Dear Dr. Koev:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) AndroGel® (testosterone gel) 1%.

Sections 505(o)(3) and 505(o)(4) of the FDCA authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes and to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Androgel 1% was approved on February 28, 2000, we have become aware of the risk of major adverse cardiovascular events associated with testosterone replacement therapy.

Androgel 1% is indicated for replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone replacement is a long-accepted, efficacious therapy in men who have an absence or deficiency of testosterone due to specific inherited or acquired diseases of the testes, hypothalamus, or pituitary (classical hypogonadism). In contrast, the efficacy of testosterone replacement therapy (TRT) has not been established for age-related hypogonadism (men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism). Despite this uncertain benefit for age-related hypogonadism, FDA’s drug utilization analysis has found a substantial increase in TRT use in recent years, particularly in men 40 years of age and older, with a majority of this use in middle-aged and older men coded to the non-specific diagnosis of “testicular hypofunction, not elsewhere classified” (International Classification of Diseases, Ninth Revision code 257.20). \(^1\) Furthermore, we have become aware of observational studies reporting a potential increased risk of major adverse cardiovascular outcomes, including myocardial infarction, stroke, and death, 

\(^1\) Mohamoud MA. Testosterone Replacement Therapy and Drug Utilization Patterns Presentation. Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. September 17, 2014.
associated with testosterone therapy.\textsuperscript{2,3} These observational studies included aging men treated with testosterone. Other available data have not definitely excluded this potential risk. Given these findings, on September 17, 2014, the FDA convened a joint meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the appropriate indicated population for TRT and the potential risk of major adverse cardiovascular events associated with its use.

Members of the September 17, 2014, joint Advisory Committee overwhelmingly voted to revise the current indication for testosterone replacement therapies. The committee concluded that the available evidence supports an indication for testosterone therapy only in men with classical hypogonadism, and that TRT product labeling should include a statement that efficacy and safety of testosterone replacement therapy have not been established in age-related hypogonadism. Committee members also stated that the TRT labels should be revised to include the potential cardiovascular risks associated with testosterone use. To further assess this potential risk, panel members commented that only a controlled clinical trial, and not observational studies, can adequately address the concerns.

The FDA has carefully considered the available data in conjunction with the recommendations from the joint Advisory Committee meeting and has determined that the indication for Androgel 1\% and all approved testosterone replacement therapies be limited to classical hypogonadism, that TRT product labeling include a limitation of use statement conveying that efficacy and safety of testosterone replacement therapy have not been established for age-related hypogonadism, and that the potential for cardiovascular risk be included in labeling to adequately inform healthcare providers and patients. The FDA has also determined that a cardiovascular study is needed to further evaluate the potential for cardiovascular risk among testosterone users, which are predominantly middle-age and aging men.

We consider this information to be “new safety information” as defined in section 505-1(b)(3) of FDCA.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Since Androgel 1\% was approved on February 28, 2000, we have become aware of new safety information, as described above.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, associated with testosterone replacement therapy, of which Androgel 1\% is a member.


Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signal of a serious risk of MACE associated with the class of testosterone therapy, of which Androgel 1% is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

XXXX-1 A randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men. We recommend that this trial also assess other important safety and efficacy outcomes associated with testosterone therapy.

The following timetable proposes the schedule by which you will conduct this trial:

- Final Protocol Submission: 06/2016
- Trial Completion: 06/2021
- Final Report Submission: 06/2022

We encourage you to work together with other holders of new drug applications approved for testosterone replacement therapy on this required clinical trial.

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that, to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.
SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, in the published literature, and at the September 17, 2014, joint Advisory Committee meeting, the new safety information should be included in the labeling for the class of testosterone replacement therapy products, of which Androgel 1% is a member, as follows:

Additions are noted by underline and deletions are noted by strikethrough.

Note that the labeling that follows addresses the safety labeling changes only and does not include the full text of product labeling. The cross references may require adjustment in your final product labeling.

HIGHLIGHTS

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INDICATIONS AND USAGE

Androgel 1% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure…

- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Important Limitations of use:

- Safety and efficacy of Androgel 1% in men with age-related hypogonadism have not been established (1).

