CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 13-718/S022

Trade Name: Oxandrin Tablets

Generic Name: Oxandrolone

Sponsor: Bio-Technology General Corporation

Approval Date: 4/21/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 13-718/S-022

Bio-Technology General Corp.
Attention: Briti Kundu
Director, Regulatory Affairs
70 One Tower Center, 14th Floor
East Brunswick, NJ 08816

Dear Ms. Kundu:

Please refer to your supplemental new drug application dated April 19, 2002, received April 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxandrin (oxandrolone, USP) Tablets.

We acknowledge receipt of your submissions dated July 11 and October 18, 2002 and March 6, 2003. Your submission of October 18, 2002 constituted a complete response to our October 11, 2002 action letter.

This supplemental new drug application provides for the inclusion of information in the package insert regarding a drug interaction between oxandrolone and warfarin.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 6, 2003.

We encourage you to issue a communication notifying health care professionals about this drug interaction.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kati Johnson, Supervisor, Project Management Staff, at (301) 827-6380.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff
4/21/03 07:04:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 13-718/S-022

Bio-Technology General Corp.
Attention: Briti Kundu
Director, Regulatory Affairs
70 Wood Avenue South
Iselin, NJ -8830

Dear Ms. Kundu:

Please refer to your supplemental new drug application dated April 19, 2002, received April 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxandrin (oxandrolone, USP) Tablets.

We acknowledge receipt of your submission dated May 2, 2002.

We note that this supplement was submitted as "Special Supplement-Changes Being Effected". However, as we notified you in our May 21, 2002 letter to this application, an approved supplement is required for this proposed change prior to distributing the drug product made with this change. Therefore, this supplement was reviewed as a prior approval supplement.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

1.

2. Under **PRECAUTIONS**:
General subsection; add the following paragraph at the end of the subsection:

Concurrent dosing of oxandrin and warfarin may result in unexpectedly large increases in INR prothrombin time

Information for patients subsection; add the following text at the beginning of this subsection:

The physician should instruct patients to report immediately any use of warfarin and any bleeding.

Drug Interaction subsection; revise your proposed wording for the Anticoagulants subsection as follows:

Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and the AUC from 4.55 to 12.08 ng*hr/ml. Similar increases in R-warfarin half-life and AUC were also detected. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day was necessary to maintain a target INR of 1.5. should be monitored closely Patients should be closely monitored for signs and symptoms of occult bleeding,

4. Under **ADVERSE REACTIONS**, add the following subsection:

Hematologic: Bleeding in patients on concomitant anticoagulant therapy

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

NOTE: Your April 19, 2002 submission implies that there are two currently approved package inserts; one containing both the 2.5 mg and 10 mg tablets, and the other containing only the 2.5 mg tablet. This is not correct. The package insert that was attached to the approval letter for supplemental application –021 (containing both the 2.5 mg and 10 mg tablet) supercedes any previously approved package insert, and is considered the currently approved package insert. Please use this labeling as the base document for the highlighted or marked-up copy requested in the previous paragraph.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with **this/these** change**(s)** prior to approval of this supplemental application.
If you have any questions, call Kati Johnson, Supervisory Consumer Safety Officer, at (301) 827-6380.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff
10/11/02 12:12:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

APPROVED LABELING

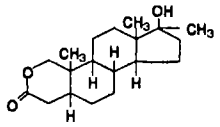
BTG PHARMACEUTICALS

C III

Oxandrin® (oxandrolone tablets, USP)

DESCRIPTION

Oxandrin® oral tablets contain 2.5 mg or 10 mg of the anabolic steroid oxandrolone. Oxandrolone is 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one with the following structural formula



Inactive ingredients include cornstarch, lactose, magnesium stearate, and hydroxypropyl methylcellulose.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

During exogenous administration of anabolic androgens, endogenous testosterone release is inhibited through inhibition of pituitary luteinizing hormone (LH). At large doses, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

INDICATIONS AND USAGE

Oxandrin is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (See **DOSAGE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

1. Known or suspected carcinoma of the prostate or the male breast.
2. Carcinoma of the breast in females with hypercalcemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
3. Pregnancy, because of possible masculinization of the fetus. Oxandrin has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
4. Nephrosis, the nephrotic phase of nephritis.
5. Hypercalcemia.

WARNINGS

PELIOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (See **PRECAUTIONS: Laboratory Tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See PRECAUTIONS: Drug Interactions).

General:
Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for patients:
The physician should instruct patients to report immediately any use of warfarin and any bleeding.

The physician should instruct patients to report any of the following side effects of androgens:
Males: Too frequent or persistent erections of the penis, appearance or aggravation of acne.
Females: Hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients: Nausea, vomiting, changes in skin color, or ankle swelling.

Laboratory Tests:
Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy. (See **WARNINGS**).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Serum lipids and high-density lipoprotein cholesterol determinations should be done periodically as androgenic anabolic steroids have been reported to increase low-density lipoproteins. Serum cholesterol levels may increase during therapy. Therefore, caution is required when administering these agents to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug interactions

Anticoagulants:
Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Oral hypoglycemic agents:
Oxandrolone may inhibit the metabolism of oral hypoglycemic agents.

Adrenal steroids or ACTH:
In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory test interactions:
Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, mutagenesis, impairment of fertility

Animal data:
Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human data:
Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (See **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy: Teratogenic effects-Pregnancy Category X (See **CONTRAINDICATIONS**).

Nursing mothers:
It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use:
Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (See **WARNINGS**).

