis of the condition
- Current treatment options
- Benefit
- Risk
- Risk management



Analysis of the Condition

- Hypogonadism is a condition resulting from insufficient endogenous secretion of testosterone
- Drug utilization data estimates indicate that use of testosterone replacement products has been growing
- What is an acceptable treatment risk?

Current Treatment Options

- Variety of testosterone replacement formulations available
- There are approved and marketed intramuscular injectable formulations available

The Benefit

- TU replaces serum testosterone to the normal range in adult men
- TU has an extended dosing interval resulting in fewer injections per year compared to the approved intramuscular injectable formulations

The Risk – POME & Anaphylaxis

- Magnitude of the risk
 - Clinical trials: incidence small but similar across studies
 - Post-marketing: events continue to occur; magnitude is unknown
- Severity of the risk
 - Severe post-injection reactions resulting in resuscitation measures and hospitalization have been reported
 - A reaction can occur during or after any dose
 - Cases of reactions during first dose, after 4 years of treatment
 - No deaths, to date
 - Long term cardiopulmonary consequences of POME are unknown
- No definitive methods to predict or prevent post-injection reactions with the current formulation
 - Risk management focus limited to informing and minimizing serious sequelae

Endo's Risk Management Proposal

- Reduce injection volume 4mL → 3mL
- Product labeling
 - Slow administration
 - 30 minute post-injection observation
- Ship directly to prescriber
- REMS - Communication Plan with a DHCP letter
- Other proposed educational materials

FDA Comments – Endo’s Risk Management Proposal

- Impact of reduced injection volume is unknown and many reactions occurred during the injection
- Distributing directly to the prescriber for administration is appropriate
 - Reactions continue to occur in Europe despite proper injection technique including slow administration
- There is little incentive for prescribers to review materials that are not required given the demands on their time and competing priorities.

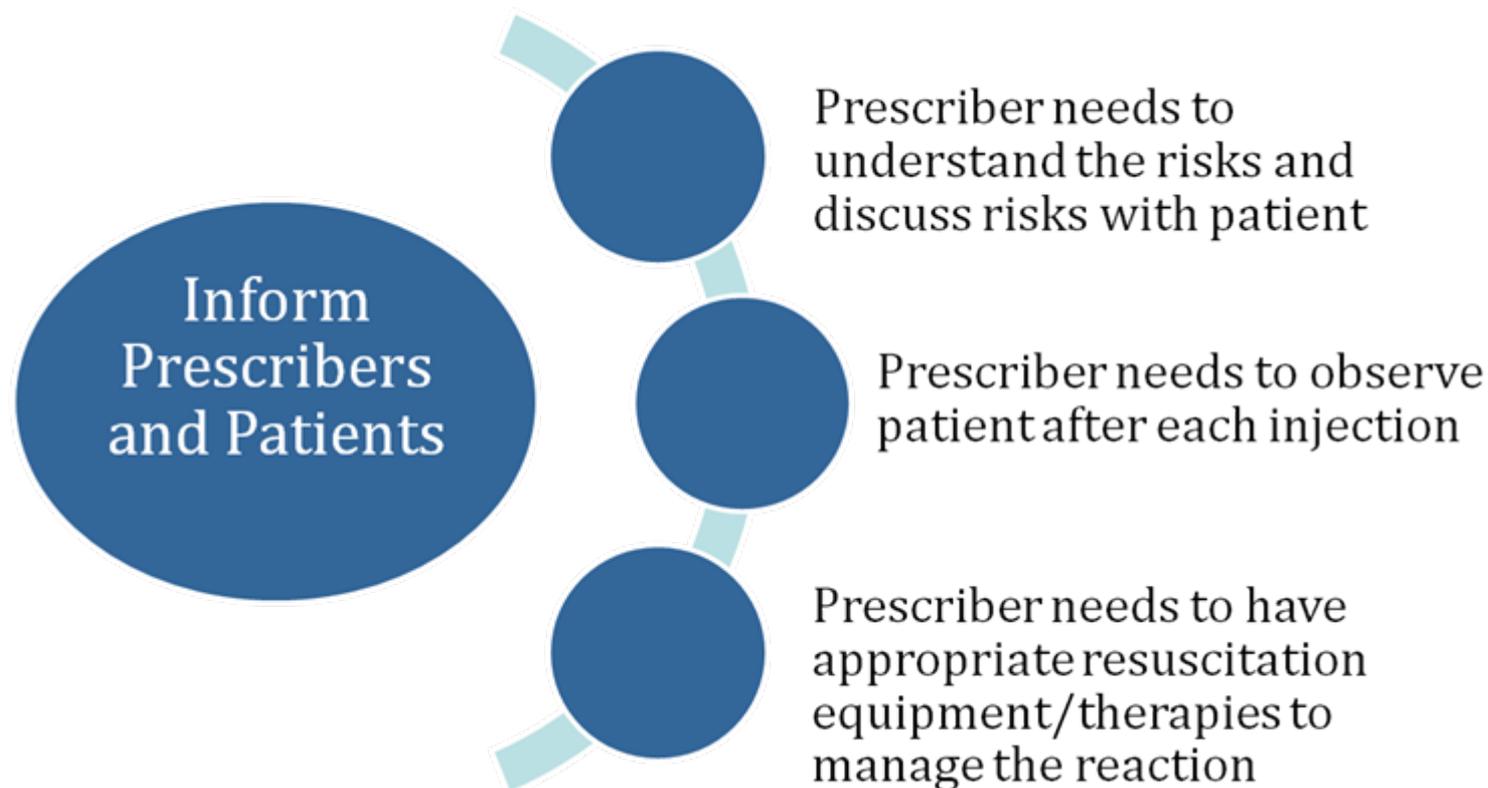
Other Risk Management Approaches

1. Reformulation

- If these reactions are due to the excipients, the most effective mechanism to prevent the events is product reformulation
- TU would need to be redeveloped beginning with Phase 1 trials

Other Risk Management Approaches

2. Communication Efforts



Other Risk Management Approaches

3. Prescribing/Distributing Restrictions

Pharmacy/Distributor Certification

Ensure only certified prescribers receive TU



Prescriber Certification



Complete required training and agree to implement safe use conditions

Only trained and certified prescribers can order/administer TU

Patient Enrollment

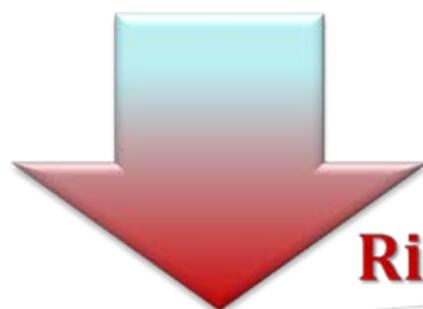
Document risk was discussed before receiving treatment

3. Prescribing/Distributing Restrictions

- Require significant resources to develop, implement, participate in, maintain, and monitor
- Considerable burden on prescribers, pharmacists/distributors, and patients

In Summary

Anaphylaxis & POME



Risk



Benefit



Fewer injections per year