



TRANSMITTED BY FACSIMILE

Joyce Pashalides, Sr. Associate Director
Regulatory Advertising & Promotional Review, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

RE: NDA 021802

Focalin XR[®] (dexmethylphenidate hydrochloride) Extended-Release Capsules CII
MACMIS# 20059

Dear Ms. Pashalides:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional One Point Leave Behind detail aid (FCL-1042739) (detail aid) for Focalin XR[®] (dexmethylphenidate hydrochloride) Extended-Release Capsules CII (Focalin XR) submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA-2253. The detail aid is false or misleading because it presents unsubstantiated superiority claims for the product. Thus, the detail aid misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(6)(ii), (xviii); (e)(7)(i) & (ii).

Background

According to the Indications and Usage section of Focalin XR's FDA-approved product labeling (PI) (in pertinent part):

Focalin XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older. . . .

Focalin XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. . . .

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.

The PI for Focalin XR contains a Boxed Warning regarding drug dependence. The PI also contains numerous Contraindications, including use in patients with marked anxiety, tension,

agitation, known hypersensitivity to methylphenidate or other components of the product, glaucoma, 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 and Precautions regarding sudden death and pre-existing structural cardiac abnormalities or other serious heart problems in children, adolescents, and adults; hypertension and other cardiovascular conditions; assessing cardiovascular status in patients being considered for or treated with stimulant medications; pre-existing psychosis; bipolar disorder; emergence of new psychotic or manic symptoms; aggression; long-term suppression of growth; seizures; visual disturbance; use in children under six years of age; and hematologic monitoring. The most common treatment-emergent adverse events associated with Focalin XR compared with placebo in pediatric patients include decreased appetite (30% vs. 9%), headache (25% vs. 11%), dyspepsia (8% vs. 4%), and anxiety (6% vs. 0%). The most common treatment-emergent adverse events associated with Focalin XR (at least 5% and twice the incidence among placebo-treated patients) in adult patients include headache, dry mouth, anxiety, dyspepsia, and pharyngolaryngeal pain.

The Clinical Studies section of the PI presents efficacy results from two randomized, double-blind, placebo-controlled, parallel-group studies that evaluated Focalin XR in the treatment of ADHD: one in pediatric patients, ages 6-17 years of age; the other in adults. The primary endpoint of the pediatric study was the mean change from baseline to endpoint in the Diagnostic and Statistical Manual 4th edition (DSM-IV) total subscale score of the Conners ADHD/DSM-IV Scales for Teachers (CADS-T). Focalin XR demonstrated a statistically significant treatment effect as compared to placebo. In the adult study, the primary endpoint was the mean change from baseline to endpoint in the DSM-IV ADHD Rating Scale. All three Focalin XR doses studied (20, 30, and 40 mg/day) were statistically significantly superior to placebo.

The PI also describes two additional pediatric studies (patients aged 6-12 years) that examined the efficacy of Focalin XR over an 11- and 11.5-hour time course using the Swanson, Kotkin, Agler, M-Flynn, & Pelham (SKAMP) rating scale combined score. In both studies, Focalin XR was found have a statistically significant treatment effect as compared to placebo at all time points studied (0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours in one study and 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours in the other study). A third study, conducted in pediatric ADHD patients aged 6-12 years of age, demonstrated a treatment effect for 20 mg/day Focalin XR at 0.5 hours post-dose using the SKAMP combined score.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The detail aid includes the following claims and graphic presentation (emphasis in original; selected footnotes removed):

- **“Two well-controlled studies confirmed the efficacy of Focalin XR versus Concerta at 2 hours postdose”** (page two)
- Graph titled **“ADJUSTED MEAN CHANGE IN SKAMP-COMBINED SCORE FROM PREDOSE TO 2 HOURS POSTDOSE,^{1,2}”** which compares Focalin XR 20 mg and Concerta 36 mg (page three)
- “Focalin XR demonstrated statistically significant superior efficacy versus Concerta 2 hours postdose^{1,2}” (page three)
- **“Conclusion**
 - Two well-controlled studies confirmed the superior efficacy of Focalin XR 20 mg versus Concerta 36 mg at 2 hours postdose^{1,2}” (page three)

These claims and graphic presentation misleadingly imply that Focalin XR is superior to Concerta, because of a benefit demonstrated at 2 hours post-dose. To support this implication, the detail aid references two clinical studies,^{1,2} which examined the efficacy of Focalin XR as compared to Concerta for the treatment of ADHD. However, these studies do not constitute substantial evidence to support the above superiority claims. Treatment for ADHD consists of symptom relief over an extended time period; thus, ADHD medications must control disease symptoms over the entire treatment course. However, the referenced clinical studies only focused on **one** specific time point (2 hours post-dose) as the primary efficacy measure in the treatment course of Focalin XR and Concerta. By focusing on the 2-hour post-dose time point, the studies did not account for the different pharmacokinetic profiles and subsequent efficacy profiles associated with Focalin XR and Concerta over the entire treatment course. Specifically, Focalin XR has been formulated to provide a biphasic release of active drug, producing two distinct concentration peaks approximately 4 hours apart. The initial release of methylphenidate from Focalin XR mimics that provided with the immediate release formulation (first peak concentration around 1.5 hours [range, 1 – 4 hours]), with the second peak occurring about 6.5 hours after dosing (range, 4.5 – 7 hours). Conversely, Concerta is formulated to deliver an initial amount of methylphenidate via immediate release, followed by gradually ascending concentrations of methylphenidate over the next 5 to 9 hours (concentration peak at 6 to 10 hours post-dose), after which a gradual decrease begins. In fact, while the two referenced studies suggest that Focalin XR may provide greater symptom relief in the earlier part of the day, such as at 2 hours, they also suggest that Concerta may deliver greater symptom relief than Focalin XR from hour nine and beyond.

¹ Muniz, R, Brams M, Mao A, et al. Efficacy and safety of extended-release dexamethylphenidate compared with *d,l*-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. *J Child Adolesc Psychopharmacol*. 2008;18(3):248-256.

² Silva R, Muniz R, McCague K, et al. Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexamethylphenidate and *d,l*-methylphenidate and placebo in a laboratory classroom setting. *Psychopharmacol Bull*. 2008;41(1):19-33.

Additionally, the detail aid includes the following claim, “When considering an ADHD medication **Think Focalin XR first for a fast start**” (bolded emphasis in original; underlined emphasis added). This claim misleadingly implies that Focalin XR is better or more effective than other ADHD medications, and therefore, should be the “first” choice when considering treatment options. This superiority claim is not supported by substantial evidence or substantial clinical experience.

Overall, the FDA is unaware of any adequate and well-controlled head-to-head clinical studies to support claims that Focalin XR is superior to other ADHD medications, including Concerta. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the detail aid misbrands Focalin XR in violation of the Act, 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(6)(ii), (xviii); (e)(7)(i) & (ii).

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 June 14, 2011, stating whether you intend to comply with this request, listing all promotional materials in use (with the 2253 submission date) for Focalin XR that contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #20059 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}

Jessica N. Cleck Derenick, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

JESSICA N CLECK DERENICK
05/31/2011