DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Sue Duvall, RN, MPA
Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

RE: NDA # 21-802
Focalin XR® (dexmethylphenidate hydrochloride) extended-release capsules CII
MACMIS ID # 15566

Dear Ms. Duvall:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional slide deck (FCL-MD-0057-A) for Focalin XR® (dexmethylphenidate hydrochloride) extended-release capsules CII (Focalin XR) submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA 2253 as well as a webpage for Focalin XR.[1] These pieces are false or misleading because they overstate the efficacy of Focalin XR and broaden the indication for the drug. Thus, the promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n), and FDA's implementing regulations. *Cf*. 21 CFR 201.100(c)(1), 201.128, 202.1(e)(6)(i).

Background

According to its FDA-approved product labeling (PI), Focalin XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older. The Indications and Usage Section of the PI also includes information regarding special diagnostic considerations, the need for comprehensive treatment, and information about long-term use.

Focalin XR's PI contains a Boxed Warning regarding drug dependence. The PI also contains numerous contraindications, including use in patients with marked anxiety, tension, and agitation, use in patients with glaucoma, use in patients with motor tics or with a family history or diagnosis of Tourette's syndrome, and use during or within 14 days of treatment with monoamine oxidase inhibitors. Additionally, the PI contains warnings regarding sudden death and pre-existing structural cardiac abnormalities or

[1] Last accessed on April 02, 2008 at http://focalinxr.com/info/living/treating/adhd_treatment_adult.jsp

other serious heart problems, hypertension and other cardiovascular conditions, pre-existing psychosis, comorbid bipolar disorder, emergence of new psychotic or manic symptoms, aggression, long-term suppression of growth, seizures, visual disturbances, and use in children under six years of age. The most common treatment-emergent adverse events associated with Focalin XR compared with placebo, in pediatric patients, include decreased appetite (30%, 9%), headache (25%, 11%), dyspepsia (8%, 4%), and anxiety (6%, 0%). The most common treatment-emergent adverse events associated with Focalin XR compared with placebo, in adult patients, include headache, anxiety, dry mouth, dyspepsia, and pharyngolaryngeal pain.

Overstatement of Efficacy

The professional slide deck contains presentations about the consequences of untreated ADHD and about the impact of treatment with Focalin XR. For example, slide seven of the professional slide deck, entitled "Potential Impact of Untreated ADHD Across the Lifespan," presents numerous statements about the consequences of untreated ADHD, including the following:

- "Low self-esteem"
- "Academic limitations"
- "Smoking and substance abuse"
- "Legal problems"
- "Injuries"
- "Impaired Family and Peer Relationships"
- "Motor vehicle accidents"
- "Occupational/vocational difficulties"

Slide nine, entitled "Desired Treatment Outcomes in Adult ADHD," presents numerous statements about the hoped for impact of treatment on adult patients with ADHD, including the following:

- "Able to pay bills…"
- "Avoiding speeding/recklessness during driving"
- "Decreased substance use"

Similarly, the Focalin XR webpage, which is entitled "**Treating ADHD**" (emphasis original), includes a prominent display of the Focalin XR logo and other references to Focalin XR and presents numerous statements about the consequences of untreated ADHD and about the impact of treatment, including:

> **Why ADHD treatment is important** (emphasis original)
>
> Children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD), if untreated, are at risk for poor academic performance. Teen pregnancy, problems with peers, car accidents, and physical injuries occur

> at a higher rate. Untreated, children and teens with ADHD are also at risk of conduct disorders, delinquency, and drug or alcohol abuse.
>
> Typically, adults with untreated ADHD experience academic hardships. These often start in childhood and are likely to worsen during college years. Untreated adults take longer to complete learning degrees. They are likely to have lower economic status, lower rates of employment, and more work-related problems. Untreated adults also have more problems in their relationships, more driving accidents, and more addiction—from alcohol to gambling.
>
> **Living with ADHD doesn't have to be this way**. People with ADHD have treatment choices. The results of untreated ADHD are serious and should not be ignored. There is no cure for ADHD. **Proper treatment can help control symptoms, helping to reduce these risks.** (emphasis added)

While these presentations do not directly assert that Focalin XR will correct the problems of untreated ADHD or lead to the hoped for outcomes, they are misleading nonetheless because the only sensible interpretation of placing the consequences of untreated ADHD in pieces promoting the use of Focalin XR for ADHD is to imply that Focalin XR may reduce the likelihood or severity of the consequences of untreated ADHD listed above (i.e., poor social–emotional development and job success, poor academic performance, impaired driving, smoking and substance abuse) and induce the desired treatment outcomes when this has not been demonstrated by substantial evidence or substantial clinical experience. While Focalin XR has been shown to improve the DSM-IV total subscale score of the Conners ADHD/DSM-IV Scales for teachers (CADS-T), which measures ADHD symptoms such as fidgeting, restlessness, and failure to complete tasks started, this scale does not measure the effect of treatment on the multiple outcomes listed above (i.e., social–emotional development and job success, academic performance, driving ability, smoking and substance abuse), and it does not necessarily follow that improvement in the DSM-IV total subscale score of the CADS-T is correlated with a positive effect on these outcomes.