ADVERSE REACTIONS

The following adverse reactions have been associated with use of anabolic steroids:
Hepatic: Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis with long-term therapy (See **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulfophthalein (BSP) retention, and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alkaline phosphatase.
In males:
Prepubertal: Phallic enlargement and increased frequency or persistence of erections.
Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.
In females:
Clitoral enlargement, menstrual irregularities.
CNS: Habituation, excitation, insomnia, depression, and changes in libido.
Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.
Breast: Gynecomastia.
Larynx: Deepening of the voice in females.
Hair: Hirsutism and male pattern baldness in females.
Skin: Acne (especially in females and prepubertal males).
Skeletal: Premature closure of epiphyses in children (See **PRECAUTIONS**: **Pediatric use**).
Fluid and electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).
Metabolic/Endocrine: Decreased glucose tolerance (See **PRECAUTIONS**: **Laboratory tests**), increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD_{50} of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSAGE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrin (oxandrolone) will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults: The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.
Children: For children the total daily dosage of Oxandrin is ≤0.1 mg per kilogram body weight or ≤0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

HOW SUPPLIED

Oxandrin 2.5 mg tablets are oval, white, and scored with BTG on one side and "11" on each side of the scoreline on the other side; bottles of 100 (NDC 54396-111-11).
Oxandrin 10 mg tablets are capsule shaped, white, with BTG on one side and "10" on the other side; bottles of 60 (NDC 54396-110-60).

Rx only Issued: March 2003

Manufactured for
BTG Pharmaceuticals by:

DSM Pharmaceuticals, Inc.
Greenville, NC 27834

G.D. Searle LLC
A Subsidiary of
PHARMACIA Corporation
Chicago, IL 60680

Address medical inquires to
BTG Pharmaceuticals
One Tower Center
Fourteenth Floor
East Brunswick, NJ 08816

 Printed in USA

BTG PHARMACEUTICALS
OXANDRIN®
(oxandrolone tablets, USP)

517213

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	13718	**APPLICATION TYPE:**	NDA
SPONSOR:	BTG	**PROPRIETARY NAME:**	Oxandrin
CATEGORY OF DRUG:	Androgen	**USAN / Established Name:**	Oxandrolone
		ROUTE:	PO
MEDICAL REVIEWER:	E.A.Koller, M.D.	**REVIEW DATE:**	9/20/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
4/19/02	4/20/02	SLR-022	Drug interaction
5/29/02	5/30/02	SLR-022	Raw data for Biopharm

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:
The sponsor provided solid data from a drug interaction study. (See prior review for 4/19/02 submission.) There was a significant interaction with coumadin resulting in overanticoagulation. Androgens themselves may be anti-coagulant or thrombotic-depending on dose. Unfortunately, these data are primarily anecdotal. The following changes to the label are recommended:

OXANDROLONE LABEL

CONTRAINDICATIONS
6. Patients with vascular hepatic lesions who require oral anticoagulant therapy.

WARNINGS

PELIOSIS HEPATITIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES, THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMPRS ARE BENIGHN AND ANDROGEN-DEPENDENT, BUT FATAL MALGINANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOICIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS.

(New Paragraph.) BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE SERIOUS IMPACT ON THE RISK OF ATHEROSLCEROSIS AND CORONARY ARTERY DISEASE.

PRECAUTIONS

General

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X and an increase in prothrombin time.

Information for patients

The physician should instruct patients to report immediately any use of ( ) and any bleeding

The physician should instruct patients to report any of the following side effects of androgens:.....

Drug interactions

Anticoagulants:

: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with Warfarin, resulted in a mean increase in S-Warfarin t1/2 from 26 to 48 hours and the AUC from 4.55 to 12.08 ng*hr/ml. A similar increase in R-Warfarin t1/2 and AUC was also detected.

A 5.5-fold decrease in the mean Warfarin dose from 6.13 mg/day to 1.13 mg/day was necessary to maintain a target INR of 1.5.

INR or PT has been achieved.

Patients should be closely monitored for signs and symptoms of occult bleeding

ADVERSE REACTIONS

Hematologic: *Bleeding in patients on concomitant anticoagulant therapy (see Boxed Warning, Contraindications).*.

Outstanding Issues:.

Internal:

1—

2—Reproductive Drugs (Dr. Shames) has been alerted to these changes and that there may be implications for other androgens.

External:

1—The proposed label changes should be sent to the sponsor and the sponsor should be requested to send a letter to health care providers alerting them to the label changes.

Recommended Regulatory Action:

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs:

Efficacy / Label Supp.: **label change** **Approvable** _____ **Not Approvable**

Signed: **Medical Reviewer:** **Elizabeth Koller, M.D.** **Date:** **9/20/02**

Medical Team Leader: _____ **Date:** _____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elizabeth Koller
9/23/02 07:07:42 PM
MEDICAL OFFICER
Drug interaction effect exceeds effect of gender and 2C9.

David Orloff
9/24/02 07:03:06 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	13718	APPLICATION TYPE:	NDA
SPONSOR:	BTG	PROPRIETARY NAME:	Oxandrin
CATEGORY OF DRUG:	anabolic androgen	USAN / Established Name:	oxandrolone
		ROUTE:	po
MEDICAL REVIEWER:	E.A. Koller, M.D.	REVIEW DATE:	5/1/02, 6/27/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
4/19/02	4/22/02	SLR 022	drug interaction study (1 volume)

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:

Background:

Oxandrolone is an oral testosterone analogue with an oxygen instead of a methylene group at the 2-position of the phenanthrene core and without 4-ene function in the A ring. Oxandrolone was approved in 1964. The indications include the bone pain of osteoporosis and wasting. A six-week, cross-over, placebo-controlled study in 220 completers with a variety of underlying disorders (including psychiatric, post-operative conditions, and gastointestinal disorders) was used to support the wasting indication.

Protocol C0245:

(No individual or outlier data were provided. The statistical section data and appendices were not included.)

Anecdotal evidence has suggested that C-17 substituted testosterone , e.g. methandrostenolone, alter anti-coagulant requirements. The sponsor submitted results of an open-label, phase I drug interaction study (C0245) assessing oxandrolone (5 or 10 mg BID) and coumadin in fasted, non-obese, non-smoking, healthy volunteers 40 screened; 16 [8 male; 8 female][5 Caucasians; 11 other racial heritage] enrolled; 15 completed). Subjects were dosed with only oxandrolone for three days to reach steady state. Then coumadin was added and titrated until a target INR of 1.5±0.2 x3 was reached. Patients were treated for up to 21 days in the first phase of the study. After a washout to eliminate oxandrolone and permit coagulation parameters to normalize, patients were entered into a second phase in which the coumadin was re-titrated to a target INR of 1.5, but no oxandrolone was given. Patients were also monitored for oxandrolone PK parameters, clotting parameters, mean target divided by coumadin dose per square meter of body surface area (CSI), liver function tests, and evidence of bleeding (clinical exam occult stool and urinary blood). (Patients were also typed for CYP2CP status [p31].)

