DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 091244

LABELING ORDER

West-Ward Pharmaceutical Corp.
U.S. Agent for Hikma Farmacêutica (Portugal), S.A.
2 Esterbrook Lane
Cherry Hill, NJ 08003

Attention: J. Barton Kalis
Director, Regulatory Affairs

Dear Mr. Kalis:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Testosterone Cypionate Injection USP, 200 mg/mL.

On August 10, 2016, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of testosterone products related to serious adverse events associated with testosterone abuse and dependence. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

Further reference is made to the email sent by Julie Call on September 21, 2016, notifying you that the labeling language proposed in the August 10, 2016, letter had been revised.

Additionally, a final reminder to submit updated labeling was sent to you via email by Kyle Snyder on September 30, 2016. You were also advised that requirements under section 505(o)(4) of the Act apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

As of the date of this letter, the Agency has received no correspondence from you.

Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the August 10, 2016, letter and September 21, 2016, email (see attachments).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the August 10, 2016 letter and September 21, 2016 email must be received by FDA by November 2, 2016, for Testosterone Cypionate Injection, USP.

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

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by October 23, 2016, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your ANDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Kyle Snyder
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3660
10903 New Hampshire Avenue
Silver Spring, MD 20993

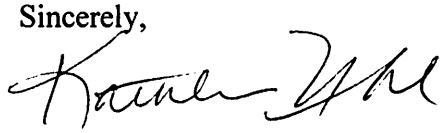
Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Amy Bertha, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. Appeals received by the Agency later than October 23, 2016, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your

product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, contact Kyle Snyder, Labeling Project Manager, at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

Sincerely,



Kathleen Uhl, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Safety Labeling Change Notification Letter
Email with Revised Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 091244

SAFETY LABELING CHANGE NOTIFICATION

West-Ward Pharmaceuticals Corp.
U.S. Agent for Hikma Farmaceutica (Portugal), S.A.
2 Esterbrook Lane
Cherry Hill, NJ 08003

Attention: J. Barton Kalis
Director, Regulatory Affairs

Dear Mr. Kalis:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Testosterone Cypionate Injection USP, 200 mg/mL.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved new drug applications (NDAs) and biological license applications (BLAs) to make safety related labeling changes based upon "new safety information," as defined in section 505-1(b)(3) of the FDCA, about which FDA becomes aware after approval of the drug or biological product. 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.

Since Testosterone Cypionate Injection, USP, was originally approved, we have become aware of serious adverse events associated with testosterone abuse and dependence, typically reported at testosterone doses higher than recommended for the approved indication and when used in combination with other anabolic androgenic steroids (AAS). Serious and potentially life-threatening cardiovascular, psychiatric, hepatic and male reproductive adverse outcomes have been reported. This information is based on FDA's comprehensive review of the published literature and on individual case reports of testosterone and AAS abuse accompanied by the serious adverse outcomes. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for testosterone products as follows:

a) Under **WARNINGS**, add the new warning text following the paragraph on risk of major adverse cardiovascular events (MACE):

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic steroids. This type of testosterone abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence].*

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. Counsel patients concerning the serious adverse reactions associated with testosterone and anabolic steroid abuse. Conversely, consider the possibility of testosterone and anabolic steroid abuse in patients who present with serious cardiovascular or psychiatric adverse events.

b) Revise the **DRUG ABUSE AND DEPENDENCE** section as follows:

Delete the current text in this section and replace with the following new subsections (note: please replace "[DRUG]" with your product specific information):

Controlled Substance
[DRUG] contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

Abuse
Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often not obtained by prescription and not obtained through a pharmacy and typically in combination with other anabolic androgenic steroids (AAS), is abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Behaviors Associated with Addiction
Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Abuse-Related Adverse Reactions
Serious adverse reactions, including cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression, have been reported in individuals who abuse anabolic androgenic steroids.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dependence
Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement 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. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS). Your supplement should only include proposed changes made in accordance with the above direction. Any other proposed labeling changes should be submitted in a separate supplement and should not be identified as a safety labeling change.

We have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is

received, and will end by November 4, 2016, unless additional discussion extensions are warranted.

Failure to submit a response within 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A), misbranding charges under section 502(z), and an order under 505(o)(4) 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) – CHANGES BEING EFFECTED

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

If you have any questions, contact Kyle Snyder, Labeling Project Manager, at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

Sincerely,

{see appended signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
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/

CAROL A HOLQUIST
08/10/2016