DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

F.O.I

September 1, 1999

TRANSMITTED BY FACSIMILE

Robert Dudley, Ph.D., President and CEO
Unimed Pharmaceuticals, Inc.
2150 E. Lake Cook Road
Buffalo Grove, Illinois 60089

RE: **NDA #16-848**
Anadrol-50 (oxymetholone) tablets
MACMIS # 6629

WARNING LETTER

Dear Dr. Dudley:

This Warning Letter concerns the dissemination of certain promotional materials[1] by Unimed Pharmaceuticals, Inc. ("Unimed"), with regard to Anadrol-50 (oxymetholone) tablets. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials as part its monitoring and surveillance program. DDMAC has concluded that the promotional materials cited in this letter promote Anadrol-50 for an unapproved use and are false or misleading. Therefore, the dissemination of these materials misbrands Anadrol-50 tablets in violation of the Federal Food, Drug, and Cosmetic Act. See 21 U.S.C. §331(a), (b), (d), §352(a) and (n), §355(a), and applicable regulations.

Background

Anadrol-50 (oxymetholone) is an oral anabolic-androgenic steroid. Anabolic-androgenic steroids are derivatives or analogues of testosterone that act on common androgenic receptors in the human body. Anadrol-50 (oxymetholone) is indicated

[1] These materials include, but are not limited to, Product Monograph ANA51106, Reimbursement Guide ANA98813, Multi-panel Display Aid ID-13274, Clinical Profile ANA51104, Brochure ANA11801, Detail Aid ANA98803, Sell Sheet ANA98700 and Anadrol Internet Home Page: http://www.phase-five.com (accessed May 7, 1999).

> in the treatment of anemias caused by deficient red blood cell production. Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs often respond....[2]

The safety and effectiveness of Anadrol-50 in the treatment of any type of weight loss, including generalized weight loss, weight loss due to chronic disease, HIV-Wasting Syndrome, or weight loss associated with continuous ambulatory peritoneal dialysis (CAPD) have not been proven in adequate and well-controlled clinical trials.

Promotion of Unapproved Use

Promotional materials are false, lacking in fair balance, or otherwise misleading if they contain a representation or suggestion that a drug is more effective, safer, or useful in a broader range of conditions and patients than has been demonstrated by substantial evidence or substantial clinical experience.

The information contained in your promotional materials state or imply that Anadrol-50 is safe and effective for a variety of off-label uses, i.e., that Anadrol-50 is safe and effective in the treatment weight loss associated with chronic diseases, HIV-Wasting Syndrome or CAPD. Your promotional materials such as your web site and your Product Monograph extensively discuss the use of anabolic steroids for the treatment of weight loss and describe the anabolic properties of Anadrol-50. The following statements from your promotional materials are illustrative of your statements or suggestions that Anadrol-50 is safe and effective in the treatment of various types of weight loss. On your web site, under the heading **"Why use Anadrol-50?"** you state:

> In addition to increasing red blood cell production, **anabolic hormones have historically been associated with sustaining protein mass and protein building** to help patients gain overall strength and overcome the side effects of anemia.[3] (Emphasis added).

This is clearly a suggestion that Anadrol-50 should be used for weight loss and wasting.

The next paragraph under the same heading on the web site compares the cost of Anadrol-50 to Oxandrin, an anabolic steroid that is indicated as adjunctive therapy to promote weight gain in certain situations. Again, your promotional message suggests that Anadrol-50 is an anabolic hormone that is an alternative to Oxandrin.

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[2] "Indications and Usage" section of the approved product labeling for Anadrol-50, (June 17, 1997).
[3] Anadrol-50 Home Page

The primary discussion in the Product Monograph concerns the features of anabolic steroids and the anabolic properties of Anadrol-50 for the treatment of weight loss in various settings, not for the treatment of the indicated anemias. For example, page four of the Monograph states:

> Recently there has been increased interest in the use of anabolic agents for the treatment of weight loss associated with severe immunosuppression, most notably in HIV disease, and also in a variety of conditions characterized by malnutrition and negative nitrogen balance such as continuous ambulatory peritoneal dialysis (CAPD).[4]

