DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-121/S-009/S-012

McNeil Consumer and Specialty Pharmaceuticals
Attention: Mimi C. Lonardo, Ph.D.
Associate Director, Developmental Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Dr. Lonardo:

Please refer to your supplemental new drug applications dated September 30, 2003 (21-121/S-009), and February 24, 2006 (21-121/S-012), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Concerta (methylphenidate hydrochloride) Extended-Release Tablets.

Reference is also made to Agency action letters dated May 22, 2006 (S-012), and June 11, 2006 (S-009), for the above supplemental applications.

Your submission dated June 29, 2006 constituted a complete response to our May 22, 2006, and June 11, 2006 letters.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to product labeling:

21-121/S-009

1. Under **"DESCRIPTION**," changed "hydroxpropyl methylcellulose" to "hypromellose" per USP.
2. Under "**CONTRAINDICATIONS-Monoamine Oxidase Inhibitors**," added clarification re: "MAO" and cross reference to the "Drug Interactions" section.
3. Under "**PRECAUTIONS-Drug Interactions"**, added a reference to drug interaction from "Contraindications" section and added a clarification re: MAO.
4. Under "**PRECAUTIONS-Pregnancy: Teratogenic Effects- Pregnancy Category C,**" added the sentence, "The safety of methylphenidate for use during human pregnancy has not been established."
5. Under "**ADVERSE REACTIONS** (after the "**Tics**" subsection), added a new subsection entitled, **Post-Marketing Experience with CONCERTA,** and added the following sentence to this new subsection: "Post-marketing experiences with CONCERTA have revealed spontaneous reports of the following adverse events: difficulties in visual accommodation, blurred vision, abnormal liver function tests (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia."
6. Under "**ADVERSE REACTIONS- Adverse Events with Other Methylphenidate HCL Products**," deleted items that were moved to the new "Post-Marketing Experience with Concerta" subsection.

NDA 21-121/S-012
As requested, in our May 22, 2006, action letter, you have incorporated the standard CNS stimulant class labeling revisions by deleting the current **WARNINGS** section of Concerta product labeling and replace it with the following language under the **WARNINGS** section of labeling:

WARNINGS
Serious Cardiovascular Events
Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems.

Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) [see Adverse Reactions-Hypertension], and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional

chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder;

such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a

similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Potential for Gastrointestinal Obstruction
Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Use in Children Under Six Years of Age
CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE
CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the

As requested, you have also created a new subsection under **ADVERSE REACTIONS** entitled Hypertension. This subsection follows immediately after the subsection entitled Tics.

ADVERSE REACTIONS
Hypertension
In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced

> average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.
>
> In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. (see Warnings)

We note that you have also updated the patient package insert (PPI) so that it is in alignment with the class labeling revisions. Although this is acceptable, at this time, we intend to request a Medication Guide in the near future for all of the CNS stimulants. The Medication Guide will then replace the PPI.

We have completed our review of these applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed labeling text.

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
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Felicia Curtis, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Thomas Laughren
9/7/2006 09:00:08 AM