CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206089

COMPLETE RESPONSE

Clarus Therapeutics, Inc.
Attention: Robert E. Dudley, Ph.D.
President and CEO
555 Skokie Blvd., Suite 340
Northbrook, IL 60062

Dear Dr. Dudley:

Please refer to your New Drug Application (NDA) dated and received, January 3, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate (TU) (oral).

We acknowledge receipt of your amendment dated June 22, 2017, which constituted a complete response to our November 3, 2014, action letter.

We acknowledge receipt of your major amendments dated September 20 and 25, 2017, which extended the goal date by three months.

We also acknowledge receipt of your amendment dated February 27, 2018, which was not reviewed for this action. You may incorporate applicable sections of this amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Deficiencies:

1. **Jatenzo causes clinically meaningful increases in blood pressure. For example, on ambulatory blood pressure monitoring (ABPM) there was a daytime average systolic blood pressure (SBP) increase of 5.0 mmHg and a larger increase among subjects with hypertension. In comparison, the daytime average SBP change from baseline in the concurrent comparator group (Topical Axiron) was -0.1 mmHg. Further, in the Jatenzo group, 7.2% of subjects in the Safety Population started antihypertensive medications after baseline or required an antihypertensive dose increase, compared to 1.8% of subjects in the Topical Axiron group. These BP changes, with a chronically administered drug such as Jatenzo, will increase the risk of major cardiovascular adverse events, including myocardial infarction, stroke and**

cardiovascular death, and would not necessarily be detected in routine clinical practice nor prompt initiation or intensification of antihypertensive therapy. These risks outweigh the benefits of Jatenzo among many men who are already at increased risk of cardiovascular disease.

Information Needed to Resolve Deficiency #1

In your resubmission, propose detailed strategies in labeling (including proposals for a Boxed Warning, Indication, Contraindication, and Warnings and Precautions) and strategies beyond labeling, such as a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, together with an assessment of how your proposal will mitigate the risks and ensure a favorable benefit/risk profile. We will determine whether your proposed strategies can ensure that the benefits outweigh the risks after a complete review of your resubmission.

2. **You propose to monitor patients treated with Jatenzo using total testosterone (T) concentrations from plasma in sodium fluoride (NaF)/ethylenediaminetetraacetic acid (EDTA) tubes instead of serum in plain tubes. You state that the NaF/EDTA tubes prevent TU to T *ex vivo* conversion, and you report higher T concentrations from serum in plain tubes compared to T concentrations from plasma in NaF/EDTA tubes in Jatenzo-treated subjects. However, serum and NaF/EDTA samples were held at different temperatures after collection and each sample type was analyzed using different LC-MS/MS methods. You have not assessed the extent to which these factors contributed to the observed differences between sample types. In addition, based on the limited data submitted, the extent to which NaF/EDTA tubes prevents TU to T *ex vivo* conversion is unknown. Further investigation of the rate and extent of TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in your Phase 3 trial are accurate and reproducible.**

Information Needed to Resolve Deficiency #2

Conduct a study that doses subjects with your product and compares the total T concentrations measured from serum in plain tubes and from plasma in NaF/EDTA tubes at different time points (e.g., 0, 15, 30, 60, 90, and 120-minutes post-sample collection) using various temperature conditions (e.g., at room temperature and on ice) to definitively determine the rate and extent of TU to T *ex vivo* conversion during the expected time course of plasma sample preparation. Prespecify in the protocol the maximum amount of T concentration overestimation from TU to T *ex vivo* conversion that would be acceptable for the matrix you propose for clinical use and to support the reliability of the efficacy data from your Phase 3 trial. You may also wish to consider evaluating plasma collected in tubes without NaF. Enroll enough subjects (e.g., 12 subjects), administer your drug product at the maximum recommended to-be-marketed dose, and achieve the same TU concentration as expected at steady state during clinical

use. Assessment of the zero timepoint (i.e., centrifuged immediately upon blood collection) for plasma in tubes with and without NaF is critical for this assessment.

In addition, conduct a study comparing total T concentrations measured from serum (in plain tubes) and plasma (in NaF/EDTA tubes and non NaF-containing plasma tubes) collected in the same subjects without administering TU and then split, prepare, and analyze these samples in the same bioanalytical laboratory. Include the correlation analysis between the total T concentrations obtained from serum and plasma from the same subjects in your study report.

