DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017849

SAFETY LABELING CHANGE NOTIFICATION

Lehigh Valley Technologies, Inc.
Attention: William Reightler
Director, Regulatory Affairs
514 North 12th St.
Allentown, PA 18102

Dear Mr. Reightler:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brethine® (terbutaline sulfate) Tablets, 2.5 mg and 5.0 mg.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Brethine (terbutaline sulfate) Tablets, 2.5 mg and 5.0 mg were approved on May 17, 1976, we have become aware of postmarketing adverse event reports describing serious cardiovascular adverse reactions, including death, associated with the use of oral terbutaline sulfate for tocolysis. We have also become aware of animal studies, published in peer-reviewed biomedical literature, in which the offspring of rat dams treated with terbutaline during the late stage of pregnancy and the lactation period exhibited alterations in behavior and brain development. 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 all oral formulations of terbutaline sulfate as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

Add a **BOXED WARNING** to the package insert as described below:

WARNING: TOCOLYSIS

Oral terbutaline sulfate has not been approved for and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for maintenance tocolysis in the outpatient or home setting.

During pregnancy, serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See *Contraindications, Tocolysis*.]

Revise the **CONTRAINDICATIONS** section of the package insert as described below:

CONTRAINDICATIONS

1. Tocolysis
Oral terbutaline sulfate is contraindicated for the treatment of acute or maintenance tocolysis. [See *Boxed Warning: Tocolysis*.]

2. Hypersensitivity
Terbutaline sulfate is contraindicated in patients known to be hypersensitive to sympathomimetic amines or any component of this drug product.

Revise the *Tocolysis* and *Pregnancy-Teratogenic Effects* subsections of the **PRECAUTIONS** section of the package insert as described below:

PRECAUTIONS

~~**Tocolysis**~~
~~Terbutaline sulfate has not been approved and should not be used for tocolysis. Serious adverse reactions may occur after administration of terbutaline sulfate to women in labor. In the mother, these include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.~~

Pregnancy - Teratogenic Effects
Pregnancy Category ~~B~~ C
~~A reproduction study in Sprague-Dawley rats revealed terbutaline sulfate was not teratogenic when administered at oral doses of 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m^2 basis). A reproduction study in New Zealand white rabbits revealed terbutaline sulfate was not teratogenic when administered at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).~~

There are ~~however,~~ no adequate and well-controlled studies of terbutaline sulfate in pregnant women. Published animal studies show that rat offspring exhibit alterations in behavior and brain development, including decreased cellular proliferation and differentiation when dams were treated subcutaneously with terbutaline during the late stage of pregnancy and lactation period. Terbutaline exposures in rat dams were approximately 6.5 times the common human dose in adults of 15 mg/day, on a mg/m^2 basis.

Oral terbutaline sulfate has not been approved for and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See *Boxed Warning: Tocolysis* and *Contraindications, Tocolysis*.]

In animal embryofetal developmental studies, no teratogenic effects were observed in offspring when pregnant rats and rabbits received terbutaline sulfate at oral doses up to 50 mg/kg/day, approximately 32 and 65 times, respectively, the maximum recommended daily oral dose for adults, on a mg/m^2 basis.

~~Because animal reproduction studies are not always predictive of human responses, this drug~~ Terbutaline sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus ~~(See PRECAUTIONS, Tocolysis)~~.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval 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. 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.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order 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) – 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 do not submit electronically, please send 5 copies of the submission.

If you have any questions, please contact Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D.
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology 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/

SALLY M SEYMOUR
02/16/2011