DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

J. Martin Carroll
President and Chief Executive Officer
Boehringer-Ingelheim
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

RE: NDA #20-667
Mirapex® (pramipexole dihydrochloride)
MACMIS ID #16795

WARNING LETTER

Dear Mr. Carroll:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed two consumer-directed pharmacy printouts (MRLS47260 and MRLS47262) and a professionally-directed labeling piece (MRLS47349) for Mirapex® (pramipexole dihydrochloride) (Mirapex), submitted by Boehringer Ingelheim (BI) under cover of separate Forms FDA-2253. The two consumer-directed printouts (MRLS47260 and MRLS47262) are misleading because they present efficacy claims for Mirapex but fail, respectively, to either communicate any risk information for Mirapex (MRLS47260) or to communicate the important risks associated with the use of Mirapex (MRLS47262). In addition, it appears that neither printout was accompanied by the FDA-approved product labeling (PI) for Mirapex in violation of 21 CFR 201.100(d). The professionally-directed labeling piece (MRLS47349) is misleading because it presents efficacy claims for Mirapex but omits material facts and broadens the indication for the drug. Thus, these materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a), 352(f)(1) & 321(n), and FDA's implementing regulations. 21 CFR 201.100(c)(1); *cf*. 21 CFR 202.1(e)(3)(i) & (e)(6)(i). These materials raise significant public health and safety concerns by suggesting that Mirapex is safer than has been demonstrated.

Background

According to its PI, Mirapex tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

Mirapex use is associated with a number of serious risks. The PI for Mirapex lists several warnings, including falling asleep during activities of daily living, symptomatic hypotension,

and hallucinations, and the adverse reactions section states that Mirapex is associated with nausea, headache, and tiredness.

Consumer Printouts

Omission of Important Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The first consumer-directed printout, MRLS47260, presents numerous efficacy claims for Mirapex, including the following:

- "What's keeping you up at night? Are your restless legs to blame?"
- "Restless Legs Syndrome (RLS) is a real condition, with real day-to-day consequences"
- "Take this quiz and share your answers with your doctor:
  - I have a strong urge to move my legs when resting. ○ Yes ○ No
  - I have feelings in my legs such as burning, creeping, crawling, aching, tingling, tugging, and itching. These feelings are worse when I rest or lay down. ○ Yes ○ No
  - Moving my legs gives me relief. ○ Yes ○ No
  - My symptoms are worse at night and when I rest. ○ Yes ○ No

  If you said YES to these questions, you may have a treatable condition called Restless Legs Syndrome (RLS)."
- "**MIRAPEX is indicated for the treatment of moderate to severe primary RLS. MIRAPEX can help relieve the frequency & severity of many of the symptoms associated with moderate to severe primary RLS, such as the urge to move.**" (emphasis in original)
- "Talk to your doctor about MIRAPEX. For a free RLS guide and money saving offer, go to www.MIRAPEX.com/CHC or call 1-877-RID-RLS1 (1-877-743-7571)."

This printout, however, fails to present **any** risk information. When a piece makes claims such as those above, it must also present risk information as necessary to ensure that the claims made are truthful and non-misleading. *Cf.* 21 CFR 202.1(e)(3). No such risk information is present here.

The second consumer-directed printout, MRLS47262, fails to reveal important warnings associated with the use of Mirapex. The printout discusses common side effects and states, "[s]ide effects are mild and decreased over time. The most common side effects are nausea, headache and tiredness." However, this presentation fails to communicate that there are serious warnings associated with Mirapex. Specifically, the printout fails to include the warnings about falling asleep during activities of daily living, symptomatic hypotension, and hallucinations. By omitting these risks, the printout misleadingly suggests that Mirapex is safer than has been demonstrated. Additionally, the statement "[s]ide effects are mild and decreased over time" in conjunction with the omission of the most serious warnings further

minimizes the risks and reinforces the message that Mirapex is safer than has been demonstrated. This statement suggests that all side effects associated with Mirapex are mild and decreased over time when this is not the case.

The statement "Please see accompanying Patient Information for MIRAPEX" included in the bottom third of these two printouts does not mitigate these misleading presentations. As a result, the promotional materials misleadingly suggest that Mirapex is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Failure to Provide Adequate Directions for Use

It appears that the PI was not included with the printouts, in violation of 21 CFR 201.100(d).[1]

Professional Labeling Piece

Omission of Material Fact/Broadening of Indication

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made. The professionally-directed piece, MRLS47439, is misleading because it includes claims and representations about restless leg syndrome and Mirapex, but fails to present the corresponding approved indication for Mirapex (i.e., that Mirapex is indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)). One side of the piece presents numerous claims regarding RLS. Although the name of the product is not mentioned on the portion of the piece containing the RLS discussion, the reverse side of the piece includes a section titled "IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX." Additionally, the product logo for Mirapex is prominently displayed on the acrylic holder. The piece thus ties use of the drug Mirapex to treatment of RLS, but fails to include the full indication for use of Mirapex anywhere on it.

Additionally, the claims presented in this piece regarding RLS misleadingly imply that Mirapex is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. For example, the piece presents claims such as:

- "Which of these patients suffers from RLS? They all do!"
- "RLS affects a range of patients."
- "**Up to 10%** of the US adult population is affected by **mild, moderate or severe** symptoms of RLS, which often goes undiagnosed." (emphasis added)

In the absence of disclosure of the approved indication, these claims are misleading because they suggest, in the context of the overall presentation, that Mirapex is safe and effective for

[1] We note that the pieces appear to have been disseminated with the patient package insert (PPI); however, as indicated above, the regulations require that any labeling which includes claims about a drug product must contain the contents of the full FDA-approved product labeling (PI). We remind you that this includes (but is not limited to) the full text of the Mirapex FDA-approved patient labeling or PPI, which must be reprinted immediately following the last section of the required FDA approved prescription drug labeling for Mirapex or, alternatively, accompany the Mirapex prescription drug labeling (PI). 21 CFR 201.80(f)(2))

use in the treatment of RLS regardless of severity (mild, moderate, or severe), when, in fact, Mirapex is only approved for use in the treatment of moderate to severe RLS.

Conclusion and Requested Action

For the reasons discussed above, the consumer printouts and professional labeling piece misbrand Mirapex in violation of the Act, 21 U.S.C. 352(a), 352(f)(1) & 321(n), and FDA's regulations. 21 CFR 201.100(c)(1); *cf.* 21 CFR 202.1(e)(3)(i) & (e)(6)(i). In addition, it appears that the FDA-approved product labeling (PI) for Mirapex did not accompany the printouts, in violation of 21 CFR 201.100(d).

DDMAC requests that BI immediately cease the dissemination of violative promotional materials for Mirapex such as those described above. Please submit a written response to this letter on or before October 14, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Mirapex, such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS #16795 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 Mirapex comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
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/

Thomas Abrams

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