- Safety and efficacy of Androgel 1% in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

DOSAGE AND ADMINISTRATION

Add as new second bullet:
Prior to initiating Androgel 1%, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2.X).

WARNINGS AND PRECAUTIONS

The new bullet follows the ‘Venous thromboembolism (VTE)’ bullet:

Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.X)

TABLE OF CONTENTS

Update the TABLE OF CONTENTS to reflect the changes in the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Androgel 1% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

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- Safety and efficacy of Androgel 1% in men with age-related hypogonadism have not been established. Age-related hypogonadism refers to men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism.
- Safety and efficacy of Androgel 1% in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for Androgel 1% differs from…

Prior to initiating Androgel 1%, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosing and Dose Adjustment
5 WARNINGS AND PRECAUTIONS
Add new Cardiovascular Risk subsection after the subsection titled “Venous Thromboembolism”

5.X Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Androgel 1%.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience
Add new Organ Class “Cardiovascular disorders;” followed by “Myocardial infarction, stroke” to Table 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
.... Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter’s syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Hypogonadal Males

In patients treated with AndroGel 1%, there were no observed differences in the average daily serum testosterone concentrations at steady-state based on age, cause of hypogonadism, or body mass index.

AndroGel 1% 50 mg/day and 100 mg/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study.
Changes in the 75 mg dose group were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with AndroGel 1% 100 mg.

AndroGel 1% treatment at 50 mg/day and 100 mg/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). The degree of penile erection as subjectively estimated by the patients, increased with AndroGel 1% treatment, as did the subjective score for “satisfactory duration of erection.” AndroGel 1% treatment at 50 mg/day and 100 mg/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 75 mg dose. DHT concentrations increased in…

MEDICATION GUIDE

In addition to the changes described above, revise the Medication Guide to include the new safety information for Androgel 1%. Your revised Medication Guide will be considered part of the proposed REMS described below.

Under “What is Androgel 1%?”

Androgel 1% is a prescription medicine that contains testosterone. DRUG is used to treat adult males who have low or no testosterone due to certain medical conditions.

Your healthcare provider will test your blood before you start and while you are taking Androgel 1%.

It is not known if Androgel 1% is safe or effective to treat men who have low testosterone due to aging.

It is not known if Androgel 1% is safe or effective in children younger than 18 years old. Improper use of Androgel 1% may affect bone growth in children.

Under “What are the possible side effects of Androgel 1%?”

Androgel 1% can cause serious side effects including:

- If you already have enlargement of your prostate gland your signs and symptoms…
- Possible increased risk of prostate cancer…
- Blood clots in the legs or lungs. Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- Possible increased risk of heart attack or stroke.
- In large doses Androgel 1% may lower your sperm count.
- Swelling of your ankles, feet, or body, with or without heart failure.
- Enlarged or painful breasts.
- Have problems breathing while you sleep (sleep apnea).
• Blood clots in the legs or lungs. Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENT

The REMS for Androgel 1% was originally approved on February 28, 2000, and the most recent REMS modification was approved on June 19, 2014. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Androgel 1% must be modified based on the information described above to ensure that the benefits of the drug outweigh its risks. This determination is based on the need to conform the approved REMS to the safety labeling changes described above.
Your proposed REMS modification must include changes to the Medication Guide.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on September 18, 2009.

The proposed REMS modification submission should include the REMS document and the revised Medication Guide.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of Androgel 1% outweigh the risks, you must submit a proposed REMS modification within 30 days of the date of this letter as a separate supplement to your NDA.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 021015
PROPOSED REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021015
PROPOSED REMS MODIFICATION-AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, call Meredith Alpert, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
02/09/2015

Reference ID: 3698850
LABELING SUPPLEMENT AND PMR REQUIRED

Endo Pharmaceuticals, Inc.
Attention: Paula Clark
Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed\(^\text{®}\) (testosterone undecanoate) intramuscular injection.

Sections 505(o)(3) and 505(o)(4) of the FDCA authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes and to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Aveed was approved on March 5, 2014, we have become aware of the risk of major adverse cardiovascular events associated with testosterone replacement therapy.

Aveed is indicated for replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone replacement is a long-accepted, efficacious therapy in men who have an absence or deficiency of testosterone due to specific inherited or acquired diseases of the testes, hypothalamus, or pituitary (classical hypogonadism). In contrast, the efficacy of testosterone replacement therapy (TRT) has not been established for age-related hypogonadism (men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism). Despite this uncertain benefit for age-related hypogonadism, FDA’s drug utilization analysis has found a substantial increase in TRT use in recent years, particularly in men 40 years of age and older, with a majority of this use in middle-aged and older men coded to the non-specific diagnosis of “testicular hypofunction, not elsewhere classified” (International Classification of Diseases, Ninth Revision code 257.20).\(^1\)

Furthermore, we have become aware of observational studies reporting a potential increased risk of major adverse cardiovascular outcomes, including myocardial infarction, stroke, and death,

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associated with testosterone therapy.\textsuperscript{2,3} These observational studies included aging men treated with testosterone. Other available data have not definitely excluded this potential risk. Given these findings, on September 17, 2014, the FDA convened a joint meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the appropriate indicated population for TRT and the potential risk of major adverse cardiovascular events associated with its use.

Members of the September 17, 2014, joint Advisory Committee overwhelmingly voted to revise the current indication for testosterone replacement therapies. The committee concluded that the available evidence supports an indication for testosterone therapy only in men with classical hypogonadism, and that TRT product labeling should include a statement that efficacy and safety of testosterone replacement therapy have not been established in age-related hypogonadism. Committee members also stated that the TRT labels should be revised to include the potential cardiovascular risks associated with testosterone use. To further assess this potential risk, panel members commented that only a controlled clinical trial, and not observational studies, can adequately address the concerns.

The FDA has carefully considered the available data in conjunction with the recommendations from the joint Advisory Committee meeting and has determined that the indication for Aveed and all approved testosterone replacement therapies be limited to classical hypogonadism, that TRT product labeling include a limitation of use statement conveying that efficacy and safety have not been established for age-related hypogonadism, and that the potential for cardiovascular risk be included in labeling to adequately inform healthcare providers and patients. The FDA has also determined that a cardiovascular study is needed to further evaluate the potential for cardiovascular risk among testosterone users, which are predominantly middle-age and aging men.

We consider this information to be “new safety information” as defined in section 505-1(b)(3) of FDCA.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Since Aveed was approved on March 5, 2014, we have become aware of new safety information, as described above.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, associated with testosterone replacement therapy, of which Aveed is a member.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signal of a serious risk of MACE associated with the class of testosterone therapy, of which Aveed is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

XXXX-1 A randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men. We recommend that this trial also assess other important safety and efficacy outcomes associated with testosterone therapy.

The following timetable proposes the schedule by which you will conduct this trial:

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Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”

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FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that, to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.
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INDICATIONS AND USAGE

Limitations of use:

- Safety and efficacy of Aveed in men with age-related hypogonadism have not been established (1).

- Safety and efficacy of Aveed in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

DOSAGE AND ADMINISTRATION

Add as new first bullet:

Prior to initiating Aveed, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).

- For intramuscular use only (2.1).

WARNINGS AND PRECAUTIONS

The new bullet follows the ‘Venous thromboembolism (VTE)’ bullet:

Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.X)
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Aveed should only be used in patients...

Limitations of use:

- Safety and efficacy of Aveed in men with age-related hypogonadism have not been established. Age-related hypogonadism refers to men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism.

- Safety and efficacy of Aveed in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

**2 DOSAGE AND ADMINISTRATION**

Prior to initiating Aveed, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

**2.1 Dosage**
Aveed is for intramuscular use...

**5 WARNINGS AND PRECAUTIONS**
Add new Cardiovascular Risk subsection after the subsection titled “Venous Thromboembolism”

**5.X Cardiovascular Risk**

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular
events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Aveed.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

Other Events

Nervous System Disorders: Stroke, cerebrovascular insufficiency, ...

MEDICATION GUIDE

In addition to the changes described above, revise the Medication Guide include the new safety information for Aveed.

Under “What is Aveed?”