We strongly recommend that you submit these protocols for review and await our comments before initiating the studies.

In your NDA resubmission, include the bioanalytical method validation and study (performance) reports for all matrices (e.g., serum, plasma, plasma in the presence of NaF).

If these studies confirm that proper dose adjustment of your product will require T concentrations from plasma samples collected in NaF/EDTA tubes, ensure that accurate and reliable T tests intended for use with NaF/EDTA plasma specimens are available by the time of approval. This may involve a companion diagnostic if you intend to propose the clinical use of a specific T assay to monitor patients taking your drug. Ensure you have adequately addressed these issues with FDA prior to NDA resubmission.

If you are unable to confirm that T concentration measurements from plasma in NaF/EDTA tubes in your Phase 3 trial are accurate and reproducible, you will need a new Phase 3 trial to establish efficacy. The results could also potentially impact the choice of dose(s) that are studied in the new trial, which may prompt the need for additional safety data as well.

In addition, due to the similarities in the chemical structure of T and TU and because of the high concentration of TU relative to T in patient specimens, it is possible that commonly used T immunoassays would significantly cross-react with TU causing an overestimation of T concentration values regardless of sample type. If commercially available assays can be used for measuring T in patients treated with your product, provide data demonstrating the rate of TU cross-reactivity with commonly used immunoassays.

3. **The submitted nonclinical studies are unacceptable to support approval of your NDA through the 505(b)(1) pathway. Specifically, your TU doses were inadequate to characterize and provide a meaningful and valid evaluation of the chronic effects of your product on male fertility and carcinogenicity. In the fertility study, the tested doses did not produce the anticipated effects on spermatogenesis and/or fertility, which may reflect insufficient exposure to T and/or TU. You did not submit toxicokinetic data to evaluate drug exposure. With regards to your 6-month carcinogenicity study in male Tg·rasH2 mice, the rationale provided in your**

November 30, 2017, letter does not satisfactorily address the nonclinical deficiency communicated in our letter dated October 4, 2017. Specifically, per International Conference on Harmonization (ICH) guidance *S1C(R2) Dose Selection For Carcinogenicity Studies (2008)*, the maximally tolerated dose (MTD), maximum feasible dose or limit dose was not identified in your 28-day dose range finding study or in your 6-month carcinogenicity study. The use of 25 males/group due to "gender specific effects" is not a valid evaluation in your 6-month carcinogenicity study, as the study remains insufficiently powered for one sex.

Information Needed to Resolve Deficiency #3

Provide justification for dose selection for the fertility study combined with the *in vivo* micronucleus test, and conduct a new, adequately designed carcinogenicity study. Submit the carcinogenicity study protocol for review by the Division and the Executive Carcinogenicity Assessment Committee per the guidance "Guidance for Industry Carcinogenicity Study Protocol Submissions" found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078924.pdf.

Alternatively, you may classify your NDA as a 505(b)(2) application without submitting additional nonclinical studies if you provide appropriate nonclinical published literature references to address the nonclinical deficiencies above. If you proceed with a 505(b)(2) NDA, the results from your completed fertility and carcinogenicity studies will not be included in the product labeling.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. You have provided insufficient data to definitively exclude a risk of adrenal insufficiency with chronic dosing. Further assessment of adrenal function over a longer duration is warranted.

2. Your product is administered orally as TU and achieves high systemic TU concentrations. Address the drug-drug interaction potential of TU as the perpetrator.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of

labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that includes your proposed revisions dated February 21, 2018, and also add the following:

- "Capsule" refers to the dosage form and is not part of the established name. Change the drug product name on both the immediate container and the carton from (b) (4) to "Jatenzo (testosterone undecanoate) Capsules, 158 mg, 198 mg, or 237 mg".

PROPRIETARY NAME

Please refer to correspondence dated, September 5, 2017, which addresses the proposed proprietary name, Jatenzo. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
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/

HYLTON V JOFFE
03/22/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206089

COMPLETE RESPONSE

Clarus Therapeutics, Inc.
Attention: Robert E. Dudley, Ph.D.
President and CEO
555 Skokie Blvd., Suite 340
Northbrook, IL 60062

Dear Dr. Dudley:

Please refer to your New Drug Application (NDA) dated and received January 3, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate (oral).