On page six of the Monograph, you discuss the anabolic and androgenic activity of Anadrol-50 compared to methyltestosterone. The monograph then describes animal studies using Anadrol-50 for weight gain. You also promote Anadrol-50 as an agent to promote weight gain by comparing it to Oxandrin (oxandrolone). For example, you state that "Oxymetholone is a 17 alpha methylated steroid and is very similar in structure to oxandrolone (Oxandrin, BTG Pharmaceuticals) another orally active AAS used principally to treat catabolic effects (e.g. weight loss) associated with chronic disease (Figure 5)."[5]

In a promotional brochure entitled "Reimbursement Guide for Anadrol-50," under Billing Code 799.4,[6] and as tagline in other promotional materials you state or suggest that Anadrol-50 is safe and effective for the treatment of cachexia [general ill health and malnutrition].

Finally, on your convention panels, you surround the name "Anadrol-50" with the expressions "HIV disease", "nephrology", and "hematology." Anadrol-50 has not been proven to be safe and effective in HIV disease or nephrology, and has only been demonstrated to be safe and effective in certain anemias in hematology.

In summary, the majority of the claims in your promotional materials state or suggest that Anadrol-50 is safe and effective for treatment of weight loss associated with various diseases, not for the indicated treatment of certain types of anemia. Since Anadrol-50 is not approved for any of these other uses, these materials misbrand Anadrol-50.

Lack of Fair Balance

Promotional materials are false, or misleading if they contain a representation or suggestion that a drug is safer, has less incidence of, or has less side effects than has been demonstrated by substantial evidence.

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[4] Product Monograph (p. 4).
[5] Product Monograph (p. 6).
[6] Brochure ANA98813

A. Content – Failure to Disclose Important Risk Information

Your promotional materials are misleading because they fail to adequately disclose important risk information associated with the use of Anadrol-50. These materials do not present reasonable balance between benefit and risk information. To the contrary, the information presented minimizes the risks associated with the use of Anadrol-50. For example, the Sell Sheet (ANA98700) fails to disclose the boxed warnings, precautions, or adverse reactions. Brochure (ANA11801) describes the boxed warning information. However, it fails to disclose that Anadrol–50 is contraindicated in patients with (1) carcinoma of the prostate or breast in males; (2) carcinoma of the breast in females with hypercalcemia; (3) pregnancy (fetal harm); (4) nephrosis or the nephrotic phase of nephritis; or (5) severe hepatic dysfunction.

The Product Monograph is a 20-page promotional brochure that contains disclosures of risk information on pages 10, 11, 13, 17, and 18. However, most of these disclosures relate to certain adverse events. This extensive promotional brochure does not disclose the numerous and significant contraindications, boxed warnings, and precautions associated with the use of Anadrol-50. In addition, although the Monograph discusses the use of Anadrol-50 in children, it fails to disclose risk information specific to that patient population such as the need to x-ray pediatric patients at 6 month intervals during therapy to avoid the risk of compromising adult height.

Finally, the Monograph states that there are "minimal signs of virilism" and "no androgenic side effects."[7] This statement, however, is inconsistent with the approved product labeling for Anadrol-50, and the studies you cited in your promotional materials.[8] The "Precautions" section of the approved product labeling states that "[w]omen should be observed for signs of virilization...[t]o prevent irreversible change, drug therapy must be discontinued when mild virilism is first detected...[s]ome virilization changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens." Thus, the monograph is also misleading with respect to the risks associated with the use of Anadrol-50.

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[7] Page 14 of the Product Monograph states: "In early studies, administration of oxymetholone to chronically underweight individuals, patients who had lost weight following gastrectomy, and geriatric patients produced significant increases in body weight with no androgenic side effects. Oxymetholone therapy in patients with a variety of syndromes, complicated by debility and weight loss, was effective in restoring normal protein metabolism with minimal signs of virilism. Stimulation of appetite and promotion of sense of well-being were also reported in many patients in these studies."

[8] In the studies cited in the Product Monograph, (Table 5, p.11), about 17 percent of the patients taking Anadrol-50 experienced virilism in the form of hirsutism, and 16 percent experienced voice changes.

B. Presentation – Prominence and Readability of Risk Information

Promotional materials must present information relating to contraindications, warning, precautions, and side effects with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the product.