Aveed is a prescription medicine that contains testosterone. Aveed is used to treat adult males who have low or no testosterone due to certain medical conditions. and have conditions associated with low or no testosterone.

Aveed is only for adult males who need testosterone replacement therapy and when the benefit of receiving Aveed is more than the risk of POME and anaphylaxis.

Your healthcare provider will test your blood before you start and while you are taking Aveed.

It is not known if Aveed is safe or effective to treat men who have low testosterone due to aging.

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Under “What are the possible side effects of Aveed?”

Aveed can cause serious side effects including:

- see “What is the most important information I should know about Aveed?”
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- liver problems...
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Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

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OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”

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SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.
If you have any questions, call Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

See appended electronic signature page

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
02/09/2015
Dear Dr. Broderick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Axiron® (testosterone) topical solution.

Sections 505(o)(3) and 505(o)(4) of the FDCA authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes and to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Axiron was approved on November 23, 2010, we have become aware of the risk of major adverse cardiovascular events associated with testosterone replacement therapy.

Axiron is indicated for replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone replacement is a long-accepted, efficacious therapy in men who have an absence or deficiency of testosterone due to specific inherited or acquired diseases of the testes, hypothalamus, or pituitary (classical hypogonadism). In contrast, the efficacy of testosterone replacement therapy (TRT) has not been established for age-related hypogonadism (men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism). Despite this uncertain benefit for age-related hypogonadism, FDA’s drug utilization analysis has found a substantial increase in TRT use in recent years, particularly in men 40 years of age and older, with a majority of this use in middle-aged and older men coded to the non-specific diagnosis of “testicular hypofunction, not elsewhere classified” (International Classification of Diseases, Ninth Revision code 257.20).\(^1\) Furthermore, we have become aware of observational studies reporting a potential increased risk of major adverse cardiovascular events associated with TRT.

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\(^1\) Mohamoud MA. Testosterone Replacement Therapy and Drug Utilization Patterns Presentation. Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. September 17, 2014.
adverse cardiovascular outcomes, including myocardial infarction, stroke, and death, associated with testosterone therapy. These observational studies included aging men treated with testosterone. Other available data have not definitely excluded this potential risk. Given these findings, on September 17, 2014, the FDA convened a joint meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the appropriate indicated population for TRT and the potential risk of major adverse cardiovascular events associated with testosterone use.

Members of the September 17, 2014, joint Advisory Committee overwhelmingly voted to revise the current indication for testosterone replacement therapies. The committee concluded that the available evidence supports an indication for testosterone therapy only in men with classical hypogonadism, and that TRT product labeling should include a statement that efficacy and safety of testosterone replacement therapy have not been established in age-related hypogonadism. Committee members also stated that the TRT labels should be revised to include the potential cardiovascular risks associated with testosterone use. To further assess this potential risk, panel members commented that only a controlled clinical trial, and not observational studies, can adequately address the concerns.

The FDA has carefully considered the available data in conjunction with the recommendations from the joint Advisory Committee meeting and has determined that the indication for Axiron and all approved testosterone replacement therapies be limited to classical hypogonadism, that TRT product labeling include a limitation of use statement conveying that efficacy and safety of testosterone replacement therapy have not been established for age-related hypogonadism, and that the potential for cardiovascular risk be included in labeling to adequately inform healthcare providers and patients. The FDA has also determined that a cardiovascular study is needed to further evaluate the potential for cardiovascular risk among testosterone users, which are predominantly middle-age and aging men.

We consider this information to be “new safety information” as defined in section 505-1(b)(3) of FDCA.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Since Axiron was approved on November 23, 2010, we have become aware of new safety information, as described above.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, associated with testosterone replacement therapy, of which Axiron is a member.

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Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signal of a serious risk of MACE associated with the class of testosterone therapy, of which Axiron is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

XXXX-1 A randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men. We recommend that this trial also assess other important safety and efficacy outcomes associated with testosterone therapy.

The following timetable proposes the schedule by which you will conduct this trial:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>06/2016</td>
</tr>
<tr>
<td>Trial Completion</td>
<td>06/2021</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>06/2022</td>
</tr>
</tbody>
</table>

We encourage you to work together with other holders of new drug applications approved for testosterone replacement therapy on this required clinical trial.