We acknowledge receipt of your amendments dated February 4, 13, 24 and 28, March 28, April 21 and 23, May 1 and 2, June 3, July 18 and 24, August 1, 4, 6, 12, and 19, September 15, 24 and 26(2), and October 1, 2014.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Your amendment dated August 6, 2014, contained bioanalytical study reports for all clinical trials as well as bioanalytical method validation data that were missing at the time of NDA submission. We did not review these bioanalytical data in their entirety as they were submitted late in the review cycle. The complete analytical validation section of your NDA will need to undergo further review in a future resubmission in the context of new trials that are conducted to support your NDA.

Deficiencies

You have not shown that your product can reliably and safely replace testosterone in hypogonadal men. You are proposing that your product be dosed once in the morning and once in the evening with meals. We agree that your product cannot realistically be dosed in the fasted state, particularly because this is not practical for the evening dose. However, based on the food effect study, there are considerable increases in testosterone undecanoate (TU), testosterone, and dihydrotestosterone (DHT) as the fat content in the meal increases. Therefore, taking your product with food will not lead to consistent serum TU, testosterone and DHT concentrations unless the fat content for every breakfast and every dinner is similar from day to day. It is not reasonable to expect patients to be able to maintain such consistency every day while taking this chronic medication nor is it reasonable to expect that patients will always be able to know the fat

content of their meals. With variations in the fat content from day-to-day, a given dose of your product may sometimes be too high (if the fat content of the accompanying meal is high) and sometimes too low (if the fat content of the accompanying meal is low). This could lead to erratic and variable exposures to TU and its metabolites from one day to the next. The data from the pivotal phase 3 trial are not able to address this concern. In your trial, subjects chose foods from a preset menu on the three pharmacokinetic sampling days (Days 30, 72 and 114). For all the other days, subjects had no food restrictions. Therefore, data used for deciding on titration as well as data collected for the primary and key secondary efficacy endpoints were all obtained on days when the subjects chose food from the preset menu. It is unlikely that the fat content in the meals on these three days is comparable to that of all the unrestricted meals that the subjects could eat on the other 111 days of the trial. Therefore, you have not shown that your product, as proposed, would lead to reliable and appropriate testosterone and DHT concentrations from one day to the next, raising both efficacy and safety concerns.

We have also identified the following additional concerns with your single, open-label, non-randomized, four-month pivotal phase 3 trial, CLAR-12011:

1. Your completer analysis in the 116 subjects who had sufficient data to calculate a 24-hour average serum total testosterone concentration (T-C_{avg}) on Day 114, showed that exactly 75% of subjects had a T-C_{avg} within the normal range, a success rate that just barely achieves the pre-defined target threshold. However, when other analytical approaches are used that account for the approximately 19% of subjects who did not have sufficient data to calculate T-C_{avg} on Day 114 , the primary efficacy results do not reach the target threshold for success.

2. None of the key secondary efficacy endpoints for testosterone C_{max} outliers met the prespecified success targets for the three C_{max} outlier categories.

3. The starting dose of 200 mg twice daily was too high, resulting in the need to down-titrate a majority of the subjects. Also, the titration regimen requires that serum testosterone concentrations be lower than 250 ng/dL before the dose is increased, preventing some subjects from achieving adequate testosterone replacement. Nearly one-fourth of subjects had a T-Cavg <300 ng/dL at the primary efficacy endpoint subsequent to all titration.

4. The mean average serum DHT concentration was above the upper limit of normal, and the mean DHT-to-testosterone concentration ratio was twice the upper limit of normal. These data are inconsistent with the goal of testosterone replacement therapy, which is to replace testosterone and its critical metabolites, DHT and estradiol, to within the normal range.

We have also identified the following additional safety concerns, based on the data contained in your NDA:

1. DHT is a potent androgen. Supraphysiological DHT concentrations and DHT-to-testosterone concentration ratios observed with your product pose an increased risk of serious androgen-related adverse effects.

2. Very high serum TU and dihydrotestosterone undecanoate (DHTU) concentrations were observed with your product and the clinical ramifications of this finding are unknown. While TU and DHTU appear to have weak affinities for the androgen receptor, at massive exposures they may have effects. In addition, TU and DHTU are further metabolized to DHT and to other steroid molecules that may have pharmacologic effects. The role that TU or its metabolites may have played, if any, in the hypocortisolemia and adrenocortical atrophy observed in dogs in the 13-week toxicity study is unknown.