To maintain an INR of 1.5, it was necessary to decrease the coumadin dose 5.5 fold (5.6 for men and 4.7 for women)(Table 1). Factor VII was the clotting factor most significantly suppressed. (There were statistically significant changes in the opposite direction for factor V-contrary to anecdotal reports.) The half-lives of both R and S coumadin enantiomers were increased when oxandrolone was used concomitantly (Table 2). The AUCs were increased for both enantiomers when the calculations were

based on baseline to last sample collected. When the calculations were based on baseline to infinity, the increases were significant only for the S enantiomer . There were five patients with hematuria and one patient with gingival bleeding during the combination drug phase. Three subjects developed increased in hepatic enzymes: a) 37 year old year old Hispanic-Caucasian woman----AST increased from 22 to 321 U/L, ALT increased from 18 to 960 U/L, LDH increased from 630 to 1743, and c) 47 year old Hispanic-Caucasian woman----AST increased from 22 to 321 U/L, ALT increased from 26 to 1131 U/L, LDH increased from 404 to 756. There was an unexplained mean increase in creatinine (0.15 mg/dl; p <0.0001; individual data not supplied). The changes were reversible with discontinuation of oxandrolone. There was no information on the relationship between CYP2CP status and oxandrolone metabolism and possible effects on the interaction with coumadin.

Table 1 The Effects of Oxandrolone in the Pharmacodynamic Effects of Coumadin

Oxandrolone Cohort	INR	Coumadin Dose (mg)	Coumadin Sensitivity Index (CSI)
Phase 1 –with oxandrolone			
5 mg BID	1.72±0.181	1.1 (men 1.5; women 0.75)	4.14 (men 3.47; women 4.80)
10 mg BID	0.53±0.135	1.1 (men 1.5; women 0.75)	3.05 (men 2.24; women 3.86)
Phase 2 –without oxandrolone			
5 mg BID	1.51±0.285	7.2 (men 8.3; women 6.0)	0.42 (men 0.33; women 0.50)
10 mg BID	1.50±0.161	5.4 (men 7.0; women 3.8)	0.84 (men 0.45; women 1.23)

(The combined gender values are estimates because individual data were not presented and 1 patient dropped out.)

Table 2 The Effects of Oxandrolone on the Pharmacokinetic Parameters of Coumadin

	AUC[0 to infinity] (ng/ml-hr)		T1/2 (hours)	
Oxandrolone Cohort	R Enantiomer	S Enantiomer	R Enantiomer	S Enantiomer
Phase 1 –with oxandrolone				
5 mg BID	31.66±21.85	15.11±10.08	59.66±51.90	36.11±19.71
10 mg BID	43.58±32.24	15.91±11.72	99.98±82.41	59.47±67.06
Phase 2 –without oxandrolone				
5 mg BID	33.47±12.84	30.65±12.85	22.62±6.45	25.69+9.98
10 mg BID	54.09±24.36	23.64±9.41	47.74±24.06	27.11±11.44

Reviewer Comments:

1—The drug interaction, although likely rare, is clinically, very significant. Bleeding into the gastrointestinal or urinary tract could be expected to have severe, semi-acute effects. Intra-cranial bleeding could result in death or profound sequelae from a stroke. the information should be included in the precautions section. This information is at least as significant as that for hepatic peliosis, which is already . In addition, hepatic peliosis is associated with blood-filled cysts in the liver. Intra-abdominal bleeding could be catastrophic if the patient had both hepatic peliosis and a drug induced bleeding diathesis.

2—Because of the significant nature of the interaction with coumadin, the CSO was asked to inform the sponsor that this submission would undergo formal review and would not be accepted as just a CBE.

3—Because of the significant interaction with coumadin, Dr. Ahn (Biopharm) was asked on 5/1/02 to expedite a Biopharm review. Dr. Wei asked the sponsor for additional data on 5/22/02:

a—appendices 1-7,

b—PK parameters with dose correction, and

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/s/

Elizabeth Koller
7/24/02 11:14:42 AM
MEDICAL OFFICER
The additional information that has been requested may help identify those patients who are most at risk and the underlying mechanism, but will not alter the need for a

David Orloff
7/31/02 12:16:45 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 13-718 (SLR 022)	**SUBMISSION DATE: 04-19-02, 05-29-02**
BRAND NAME:	**Oxandrin®**
GENERIC NAME:	**Oxandrolone**
REVIEWER:	**Xiaoxiong "Jim" Wei, M.D., Ph.D.**
SPONSOR:	**Bio-Technology General Corp. Iselin, NJ**
TYPE OF SUBMISSION:	**Supplement for labeling change**

SYNOPSIS:

On April 19, 2002, Bio-Technology submitted a supplement to NDA 13-718 for a proposed labeling change regarding drug interaction between oxandrolone and warfarin. The sponsor conducted a phase 1, multidose pharmacodynamic and pharmacokinetic study of the metabolic interaction between oxandrolone and warfarin in healthy subjects. The sponsor assessed the steady state pharmacodynamic effect of the oxandrolone-warfarin interaction on INR (International Normalized Ratio) at two different oxandrolone dose levels (5 mg Bid and 10 mg Bid) and also assessed the steady state of the oxandrolone-warfarin interaction on warfarin enantiomer pharmacokinetics. The study results revealed the significant increase in INR from oxandrolone-warfarin interaction and in pharmacokinetic parameters, AUC, Cmax and t1/2 in both S- and R-warfarin in concurrent treatment. Consequently, the warfarin dose was decreased by an average of 5.5 fold to maintain a target INR of 1.3 – 2.0 when oxandrolone was concurrently administered.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 13-718/Supplement No.22 (oxandrolone, Oxandrin®) submitted on April 19, 2002. The study report of metabolic drug interaction between oxandrolone and warfarin is acceptable to OCPB. This recommendation, reviewer's comment and labeling comments should be sent to the sponsor as appropriate.

