DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Celeste M. Reisch
Corporate Labeling Manager
Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

RE: NDA # 21-475, 21-419
Methylin® (methylphenidate HCl) Chewable Tablets [CII]
Methylin® (methylphenidate HCl) Oral Solution [CII]
MACMIS ID # 15565

Dear Ms. Reisch:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a patient brochure (MET 221) for Methylin (methylphenidate HCl) Chewable Tablets and Methylin (methylphenidate HCl) Oral Solution (hereinafter collectively referred to as Methylin) issued by Mallinckrodt Inc. (Mallinckrodt) and Alliant Pharmaceuticals, Inc.[1] (Alliant), which until recently marketed Methylin on behalf of Mallinckrodt. This piece is false or misleading because it overstates the efficacy of Methylin, omits and minimizes risks associated with Methylin, and contains unsubstantiated claims about the drug, including unsubstantiated comparative claims. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i), (ii), & (e)(7)(viii).

Background

According to the FDA-approved product labeling (PI), Methylin is indicated for (in pertinent part):

> Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome,

[1] A June 12, 2007, press release from Sciele Pharma, Inc., (found on the Internet at http://phx.corporate-ir.net/phoenix.zhtml?c=120763&p=irol-newsArticle_Print&ID=1014610&highlight=) announced that Sciele Pharma, Inc. had completed its acquisition of Alliant Pharmaceuticals, Inc.

> Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.
>
> Methylin® is indicated as an integral part of a total treatment program....

Methylin's PI contains a Boxed Warning regarding drug dependence. The PI also contains numerous contraindications, including use in patients with marked anxiety, tension, or agitation, glaucoma, motor tics, in patients with a family history or diagnosis of Tourette's syndrome, or during treatment with monoamine oxidase inhibitors (MAO-I) and also within a minimum of 14 days following discontinuation of an MAO-I.

Methylin is associated with a number of serious risks, some of which are potentially fatal. The PI for Methylin includes warnings regarding sudden death in patients with pre-existing structural cardiac abnormalities, use in children under six years of age, long-term use due to potential for suppression of growth, use for severe depression, prevention or treatment of normal fatigue states, the lowering of the convulsive threshold in a number of circumstances, use in patients with hypertension, and visual disturbances. Nervousness and insomnia are the most common adverse events associated with the drug. Other adverse events include anorexia and nausea, as well as abdominal pain and weight loss during prolonged therapy, which may occur more frequently in children.

Overstatement of Efficacy

Under a header that states **"How can ADHD impact my child?"** (emphasis original), the patient brochure claims:

> Without diagnosis and proper management, ADHD can have devastating consequences, including failure in school, depression, violent behavior, substance abuse, relationship problems, and failure to keep a job.

The brochure also contains numerous claims and presentations on the pages surrounding the above presentation that promote the use of Methylin for the treatment of ADHD. While the presentation excerpted above does not directly assert that Methylin will correct the problems of untreated ADHD, it is nevertheless misleading because it implies, in the context of the piece as a whole, that Methylin may reduce the likelihood or severity of the consequences of untreated ADHD listed above (i.e., poor academic performance, poor social–emotional development, violent behavior, substance abuse, and employment problems) when this has not been demonstrated by substantial evidence or substantial clinical experience. While Methylin is approved for the treatment of attention deficit disorders based on a demonstration of bioequivalence with the reference listed drug (Ritalin® (methylphenidate hydrochloride)), we are not aware of substantial evidence or substantial clinical experience demonstrating a positive effect of treatment with Methylin (or of treatment with the reference listed drug) on the outcomes listed above (i.e., academic performance, depression, violent behavior,

substance abuse, and stable employment). If you have such data, please submit them to FDA for review.

Omission/Minimization of Risk

Promotional materials are misleading if they fail to reveal material facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The patient brochure is misleading because it omits important risks associated with Methylin. In particular, it fails to convey that Methylin is contraindicated during treatment with an MAO-I and also within a minimum of 14 days following discontinuation of an MAO-I. It also fails to disclose warnings regarding sudden death in patients with pre-existing structural cardiac abnormalities, long-term suppression of growth, use for severe depression, prevention or treatment of normal fatigue states, the lowering of the convulsive threshold in a number of circumstances, and visual disturbances.

