DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

April 4, 2006

Albert Beraldo
President and CEO
Bioniche Pharma Group Limited
One Holiday Avenue
Pointe-Claire, QC H9R 5N3
Canada

RE: ANDA # 40-541
Sotradecol (sodium tetradecyl sulfate injection)
MACMIS ID # 13985

WARNING LETTER

Dear Mr. Beraldo:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the product brochure (MLC203 Rev A) for Sotradecol™ (sodium tetradecyl sulfate injection) submitted by Bioniche Pharma Group (Bioniche) under cover of Form FDA 2253 and available on the product website (http://www.sotradecolus.com). The product brochure is false or misleading in that it presents numerous efficacy and safety claims but fails to reveal material facts, minimizes the risks associated with Sotradecol treatment, broadens the indication, includes unsubstantiated claims, and presents misleading graphics. Thus, the product brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§352(a) and 321(n). See 21 CFR 202.1(e)(6)(i) and (e)(6)(xviii). These violations are concerning from a public health perspective because they suggest that Sotradecol is safer and more effective than has been demonstrated.

Background

According to the FDA-approved product labeling (PI):

> Sotradecol® (sodium tetradecyl sulfate injection) is indicated in the treatment of small uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves. The benefit-to-risk ratio should be considered in selected patients who are great surgical risks.

The PI also explains that Sotradecol is associated with certain risks. It states (in pertinent part):

CONTRAINDICATIONS

Sotradecol® (sodium tetradecyl sulfate injection) is contraindicated in previous hypersensitivity reactions to the drug; in acute superficial thrombophlebitis; valvular or deep vein incompetence; huge superficial veins with wide open communications to deeper veins; phlebitis migrans; acute cellulitis; allergic conditions; acute infections; varicosities caused by abdominal and pelvic tumors unless the tumor has been removed; bedridden patients; such uncontrolled systemic diseases as diabetes, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases.

WARNINGS

Sotradecol® (sodium tetradecyl sulfate injection), should only be administered by a physician familiar with venous anatomy and the diagnosis and treatment of conditions affecting the venous system and familiar with proper injection technique. Severe adverse local effects, including tissue necrosis, may occur following extravasation; therefore, extreme care in intravenous needle placement and using the minimal effective volume at each injection site are important.

Emergency resuscitation equipment should be immediately available. Allergic reactions, including fatal anaphylaxis, have been reported. As a precaution against anaphylactic shock, it is recommended that 0.5 mL of Sotradecol be injected into a varicosity, followed by observation of the patient for several hours before administration of a second or larger dose. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat it appropriately. (Emphasis in original.)

Because of the danger of thrombosis extension into the deep venous system, thorough preinjection evaluation for valvular competency should be carried out and slow injections with a small amount (not over 2 mL) of the preparation should be injected into the varicosity. Deep venous patency must be determined by angiography or noninvasive testing such as duplex ultrasound. Venous sclerotherapy should not be undertaken if tests such as Trendelenberg and Perthes, and angiography show significant valvular or deep venous incompetence.

The development of deep vein thrombosis and pulmonary embolism have been reported following sclerotherapy treatment of superficial varicosities. Patients should have post-treatment follow-up of sufficient duration to assess for the development of deep vein thrombosis. Embolism may occur as long as four weeks after injection of sodium tetradecyl sulfate. Adequate post-treatment compression may decrease the incidence of deep vein thrombosis.

PRECAUTIONS - GENERAL

Extreme caution must be exercised in the presence of underlying arterial disease such as marked peripheral arteriosclerosis or thromboangiitis obliterans (Buerger's Disease).

ADVERSE REACTIONS

Local reactions consisting of pain, urticaria or ulceration may occur at the site of injection. A permanent discoloration may remain along the path of the sclerosed vein segment. Sloughing and necrosis of tissue may occur following extravasation of the drug.

Allergic reactions such as hives, asthma, hayfever and anaphylactic shock have been reported. Mild systemic reactions that have been reported include headache, nausea and vomiting.

At least six deaths have been reported with the use of Sotradecol®. Four cases of anaphylactic shock leading to death have been reported in patients who received Sotradecol®. One of these four patients reported a history of asthma, a contraindication to the administration of Sotradecol®....

One death has been reported in a patient who received Sotradecol® and who had been receiving an antiovulatory agent. Another death (fatal pulmonary embolism) has been reported in a 36-year-old female treated with sodium tetradecyl acetate and who was **not** taking oral contraceptives. (Emphasis in original.)

Omission and Minimization of Risk Information

Promotional materials are false or misleading if they fail to reveal facts that are material in light of the representations made in the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. The product brochure is misleading because it fails to provide any risk information in the body of the piece. In particular, although the product brochure presents numerous efficacy and safety claims for Sotradecol, it fails to include the most serious and frequently occurring risks from the PI. By omitting this information, the product brochure misleadingly suggests that Sotradecol is safer than has been demonstrated.