The risk information you disclose in your promotional materials discussed in this letter is not presented with a prominence and readability reasonably comparable to the presentation of information relating to effectiveness of the drug. For example, the risk information in many of your promotional brochures appears in significantly smaller type at the bottom of the page. Such presentations are not reasonably comparable to the presentations of the alleged benefits that are clearly and prominently disclosed in a bullet format with contrasting type.[9]

Misleading Claims about Drug Interactions

Promotional materials are false, lacking in fair balance, or otherwise misleading if they contain a representation or suggestion that a drug is more effective, safer, or useful in a broader range of conditions and patients than has been demonstrated by substantial evidence or substantial clinical experience.

The Anadrol-50 Internet Home Page and promotional brochure (ANA11801 (p.5)) state that Anadrol-50 does not interact with Cytochrome P4503A4 and only mildly inhibits the 2D6 isoenzyme.[10] These claims, however, are based on *in vitro* studies. After clearly and boldly presenting claims alleging a lack of interaction for three-fourths of a page, Unimed discloses in a footnote, in small type, that these *in vitro* data have no known clinical significance. This disclosure is not adequate to correct the misleading impression made by your claims. Finally, you failed to disclose the clinically significant information in the "Precautions" section of the approved product labeling that anabolic steroids may increase sensitivity to anticoagulants, and may interfere with various clinical laboratory tests including thyroid level, prothrombin time, fasting blood sugar, and glucose tolerance tests.

False or Misleading Comparative Cost Claims

On your web site, you state that: "Anadrol-50 does not require an injection and is less expensive than Oxandrin and other anti-anemics, such as blood growth factors for the reproduction of red blood cells." The claim that Anadrol-50 is less expensive than Oxandrin is not a valid comparison and is false or misleading because these drugs are

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[9] Detail Aid ANA98803 and Brochure ANA99001.
[10] Anadrol-50 Home Page

not indicated for the same uses. A cost comparison between a drug used in the treatment of certain types of anemia and a drug used as adjunctive therapy to promote weight gain in certain clinical situations is misleading and not supportable.

In addition, the claim that Anadrol-50 is "less expensive" than other (injectable) anti-anemics is also misleading, because the expression "less expensive" is not defined. It is unclear whether the "less expensive" claim represents a price comparison between physical units of the product, the cost of treatment per se or at particular dosing levels, or the cost of therapy per day.

Failure to Submit Post-Marketing Promotional Materials

All promotional labeling and advertising materials used in promotion must be submitted to FDA pursuant to the post-marketing reporting requirements, 21 C.F.R. §314.81(b)(3)(i). According to our records, you have not submitted many of your promotional materials discussed in this letter including the Product Monograph.

Conclusions and Requested Actions:

You disseminated promotional materials that promoted Anadrol-50 tablets for off-label uses. You also disseminated promotional materials that were false, misleading, or lacking in fair balance. Accordingly, you should propose an action plan to correct the misleading message disseminated as a result of these violations. As part of this plan, you should:

1) Immediately cease the dissemination of the promotional materials and other promotional materials that contain the same or similar violations.

2) Submit in writing your intent to comply with "1" above.

3) Submit a proposed "Dear Healthcare Provider Letter" that will correct the false or misleading information you disseminated.

4) Provide a complete list of all advertising and promotional labeling materials that you intend to continue using.

Because of the scope of your violative promotional campaign, the "Dear Healthcare Professional" letter and your action plan should be submitted to DDMAC for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail.

The violations discussed in this letter are not intended to be a complete listing. We are evaluating other aspects of your promotional campaign for Anadrol-50, and additional violations may be identified. Consequently, we may determine that additional remedial measures may be necessary at a later date to fully correct the false impressions resulting from your improper conduct.

Please respond in writing by September 15, 1999 regarding the steps taken in response to the requested actions. If you have any questions about this letter, please contact Patricia Kuker Staub, Esq. RPh., Leah Palmer, Pharm.D., or Thomas W. Abrams, R.Ph., M.B.A. by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm. 17-B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this letter, please refer to MACMIS ID # 6629, in addition to the NDA number of the drug. Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely.

Norman A. Drezin, R.Ph., J.D.
Acting Director,
Division of Drug Marketing,
Advertising, and Communications