CLINICAL PHARMACOLOGY

Drug Interaction

Does oxandrolone significantly potentate the pharmacodynamics and pharmacokinetics of warfarin?

The sponsor conducted a multidose pharmacodynamic and pharmacokinetic study of the metabolic interaction between oxandrolone and warfarin in healthy subjects. The sponsor assessed the steady state pharmacodynamic effect of the oxandrolone-warfarin interaction on INR (International Normalized Ratio for prothrombin time) at two different oxandrolone dose levels (5 mg Bid and 10 mg Bid) and also assessed the steady state of the oxandrolone-warfarin interaction on enantiomers S-warfarin and R-warfarin pharmacokinetics. The study design was valid in terms of spontaneous evaluation of pharmacodynamics and phamracokinetics of warfarin drug interactions. The study flow is summarized in Table 1.

Table 1. Study design

Test	Day	Group 1 (8 subjects)	Group 2 (7 subjects)

period		Oxandrin®	Warfarin	Oxandrin®	Warfarin
TP1	1	5 mg BID	No	10 mg BID	No
	2				
	3				
	4		Titration from 2 mg to maintain INR 1.3 – 2.0		Titration from 2 mg to maintain INR 1.3 – 2.0
	5				
	6				
	7				
	8	Measuring S- and R-warfarin		Measuring S- and R-warfarin	
TP2	9	No Oxandrin®	Same dose as TP1	No Oxandrin®	Same dose as TP1
	10				
	11				
	12 to steady state of INR		Titration to reach INR 1.3 – 2.0		Titration to reach INR 1.3 – 2.0
		Measuring S- and R-warfarin		Measuring S- and R-warfarin	

The pharmacokinetic parameters of both enantiomers S- and R-warfarin were significantly increased in concurrent treatment period (TP1). However, the effect of two different doses (5 mg BID and 10 mg BID) on warfarin did not show statistically different, which means 5 mg bid regimen may have reached maximal inhibitory effect on warfarin metabolism. Interestingly, it seems that oxandrin® inhibited the metabolism of both enantiomers S- and R-warfarin at the almost same extent (Table 2).

Table 2. Mean PK Parameters for S- and R -Warfarin by Oxandrolone Group

Parameter	5 mg Bid Group			10 mg Bid Group		
	TP1(test)	TP2(control)	TP2/TP1	TP1(test)	TP2(control)	TP2/TP1
	S-Warfarin					
AUC_L	5.04±2.99	13.84±4.28	**2.75**	4.05±1.02	10.32±2.66	**2.55**
Cmax	0.29±0.16	0.73±0.19	**2.52**	0.20±0.05	0.58±0.12	**2.9**
T1/2	36.11±19.71	25.69±9.98	**0.71**	59.47±67.06	27.11±11.44	**0.46**
	R-Warfarin					
AUC_L	7.51±2.92	16.62±5.61	**2.21**	6.77±2.39	15.47±2.13	**2.29**
Cmax	0.38±0.15	0.89±0.25	**2.34**	0.33±0.12	0.80±0.13	**2.42**
T1/2	59.66±51.90	22.62±6.45	**0.38**	99.89±82.41	47.74±24.06	**0.48**

Because warfarin was titrated to maintain INR at 1.3 – 2.0 under the condition of oxandrin® treatment, warfarin doses were significantly reduced to an average of 5.5 fold (Table 3).

Table 3. Mean Daily Maintenance Warfarin Dose at Each Test Period

Test Period	5 mg Bid Group	10 mg Bid Group
TP1 (test)	1.125 ± 0.88	1.125 ± 0.52
TP 2 (control)	7.0 ± 1.73	5.4 ± 2.88
Fold difference (TP2/TP1)	6.2	4.8
Warfarin dose reduction in TP1	84%	79%

Since S-warfarin, the more potent anticoagulant form is mainly metabolized through CYP2C9, which is a polymorphically expressed enzyme in human, the sponsor genotyped all subjects for CYP2C9. The frequency of mutant CYP2C9 in this study group (total 15 subjects) was unusually high, 6 subjects carried mutant alleles, *2 or *3. Assuming they were all heterozygous, the frequency was still as high as

20% (6 out of 30 alleles) (Table 4). The racial composition in the study group was 5 Caucasian, 2 African American, 9 other races. In general, the ethnic distribution of CYP2C9 polymorphism is up to 10% in Caucasian, < 3% in Asian and African Americans. However, it can be as high as 30% in East Africans.

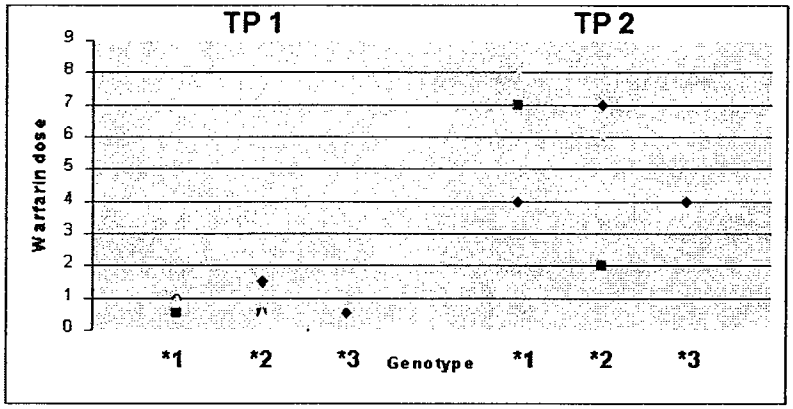
Table 4. Genotype for warfarin by gender and oxandrolone treatment group

Genotype	5 mg Bid Group	10 mg Bid Group
Male subject		
CYP2C9*1	**3**	**3**
CYP2C9*2	**1**	**1**
Female subject		
CYP2C9*1	**1**	**2**
CYP2C9*2	**2**	**1**
CYP2C9*3	**1**	**0**

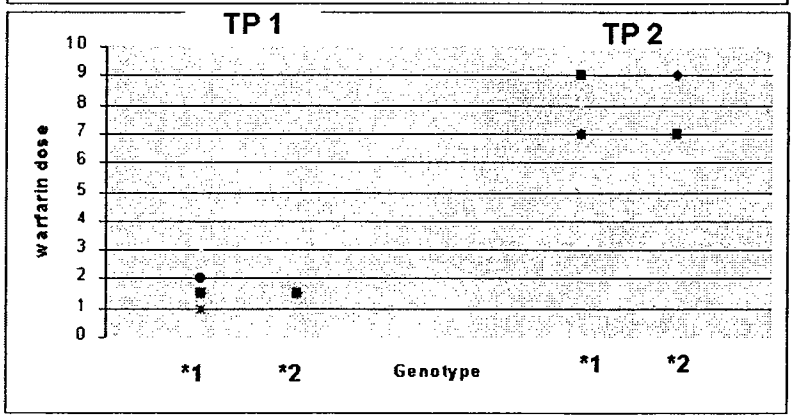
This reviewer analyzed the correlation between genotype and warfarin dose in both test periods (TP1 and TP2). Apparently, there was no correlation between them based on the following figure.

Correlation between Genotype and Warfarin Dose

Female subjects



Male subjects



Reviewer's comments:

1) The magnitudes of changes in PD parameters and PK parameters caused by drug interactions were very different. PK parameters (AUC and Cmax) were increased 2 - 3 fold when oxandrin and warfarin were co-administered. However, warfarin dose reduction to maintain INR at 1.3 – 2.0 was up to 5.5 fold. To the current knowledge about warfarin drug interaction, oxandrin® may be one of the most

potent inhibitory drugs on warfarin.

2) Oxandrin® seems equally potently inhibits metabolism of both S-warfarin and R-warfarin, which means that it may inhibit both CYP2C9 and CYP3A4 as well as other CYP enzymes.

3) The frequency of mutant CYP2C9 in the study group seems too high although it did not show any significant impact on warfarin dosing. Was the genotyping confirmed by different methods?

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

Precaution/Drug interactions/Anticoagulant:

Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg bid in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin t1/2 from 26 to 48 hours, and AUC from 4.55 to 12.08 ng*hr/mL, respectively. A similar increase in R-warfarin t1/2 and AUC was also detected. A 5.5 fold decrease in mean warfarin dose from 6.13 mg daily to 1.13 mg daily was necessary to maintain a target INR of 1.5.

☞ Location of the proposed labeling change by the sponsor is precaution section. Because of potent interaction between oxandrin® and warfarin,

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Xiaoxiong (Jim) Wei, M.D., Ph.D.

RD/ FT initialed by Hae-Young Ahn, Ph.D., Team Leader

Attachment: 1) Study Synopsis 2) Proposed package insert

Study synopsis

Title of study: A pharmacodynamic and pharmacokinetic dose response evaluation of the metabolic interaction between oxandrolone and warfarin

Investigator(s): Marc A. Saltzman, MD

Publication (s): None

Study period: first subject screened:12 February 2001 last subject evaluated: 07 May 2001

Objectives: The primary objective was to quantify the pharmacodynamics and pharmacokinetics of the known metabolic drug interaction between oxandrolone and warfarin. The secondary objective was to assess the potential effects of concurrent administration of oxandrolone and warfarin on steady-state pharmacokinetics of the R and S enantiomers of the racemate.

Design: This was a single center, phase 1, multidose, pharmacodynamic and pharmacokinetic study of the interaction between oxandrolone and warfarin.

Number of subjects: There were 16 subjects planned to be enrolled, 40 subjects screened and 15 subjects completed the trial.

Criteria for inclusion:

The key inclusion criteria were: (1) healthy adult men and women aged 18 to 60 years, and (2) total body weight within 15 percent of desirable weight as established by the 1983 Metropolitan Height and Weight Tables.

Investigational drug: oxandrolone (Oxandrin® 2.5 mg strength tablets, lot no. 080), and warfarin (Coumadin®) 1 mg tablets (lot No. EOC094A, expiration: 02/03), 2 mg tablets (lot no. ENL576A, expiration: 09/02), and 4 mg tablets (lot no. EOE255A, expiration: 05/03)

Comparator drug: There was no comparator drug in this study

Duration of treatment: Up to 21 days for Test period 1 and up to 7 days for Test period 2

Criteria for evaluation:

Safety and tolerability:

Safety was assessed by reported/observed adverse events and any changes in laboratory parameters and vital signs.

Pharmacodynamics:

Assessment of the steady state pharmacodynamic effect of the oxandrolone-warfarin interaction on INR and WSI at two different dose levels.

Pharmacokinetics:

Assessment of the steady state pharmacodynamic effect of the oxandrolone-warfarin interaction on warfarin enantiomer pharmacokinetics at two different dose levels.

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Statistical methods:

GLM (general linear model) was performed on warfarin dose, average INR, average INR divided by warfarin dose, and WSI at steady state; on AUC_L, AUC_I, C_{max}, T_{max}, $t_{½}$, and λ_Z for S, R, S plus R-warfarin blood concentrations to test differences between oxandrolone dose groups, gender, and test periods.

Changes of clotting Factors II, V, VII, and X between test periods were tested by T-test within each oxandrolone dose group, and gender group. The descriptive statistics and 95% confidence intervals of means for the original values and changes of these clotting factors are also presented.

Correlations of AUC_I for S and R-warfarin with WSI in different oxandrolone dose groups, gender groups, and test periods were computed.

Results:

Safety and tolerability:

There were no serious adverse events, or deaths. There were no adverse events leading to discontinuation from study. There were three cases of elevations in liver enzymes which were reported at the end of TP1. Two of these cases were considered by the investigator as being related to oxandrolone. There were no clinically significant laboratory findings for hematology or clinical chemistries. Eleven subjects reported one or more non-serious adverse event. The most frequently occurring adverse events during Test period 1, and between Test periods 1 and 2 were hematuria and headache followed by upper respiratory infection, constipation and increased liver function tests. Eleven events were judged to be either possibly or probably drug related. Nine events were assessed as moderately severe with the rest considered mild. None were determined to be serious and all events resolved by study completion. The transient appearance of trace blood in urine in several subjects is a common occurrence in subjects treated with warfarin. In most cases the changes in mean values for the measured laboratory parameters were within normal limits.

Pharmacodynamics:

At the end of TP1, the mean INR for the 5 mg bid oxandrolone dose group was 1.72 ±0.181 and 1.52 ±0.135 for the 10 mg bid oxandrolone dose group. The between group difference was not statistically or clinically significant. Similarly, at the end of TP2, the between group difference in the INR was not statistically different. The difference between mean target INR at TP1 and TP2 was not statistically significant, confirming that the study as executed was a valid test for both the 5 mg bid oxandrolone dose group and the 10 mg bid oxandrolone dose group.

The differences between mean target INR at TP1 and TP2 were not statistically significant for either gender.

At the end of TP1, the difference in the steady state warfarin dose by oxandrolone group (5 mg bid group vs. 10 mg bid group) was 1.125 ±0.88 vs. 1.125 ±0.52 which demonstrates that there was no dose dependency for the interaction in the range of oxandrolone doses tested. At the end of TP2, the difference in the steady state warfarin dose by oxandrolone group (5 mg bid group vs. 10 mg bid group) was 7.0 ±1.73 vs. 5.4 ±2.88. The between group difference was not statistically significant. The mean steady state warfarin dose changes between TP1 and TP2 for both oxandrolone dose groups were highly statistically significant, indicating the presence of a potent drug-drug interaction.

At the end of TP1, the mean warfarin dose for the men in the 5 mg bid oxandrolone dose group was the same as the men in the 10 mg bid oxandrolone dose group (1.50 ±1.08 vs. 1.50 ±0.41). At the end of TP1, the mean warfarin dose for the women in the 5 mg bid oxandrolone dose group was the same as the

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women in the 10 mg bid oxandrolone dose group (0.75 ±0.50 vs. 0.75 ±0.29). The gender difference between the mean steady state warfarin doses was statistically significant (p=0.0048). At the end of TP2, the mean steady state warfarin dose for the men in the 5 mg bid oxandrolone dose group was 8.33 ±1.16 vs. 7.00 ±1.63 for the men in the 10 mg bid oxandrolone dose group. Also, at the end of TP2, the mean steady state warfarin dose for the women in the 5 mg bid oxandrolone dose group was 6.00 ±1.41 vs. 3.75 ±3.10 for the women in the 10 mg bid oxandrolone dose group.

At the end of TP1, the mean calculated WSI for the 5 mg bid oxandrolone dose group was 4.14 ±2.10 and 3.05 ±1.46 for the 10 mg bid oxandrolone dose group. The between group difference was not statistically or clinically significant. At the end of TP2, the mean calculated WSI for the 5 mg bid oxandrolone dose group was 0.42 ±0.174 and 0.84 ±0.76 for the 10 mg bid oxandrolone dose group. The between group difference was not statistically or clinically significant. The between treatment difference was highly significant at p<0.0001. At the end of TP1, the mean calculated WSI for the men in the 5 mg bid oxandrolone dose group was 3.47 ±2.39, and 2.24 ±0.86 for the men in the 10 mg bid oxandrolone dose group. Additionally, during TP1, the mean calculated WSI for the women in the 5 mg bid oxandrolone dose group was 4.80 ±1.85, and 3.86 ±1.59 for the women in the 10 mg bid oxandrolone dose group. Further, at the end of TP2, the calculated WSI for the women in the 5 mg oxandrolone bid dose group was 0.50 ±0.19 and 1.22 ±0.96 for the women in the 10 mg oxandrolone bid dose group.

The statistical difference between genders for calculated WSI at TP1 was not significant (p=0.105).

The results from mean daily warfarin dose and WSI showed approximately 5.6 fold warfarin change between TP1 and TP2 for the 5 mg bid oxandrolone male subjects, whereas an approximate 4.7 fold change was seen for the 10 mg bid oxandrolone male subjects at average (stable) INRs. The results from mean daily warfarin dose and WSI showed approximately 8.0 fold warfarin dose change between TP1 and TP2 for the 5 mg bid oxandrolone female subjects, whereas an approximate 5.0 fold change was seen for the 10 mg bid oxandrolone female subjects at average (stable) INRs.

Pharmacokinetics:

For the S-enantiomer, significant statistical differences existed in AUC_L, AUC_I, and C_{max} between the two test periods, and in C_{max} between oxandrolone dose groups. Also, significant statistical differences existed for the R enantomier measures on AUC_L, C_{max}, $t_{½}$, and λ_Z between the two test periods, and in λ_Z between oxandrolone dose groups. Assessment of the combination S and R warfarin, showed significant statistical differences existed in AUC_L, AUC_I, C_{max}, $t_{½}$, and λ_Z between the two test periods, and in AUC_L and C_{max} between the two oxandrolone dose groups.

The correlation between AUC_L for the combination of S and R warfarin and WSI was negative in general for the two oxandrolone dose groups and gender at the two test periods. The only exceptions were for 5 mg bid oxandrolone dose group and male subject group at Test period 2 with positive correlation.

No between test period differences for clotting Factors II and X were detected. In both oxandrolone dose groups, a between test period increase in Factor VII was found. However, this increase was only significant for the 10 mg bid oxandrolone dose group. In both oxandrolone dose groups there was a highly significant suppression of Factor V when subjects were dosed with warfarin alone (TP2, p=0.0004 and p=0.000) for 5 mg and 10 mg bid oxandrolone dose groups, respectively), when compared to concurrent administration with oxandrolone. Statistically significant mean clotting factor changes in both gender groups were seen with Factor V and VII with the male subject group, and Factor V with female subject group.

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Conclusions: As expected, there was a wide variability in subject response to warfarin. At steady state, warfarin dose was significantly higher in men than in women, and significantly higher at Test period 2 than at Test period 1. Correspondingly, WSI was significantly higher at Test period 1 than at Test period 2.

S-warfarin pharmacokinetics showed significant differences in AUC_L, AUC_I, and C_{max} between the two test periods, and in C_{max} between oxandrolone dose groups. R-warfarin pharmacokinetics showed significant differences in AUC_L, C_{max}, $t_{½}$, and λ_Z between the two test periods, and in λ_Z between oxandrolone dose groups. For S plus R warfarin, significant differences existed in AUC_L, AUC_I, C_{max}, $t_{½}$, and λ_Z between the two test periods, and in AUC_L and C_{max} between oxandrolone dose groups. Clotting Factor V was significantly higher at Test period 1 than at Test period 2 for the 5 mg oxandrolone dose group and 10 mg oxandrolone bid dose group. Regardless of gender, clotting Factor VII was significantly higher at Test period 2 than at Test period 1 for the 10 mg oxandrolone dose group and for the male subjects.

All adverse events were mild or moderate. No adverse event definitely related to study drug was reported.

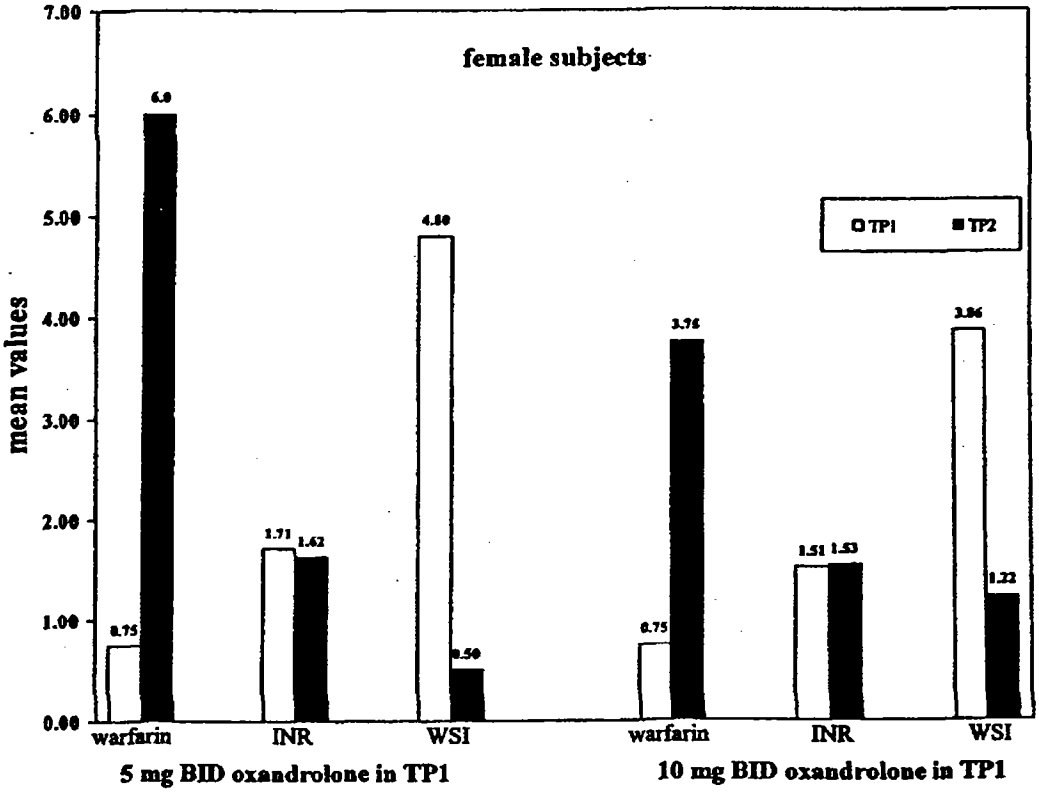
Despite the small sample size and large inter-subject variability, the metabolic interaction between warfarin and oxandrolone was confirmed.

A significant reduction of warfarin dose and close monitoring of INR is warranted when co-administered with oxandrolone.

Based on the results of this study, when oxandrolone is added to warfarin, the warfarin dose should be decreased by approximately 78-88%. Patient INR values should be monitored closely for at least three weeks, or until the INR is clinically stable. Further monitoring of INR and patient response is also warranted.