The product brochure not only fails to communicate the risks associated with Sotradecol treatment, but also presents claims that minimize the risks associated with it. For example, it states, "FDA-approved Sotradecol by Bioniche Pharma is now available in the US Market, which **guarantees safety** compared to compounded forms that may not meet FDA standards and are not guaranteed." (Emphasis added.) While it may be acceptable to promote the advantages of an approved product over unapproved compounded forms, the claim that FDA approval "guarantees" Sotradecol's safety, particularly in the absence of an appropriate risk presentation, misleadingly implies that treatment with Sotradecol is without risk. Given the risks associated with the product, one cannot simply say that FDA approval, or compliance with good manufacturing practice, guarantees safety. Rather numerous other factors impact whether or not a drug is "safe" for a patient. For example, appropriate patient selection, which includes screening for contraindicated conditions and medications, as well as proper drug preparation and administration, must be considered. To imply that FDA approval "guarantees safety" regardless of these and other factors is misleading.

Broadening of Indication

The product brochure is also misleading because it implies Sotradecol is safe and effective for use in a broader patient population and under broader conditions than has been demonstrated by substantial

evidence. The Indications section of the PI specifically states, "Sotradecol® (sodium tetradecyl sulfate injection) is indicated in the treatment of small uncomplicated varicose veins of the lower extremities **that show simple dilation with competent valves. The benefit-to-risk ratio should be considered in selected patients who are great surgical risks.**" (Emphasis added.) The Contraindications and Precautions section also list numerous conditions in which Sotradecol is either inappropriate or should be used with extreme caution (see Background section). However, the product brochure misleadingly suggests that Sotradecol is appropriate for use in all patients with "small uncomplicated varicose veins of the lower extremities" when this is not the case. For example, pages two and three present the claims, "Sclerosing Solution for small uncomplicated Varicose Veins of lower extremities," "Right treatment for small uncomplicated Varicose Veins of lower extremities," and "Sotradecol...gives greater flexibility to treat varied sizes and magnitudes of Varicose Veins." These claims omit the qualifiers that: 1) the veins to be treated should show simple dilation with competent valves; and 2) the benefit-to-risk ratio should be considered in selected patients who are great surgical risks. In conjunction with statements such as "Offering solution to variety of patients in hospitals and clinics," the piece misleadingly broadens Sotradecol's approved patient population.

Unsubstantiated Claims

The product brochure includes claims such as:

- "Well-Known Molecule in the US Sclerotherapy Market...Sodium Tetradecyl Sulfate has been used extensively as the **preferred sclerotherapy treatment** for a long time" (Second emphasis added.)
- "**Right treatment** for small uncomplicated Varicose Veins of lower extremities." (Emphasis added.)
- "**S**afer than pharmacy-compounded non-manufactured STS molecules" (Emphasis in original.)

Phrases such as "preferred therapy," "right treatment," and "safer" suggest a comparison and misleadingly imply that Sotradecol is universally considered the sclerosant of choice, offering unspecified clinical benefits and safety over other treatment options, in absence of any evidence.

Misleading Graphic Matter

Pages one, two, and three of the product brochure present graphics of clear, varicose vein-free skin without blemishes or visual imperfections. Page three of the product brochure also presents the claim "**L**ife quality improved." (Emphasis in original.) To our knowledge, Sotradecol has not been shown to provide complete cosmetic correction of varicose veins or improved quality of life. Moreover, the product brochure fails to appropriately emphasize that patients may achieve a range of results depending on variables including, but not limited to, varicose vein severity, disease progression, depth of skin tone, technical skill of the practitioner, clinical time point assessment, and number of treatments. See 21 CFR §§202.1(e)(6)(i) and (e)(6)(xviii). Further, the graphics and text fail to present the potential for "permanent discoloration along the path of the sclerosed vein segment" as detailed in the Adverse Reactions section of the PI. Therefore, the product brochure is misleading.

Conclusion and Requested Action

For the reasons discussed above, the product brochure is false or misleading in that it presents numerous efficacy and safety claims but fails to reveal material facts, minimizes the risks associated with Sotradecol treatment, broadens the indication, includes unsubstantiated claims, and presents misleading graphics. Therefore, it misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§352(a) and 321(n). See 21 CFR 202.1(e)(6)(i) and (e)(6)(xviii).

DDMAC requests that Bioniche immediately cease the dissemination of violative promotional materials for Sotradecol such as those described above. Please submit a written response to this letter on or before April 18, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Sotradecol such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301.796.9877. In all future correspondence regarding this matter, please refer to MACMIS # 13985 in addition to the ANDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Sotradecol comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications