



ANDA 204255

TENTATIVE APPROVAL

Perrigo Company
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd
515 Eastern Avenue
Allegan, MI 49010
Attention: Valerie Gallagher
Director, ANDA/NDA Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 3, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Testosterone Topical Solution, 30 mg/1.5 mL.

Reference is also made to the complete response letter issued by this office on October 31, 2013, and to your amendments dated July 24, 2014; June 4, August 18 & 27; and September 9, 2015.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the FD&C Act.

The reference listed drug (RLD) upon which you have based your ANDA, Axiron (testosterone topical solution), 30 mg/1.5 mL, of Eli Lilly and Company (Lilly), is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
6,299,900 (the '900 patent)	February 19, 2017
6,818,226 (the '226 patent)	February 19, 2017

6,923,983 (the '983 patent)	February 19, 2017
8,071,075 (the '075 patent)	February 19, 2017
8,419,307 (the '307 patent)	February 26, 2027
8,435,944 (the '944 patent)	September 27, 2027
8,784,878 (the '878 patent)	July 13, 2023
8,807,861 (the '861 patent)	February 26, 2027
8,993,520 (the '520 patent)	June 2, 2026

Your ANDA contains paragraph III certifications to the '900, '226, '983, and '075 patents under section 505(j)(2)(A)(vii)(III) of the FD&C Act stating that Perrigo Israel Pharmaceuticals, Ltd. (Perrigo) will not market Testosterone Topical Solution, 30 mg/1.5 mL, prior to the expiration of these patents. Therefore, final approval of your ANDA may not be made effective pursuant to section 505(j)(5)(B)(ii) of the FD&C Act until the '900, '226, '983, and '075 patents have expired, currently, February 19, 2017.

With respect to the '307, '944, '878, '861, and '520 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that each of the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Testosterone Topical Solution, 30 mg/1.5 mL, under this ANDA. You have notified the agency that Perrigo complied with the requirements of section 505(j)(2)(B) of the FD&C Act. The agency notes that these patents were listed after submission of your ANDA, and litigation, if any, with respect to any of them does not create a statutory bar to approval. See section 505(j)(5)(B)(iii) of the FD&C Act.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, an ANDA is required to have a REMS if the applicable listed drug has an approved REMS.

In accordance with section 505-1 of the FD&C Act, we have determined that a REMS is necessary for topical products containing testosterone, including Testosterone Topical Solution, to ensure the benefits of the drugs outweigh the risk of secondary exposure of children to testosterone due to drug transfer from adult men using the drug.

Your proposed REMS, submitted on August 18, 2015 and appended to this letter, can be approved with your application. The REMS consists of a Medication Guide.

We will review your proposed REMS to ensure that it matches the REMS for the applicable reference listed drug (RLD) before final approval of your application.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your

request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to Agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either “major” or “minor” changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the FD&C Act, and will not be listed in the “Orange Book.”

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay

fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Scott Dallas, Regulatory Project Manager, at 240-402-8618.

Sincerely yours,

Carol A. Holquist -S

Digitally signed by Carol A. Holquist -S
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Date: 2015.10.16 08:58:36 -04'00'

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

REMS