The patient brochure is also misleading because it suggests that Methylin is safer than has been demonstrated by substantial evidence or substantial clinical experience. The patient brochure includes the claims (emphasis original):

> **If any of the following apply to you, talk to your doctor about Methylin Oral Solution and Methylin Chewable Tablets.**
>
> ....
>
> **For younger adolescent and adult ADHD patients:**
>
> ....
>
> - Who need a medication they can take around meals to avoid appetite decline

This claim is misleading because it suggests that use of Methylin will help to reduce or avoid appetite decline. According to the Adverse Reactions section of the PI, Methylin may cause "... anorexia... [and] weight loss during prolonged therapy." Furthermore, the PI states, "In children, **loss of appetite**, abdominal pain, [and] weight loss during prolonged therapy... may occur more frequently." (emphasis added). Although the piece does disclose, in the Special Precautions section on the same page, that "Additional effects may include, but are not limited to, skin rash, **loss of appetite**..." (emphasis added), this disclosure, as well as the similar disclosure in the last sentence in the footnote of the previous spread, is insufficient to mitigate the misleading impression created by the claim above that use of Methylin, when taken around meals, will not result in appetite decline.

We note that the problems above are magnified because the brochure fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of Methylin. *Cf.* 21 CFR 202.1(e)(7)(viii). Specifically, the patient brochure presents efficacy claims in

consumer-friendly language using colorful, bolded headers and bulleting but presents risk information in medical terminology in paragraph form below the reference list and product logos, spanning across the main spread of the brochure, and without any presentation elements that indicate to the reader that it is important risk information.

Unsubstantiated Comparative Claims

The patient brochure claims (emphasis original):

> **If any of the following apply to you, talk to your doctor about Methylin Oral Solution and Methylin Chewable Tablets.**
>
> **For younger adolescent and adult ADHD patients:**
> ....
>
> - Who are highly sensitive to medications and need a low or precise dose

This claim is misleading because it suggests that Methylin offers a safety benefit for patients who are "highly sensitive to medications" as compared to other ADHD medications when this has not been demonstrated by substantial evidence or substantial clinical experience. We acknowledge that the availability of Methylin as an oral solution and 2.5 mg tablet may offer some utility in patients who need a low or intermediate dose of methylphenidate. However, it is misleading to claim that the treatment solution for younger adolescent and adult ADHD patients who are "highly sensitive" to medications is to prescribe a "low or precise dose" of Methylin, as patients who have previously demonstrated sensitivity to medication may not be equally sensitive to all medications, and furthermore, the solution to medication sensitivity is not necessarily giving patients a lower dose, as sensitivity can have many causes and is not necessarily dose-dependent.

Unsubstantiated Claims

The patient brochure claims that "83% of patients rated the taste of Methylin Oral Solution as positive." (footnote omitted) This claim is misleading because it is not supported by substantial evidence or substantial clinical experience. The reference[2] cited, which consisted of survey responses from 44 patients, asked patients to rate their response as: "very pleasant," "OK," "Unsure," and "Unpleasant." The percentage of patients in the claim above was derived from the combined total of patients who responded "very pleasant," "OK," and "Unsure." Thus, the claim categorizes the "Unsure" responses as "positive." It is misleading to categorize these responses in this manner because the response "Unsure" is inconclusive as to whether patients felt positively or negatively about the taste. FDA is not aware of any evidence to support this claim. If you have data to support it, please submit them to FDA for review.

---

[2] Data on file, Alliant Pharmaceuticals, Inc.

In addition, the patient brochure presents the claim that "100% of patients said they would rather take their ADHD medication in the form of a liquid or an oral solution than crush their medication or mix it with applesauce." (footnote omitted) This claim is misleading because it is not supported by substantial evidence or substantial clinical experience. The reference[2] cited, which consisted of survey responses from 44 patients, includes responses that showed patients preferred chewable or oral solution dosage forms when given a choice among four dosage options: with foods; chewable tablets; oral solution; or patch. The answer choice, "with food," fails to capture what is claimed in the patient brochure – i.e., "crush medication" or "mix it with applesauce." It also is unclear whether the responding patients actually experienced all four options before choosing a preferred dosage form. Thus, this survey is not sufficient to support this claim. If you have data to support it, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the patient brochure misbrands Methylin in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i), (ii) & (e)(7)(viii).

DDMAC requests that Mallinckrodt immediately cease the dissemination of violative promotional materials for Methylin 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 Methylin 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 # 15565 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 Methylin 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

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

/s/

Robert Dean
9/25/2008 03:58:41 PM