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that, to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.
SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, in the published literature, and at the September 17, 2014, joint Advisory Committee meeting, the new safety information should be included in the labeling for the class of testosterone replacement therapy products, of which Axiron is a member, as follows:

Additions are noted by underline and deletions are noted by strikethrough.

Note that the labeling that follows addresses the safety labeling changes only and does not include the full text of product labeling. The cross references may require adjustment in your final product labeling.

HIGHLIGHTS

RECENT MAJOR CHANGES
- Indications and Usage XX/2015
- Dosage and Administration XX/2015
- Warnings and Precautions (5.X) XX/2015

INDICATIONS AND USAGE

Important Limitations of use:

- Safety and efficacy of Axiron in men with age-related hypogonadism have not been established (1).
- Safety and efficacy of Axiron in males less than 18 years old have not been established (8.4).

DOSAGE AND ADMINISTRATION

Add as first paragraph:

Prior to initiating Axiron, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).

- Starting Axiron dose is…

WARNINGS AND PRECAUTIONS

The new bullet follows the ‘Venous thromboembolism (VTE)’ bullet:

Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.X)
TABLE OF CONTENTS

Update the TABLE OF CONTENTS to reflect the changes in the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION

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

• Primary hypogonadism (congenital or acquired): testicular failure …
• Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Important Limitations of use:

• Safety and efficacy of Axiron in men with age-related hypogonadism have not been established. Age-related hypogonadism refers to men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism.

• Safety and efficacy of Axiron in males less than 18 years old have not been established [see Use in Specific Populations (8.4)].

2 DOSAGE AND ADMINISTRATION

Prior to initiating Axiron, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosing and Dose Adjustment
The recommended starting dose of Axiron…

5 WARNINGS AND PRECAUTIONS

Add new Cardiovascular Risk subsection after the subsection titled “Venous Thromboembolism”

5.X Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular
events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Axiron.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

Cardiovascular Disorders: myocardial infarction, stroke [see Warnings and Precautions (5.X)].

Vascular Disorders: Venous thromboembolism [see Warnings and Precautions (5.4)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

…. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter’s syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

MEDICATION GUIDE

In addition to the changes described above, revise the Medication Guide to include the new safety information for Axiron. Your revised Medication Guide will be considered part of the proposed REMS described below.

Under “What is Axiron?”

Axiron is a prescription medicine that contains testosterone. Axiron is used to treat adult males who have low or no testosterone due to certain medical conditions.

Your healthcare provider will test your blood before you start and while you are taking Axiron.

It is not known if Axiron is safe or effective to treat men who have low testosterone due to aging.
It is not known if Axiron is safe or effective in children younger than 18 years old. Improper use of Axiron may affect bone growth.

Under “What are the possible side effects of Axiron?”

**Axiron can cause serious side effects including:**

- If you already have enlargement of your prostate gland your signs and symptoms…
- Possible increased risk of prostate cancer…
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- Possible increased risk of heart attack or stroke.
- In large doses Axiron may lower your sperm count.
- Swelling of your ankles, feet, or body, with or without heart failure.
- Enlarged or painful breasts.
- Have problems breathing while you sleep (sleep apnea).
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT**

**OR**

**SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”**

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:
SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENT

The REMS for Axiron was originally approved on November 23, 2010, and the most recent REMS modification was approved on June 19, 2014. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Axiron must be modified based on the information described above to ensure that the benefits of the drug outweigh its risks. This determination is based on the need to conform the approved REMS to the safety labeling changes described above.

Your proposed REMS modification must include changes to the Medication Guide.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on November 23, 2010.

The proposed REMS modification submission should include the REMS document and the revised Medication Guide.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of Axiron outweigh the risks, you must submit a proposed REMS modification within 30 days of the date of this letter as a separate supplement to your NDA.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 022504
PROPOSED REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022504
PROPOSED REMS MODIFICATION-AMENDMENT
If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, call Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
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/s/

CHRISTINE P NGUYEN
02/09/2015