3. Significantly decreased sex hormone binding globulin (SHBG) was observed with your product and the clinical ramifications of this finding are unknown.

4. Clinically meaningful increases in systolic and diastolic blood pressure were observed with your product in Study CLAR-09007, with a larger blood pressure increase compared to Androgel 1%. The extent to which these blood pressure differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. Blood pressure was also meaningfully increased in Study CLAR-12011, albeit to a lesser degree than in Study CLAR-09007.

5. Clinically meaningful increases in hematocrit were observed with your product in Study CLAR-09007, with a larger increase compared to Androgel 1%. Almost 10% of subjects treated with your product in Study CLAR-09007 had at least one hematocrit value >54%, a clinically meaningful level. The extent to which the hematocrit differences between your product and Androgel 1% are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. An increase in hematocrit was also observed with your product in Study CLAR-12011.

6. A small number of cardiovascular adverse events were reported with your product in the Phase 3 studies, including events of acute myocardial infarction and stroke. The role played by your product in these events is currently unknown. However, several possible biomarkers of cardiovascular risk, including blood pressure (described above), HDL-cholesterol and high-sensitivity C-reactive protein (hs-CRP) were adversely affected by your product. The extent of worsening of HDL-cholesterol and hs-CRP was greater for your product compared to Androgel 1% in Study CLAR-09007. The extent to which these differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear.

Information Needed to Resolve the Deficiencies

You will need to conduct new clinical investigations to show that your product consistently leads to reliable and appropriate exposures to testosterone and DHT in the face of day-to-day variability in meal content that is expected to occur in men who will use the product, if approved. One possible approach may be to first conduct a timed food effect study to assess whether taking your product before or after food (e.g., 1 hour before food, or 1 or 2 hours after food) could minimize the food effect and lead to more predictable testosterone and DHT concentrations. If this is successful, the next step could be to conduct a new phase 3 trial with subjects using the appropriate timing of product administration in relation to food, as determined from the timed food effect study. This new phase 3 trial would need to consider the optimal starting dose and titration thresholds to ensure that the tested dosing and titration regimen results in exposures to

testosterone and DHT, and DHT-to-testosterone ratios that are within the normal range for eugonadal males. If this new titration algorithm is again expected to lead to considerable reductions in SHBG, you will need to address whether bioavailable testosterone concentrations are within the normal range for eugonadal males. In addition, this new trial would need to be adequately designed to avoid other deficiencies involving the completed phase 3 trial that were described above, such as the large extent of missing data for the primary efficacy endpoint. You will also need to provide convincing evidence that the effects of your product on important cardiovascular risk factors, such as blood pressure, hematocrit, and HDL cholesterol, do not pose an unacceptable risk to the indicated patient population.

In summary, additional investigations of efficacy and safety and the effect of food, will be necessary, including possible changes to the dose and titration algorithm. One possible approach is described above. Based upon the extent and complexity of the deficiencies, you are encouraged to meet with the Division to discuss a path forward towards resolving all the deficiencies.

In addition, you will need to address the following concerns related to the very high TU and DHTU concentrations:

- Whether your product has effects on the human hypothalamic-pituitary-adrenal axis. In the nonclinical repeat-dose toxicity study, dogs developed moderate to marked atrophy of the adrenal cortex with an accompanying reduction in serum cortisol. These findings raise the possibility that your product or its metabolite(s) may have glucocorticoid activity, leading to secondary adrenal insufficiency.

- Whether the findings from the *in vitro* androgen receptor binding study (which compared the affinity of TU, DHTU, testosterone and DHT for the rat androgen receptor) are generalizable to the human androgen receptor.

- Whether the very high concentrations of TU and DHTU compete with testosterone and DHT at the androgen receptor and whether any of the metabolites of TU and DHTU have pharmacologic effects.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the package insert conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following recommendation that is not an approvability issue:

- Conduct an *in vivo* interaction study with alcohol to determine whether co-administration with alcohol could alter the bioavailability of your product and exposure to its metabolites. Based on physicochemical properties, it is possible that alcohol will solubilize your product, leading to increased absorption via the portal vein, a high first pass effect, and reduced TU bioavailability. However, it is also possible that alcohol could instead enhance absorption via the lymphatics, leading to increased bioavailability of TU. Given these uncertainties, it would be useful to study the potential for interaction with alcohol.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
11/03/2014