None of the references cited[2,3,4,5,6,7] in support of the presentations above from the slide deck present data on the effect of treatment with Focalin XR on the outcomes

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[2] American Academy of Pediatrics. Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. 2000;105:1158-1170.
[3] Kelly PC, Cohen ML, Walker WO, et al. Self-Esteem in Children Medically Managed for Attention Deficit Disorder. *Pediatrics*. 1989;83:211-217.
[4] Murphy K, Barkley RA. Attention Deficit Hyperactivity Disorder Adults: Comorbidities and Adaptive Impairments. *Compr Psychiatry*. 1996;37:393-401.
[5] Biederman J. Impact of Comorbidity in Adults With Attention-Deficit/Hyperactivity Disorder. *J Clin Psychiatry*. 2004;65:3-7.
[6] Barkley RA, Murphy KR, Kwasnik D. Motor Vehicle Driving Competencies and Risks in Teens and Young Adults with Attention Deficit Hyperactivity Disorder. *Pediatrics*. 1996;98:1089-1095.

presented on the slides. While Focalin XR is indicated for the treatment of ADHD, FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Focalin XR can help patients avoid these consequences.

Broadening of Indication

The slide deck presents numerous claims about the long-term effectiveness and safety of Focalin XR. For example, slides 25-27 contain the following claims:

- "Focalin® XR Demonstrated Long-Term Symptom Control As Shown By ADHD Total Symptom Scores" (slide 25)
- "Patients Continued to Experience Symptom Improvement With Focalin® XR" (slide 26)
- "Improvements are sustained over 6 months" (slide 27)

These presentations misleadingly imply that Focalin XR is effective for long-term use when this has not been demonstrated by substantial evidence or substantial clinical experience. Indeed, the Indications and Usage section of the Focalin XR PI, under the subheading "Long-Term Use," states (in pertinent part):

> The effectiveness of Focalin XR for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Focalin XR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient….

In fact, no well-controlled trial supports long-term effectiveness, and the reference in slides 25-27 refers to an open-label, not concurrently controlled study that would not be considered substantial evidence of long-term effectiveness. An open-label (non-blinded) study is not an appropriate study design to evaluate subjective endpoints, such as those measured by the Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) or the Conners ADHD/DSM-IV Scales for Teachers (CADS-T). Blinding is intended to minimize potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.[8] Thus, because the study was not blinded, the findings for Focalin XR are not unbiased and the study can not be relied upon as substantial evidence in support of the claims.

Second, because the cited study lacked a control group, there is no way to distinguish patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused

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[7] Swensen A, Birnbaum HG, Hamadi RB, et al. Incidence and Costs of Accidents Among Attention-Deficit/Hyperactivity Disorder Patients. *J Adolesc Health*. 2004;35:346.e1-9.
[8] Guidance for Industry E 10 Choice of Control Group and Related Issues in Clinical Trials, at 4, http://www.fda.gov/cder/guidance/4155fnl.pdf.

by the test treatment from outcomes caused by other factors, such as natural progression of the disease, observer or patient expectations, or other treatment.[9]

While slide 41, entitled "Maintenance/Extended Treatment," states, "Effectiveness of Focalin XR for long-term use (>7 weeks) has not been systematically evaluated in controlled trials," and "Patients should periodically be re-evaluated, with periods off medication," these disclaimers are insufficient to mitigate the misleading impression that Focalin XR has been proven to be effective for long-term use.

Conclusion and Requested Action

For the reasons discussed above, the professional slide deck and website misbrand Focalin XR in violation of the Act, 21 U.S.C. 352(a) & (n), and FDA's implementing regulations. *Cf*. 21 CFR 201.100(c)(1), 201.128, 202.1(e)(6)(i).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Focalin XR such as those described above. Please submit a written response to this letter on or before October 7, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Focalin XR the same as or similar to those described above, and explaining your plan for discontinuing use of such 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, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 15566 in addition to the NDA 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 Focalin XR comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Robert Dean, M.B.A.
Group Leader
Direct to Consumer (DTC) Group 1
Division of Drug Marketing,
Advertising, and Communications

[9] Guidance for Industry E 10 Choice of Control Group and Related Issues in Clinical Trials, at 3, http://www.fda.gov/cder/guidance/4155fnl.pdf

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/s/

Robert Dean

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