DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

SUPPLEMENT APPROVAL

NDA 20-394/S-012
Boehringer Ingleheim
900 Ridgebury Rd/PO box 368
Ridgefield, CT 06877-0368

Attention: Amy Van Andel
Senior Associate Director, Drug Regulatory Affairs

Dear Ms. Van Andel:

Please refer to your Supplemental New Drug Application (sNDA) dated July 23, 2010, received July 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atrovent (ipratropium bromide) 0.06% Nasal Spray.

This "Changes Being Effected" supplemental new drug application proposes to harmonize labeling with other Boehringer Ingelheim ipratropium bromide products .

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below in **bold**.

Pregnancy

Teratogenic Effects: *Pregnancy Category B*

There are no adequate and well-controlled studies for Atrovent in pregnant women. Because animal reproduction studies are not always predictive of human response, Atrovent Nasal Spray 0.06% should be used during pregnancy only if clearly needed.

Oral reproduction studies were performed at **ipratropium** doses of 10 mg/kg in mice, 1,000 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond, in each species, respectively, to approximately 60, 12000, and 3000 times the maximum recommended daily intranasal dose **(MRDID)** in adults on a mg/m^2 basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 20 and 45 times, respectively, the **MRDID** in adults on a mg/m^2 basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses 90 mg/kg and above in rats (approximately 1100 times the

MRDID in adults on a mg/m^2 basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. ~~However, no adequate or well controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, Atrovent® (ipratropium bromide) Nasal Spray 0.06% should be used during pregnancy only if clearly needed.~~

Labor and Delivery

The effect of ipratropium bromide on labor and delivery is unknown.

Nursing Mothers

It is known that some ipratropium bromide is systemically absorbed following nasal administration; however, the portion which may be excreted in human milk is unknown. Because lipid-insoluble quaternary cations pass into breast milk, caution should be exercised when ATROVENT Nasal Spray 0.06% is administered to a nursing mother.

OVERDOSAGE

Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. Following administration of a 20 mg oral dose (equivalent to ingesting more than two bottles of Atrovent® (ipratropium bromide) Nasal Spray 0.06%) to 10 male volunteers, no change in heart rate or blood pressure was noted. Following a 2 mg intravenous infusion over 15 minutes to the same 10 male volunteers, plasma ipratropium concentrations of 22-45 ng/mL were observed (>100 times the concentrations observed following intranasal administration). Following intravenous infusion these 10 volunteers had a mean increase of heart rate of 50 bpm and less than 20 mmHg change in systolic or diastolic blood pressure at the time of peak ipratropium levels.

(b) (4)

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.
If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Angela Ramsey, Senior Regulatory Project Manager, at (301) 796-2284

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
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/

BADRUL A CHOWDHURY
02/18/2011