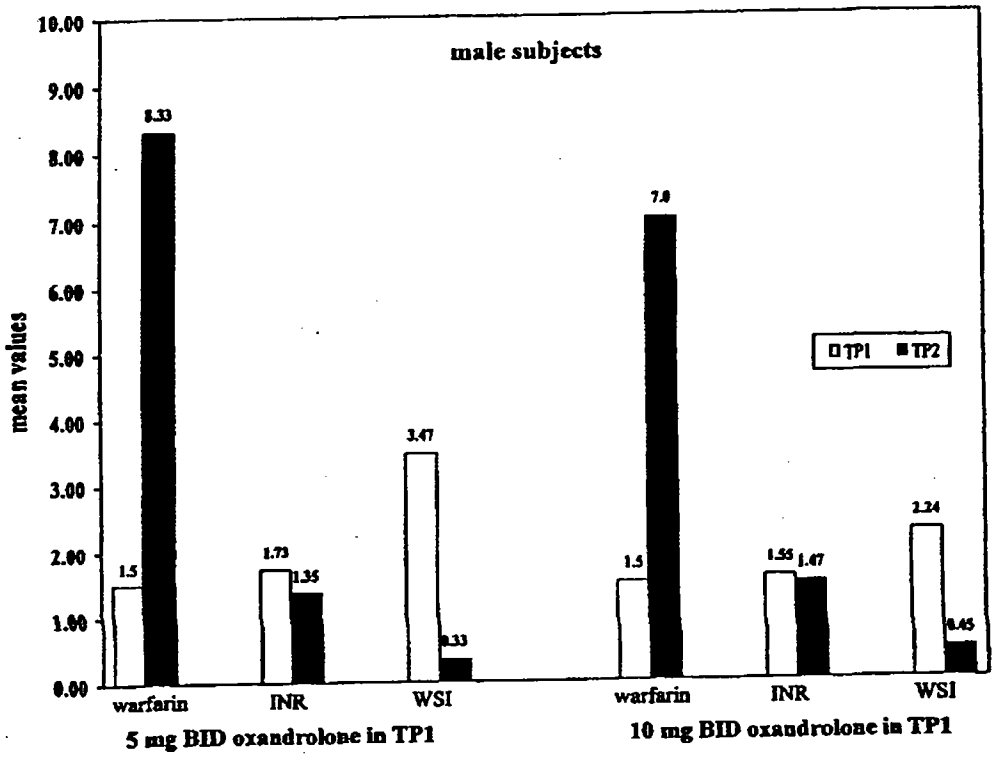
Date of the report: 28 March 2002

Figure 7-2: Mean daily warfarin dose and WSI for female subjects at Test periods 1 and 2 for the two oxandrolone dose groups



Warfarin=daily warfarin dose
INR=average INR at steady state
WSI=calculated warfarin sensitivity index
TP1=Test period 1; TP2=Test period 2
Source: Statistical documentation tables 2.1, 2.1.4

Figure 7–1: Mean daily warfarin dose and WSI for male subjects at Test periods 1 and 2 for the two oxandrolone dose groups



Warfarin=daily warfarin dose
INR=average INR at steady state
WSI=calculated warfarin sensitivity index
TP1=Test period 1, TP2=Test period 2
Source: Statistical documentation tables 2.1, 2.1.4

The results showed approximately a 5.6 fold change in warfarin dose between TP1 and TP2 for the 5 mg bid oxandrolone male subjects, whereas an approximate 4.7 fold change in warfarin dose was seen for the 10 mg bid oxandrolone male subjects at average (stable) INRs.

Genotype for Warfarin

Subject	Gender	Treatment Dosage	Genotype
F09	Female	2-2.5 mg Oxandrolone tablets BID	CYP2C9*2
F10	Female	4-2.5 mg Oxandrolone tablets BID	CYP2C9*2
F11	Female	2-2.5 mg Oxandrolone tablets BID	CYP2C9*3
F12	Female	4-2.5 mg Oxandrolone tablets BID	CYP2C9*1
F13	Female	2-2.5 mg Oxandrolone tablets BID	CYP2C9*2
F14	Female	4-2.5 mg Oxandrolone tablets BID	Not Done
F15	Female	2-2.5 mg Oxandrolone tablets BID	CYP2C9*1
F16	Female	4-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M01	Male	2-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M02	Male	4-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M03	Male	2-2.5 mg Oxandrolone tablets BID	CYP2C9*2
M04	Male	4-2.5 mg Oxandrolone tablets BID	CYP2C9*2
M05	Male	2-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M06	Male	4-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M07	Male	2-2.5 mg Oxandrolone tablets BID	CYP2C9*1
M08	Male	4-2.5 mg Oxandrolone tablets BID	CYP2C9*1

2 page(s) of revised draft labeling has been redacted from this portion of the review.

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/s/

Xiao-xiong Wei
8/16/02 06:11:00 PM
BIOPHARMACEUTICS

Hae-Young Ahn
8/19/02 04:21:08 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 13-718/S022

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

MEMORANDUM

Date: 05/24/02

Subject: Incomplete Submission of Supplement NDA13-718, Submission Date: 04-19-02

To: File of NDA 13-718

From: Xiaoxiong (Jim) Wei, M.D., Ph.D.

Through: Hae-Young Ahn, Ph.D., Team Leader

Bio-Technology General Corp submitted a supplemental application to their NDA 13-718 on April 19, 2002 regarding significant drug interactions between Oxandrolone and Warfarin. This reviewer started to review and found that the submission did not include any Appendex (1 – 7). The sponsor submitted only the first volume, which includes a study summary, protocol and protocol amendment. The pharmacokinetic information is incomplete and There is no individual data. This reviewer called Briti Kundu, Director of Regulatory Affairs May 22, 2002 to request the following additional information:

1) Appendex 1 – 7
2) Pharmacokinetic parameters with dose correction
3) Individual CYP2C9 genotyping information and corresponding individual pharmacokinetics data.

Ms. Kundu acknowledged the request and indicated that the additional data requested are in house and will try to submit before the filing date, June 21, 2002.

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/s/

Xiao-xiong Wei
5/24/02 03:17:22 PM
BIOPHARMACEUTICS

Hae-Young Ahn
5/29/02 02:49:16 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 13-718/S-022

PRIOR APPROVAL SUPPLEMENT

Bio-Technology General Corp.
Attention: Briti Kundu
Director, Regulatory Affairs
70 Wood Avenue South
Iselin, NJ 08830

Dear Ms. Kundu:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Oxandrin (oxandrolone, USP) Tablets

NDA Number: 13-718

Supplement Number: S-022

Date of Supplement: April 19, 2002

Date of Receipt: April 22, 2002

This supplemental application, submitted as a "Changes Being Effected" supplement, proposes the following change: Include additional information in the package insert regarding a drug interaction between oxandrolone and warfarin. Changes of this kind cannot be put into effect prior to approval of a supplement. An approved supplement is required for this proposed change prior to distributing drug product made with this change.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 21, 2002, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that supplemental drug applications submitted as "Changes Being Effected" supplements must include final printed labeling for filing.

If you have any questions, call me at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

William Koch
5/21/02 02:52:07 PM