



TRANSMITTED BY FACSIMILE

Mr. Daniel Glassman
Chief Executive Officer
Bradley Pharmaceuticals, Inc.
383 Route 46 West
Fairfield, NJ 07004

Re: NDA # 08-848, 08-848/S-024
Pamine® (methscopolamine bromide) 2.5 mg Tablets
Pamine® Forte (methscopolamine bromide) 5 mg Tablets
MACMIS ID # 12413

WARNING LETTER

Dear Mr. Glassman:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional sales aid (PA589) for Pamine® (methscopolamine bromide) 2.5 mg Tablets and a patient brochure (PA630) for Pamine® Forte (methscopolamine bromide) 5 mg Tablets submitted by Kenwood Therapeutics (Kenwood), a Division of Bradley Pharmaceuticals, Inc., under cover of Form FDA 2253. In addition, DDMAC has reviewed a page of the Bradley Pharmaceuticals, Inc. website that promotes Pamine (www.bradpharm.com/pamine.htm). The professional sales aid, patient brochure, and website contain numerous effectiveness claims for Pamine and Pamine Forte that are not, to our knowledge, supported by substantial evidence or substantial clinical experience. They also omit risk information for these drugs. Finally, the professional sales aid and website misrepresent the safety of Pamine. The professional sales aid, patient brochure, and website are, therefore, false or misleading under the Federal Food, Drug, and Cosmetic Act (Act), *see* 21 U.S.C. §§ 352(a), (n); 321(n); 21 CFR 202.1(e)(5), and pose a potential risk to the public health because they suggest Pamine and Pamine Forte are safer and more effective than has been demonstrated. In addition, the website was not submitted to DDMAC under cover of Form FDA 2253 at the time of initial dissemination or publication, as required by 21 CFR 314.81(b)(3)(i).

Background

According to the FDA-approved labeling (PI), Pamine and Pamine Forte are indicated as “Adjunctive therapy for the treatment of peptic ulcer.” Although the Clinical Pharmacology section of the PI states that methscopolamine bromide possesses most of the pharmacologic actions of the drug class anticholinergics, including inhibition of gastrointestinal motility, Pamine and Pamine Forte have not been found by FDA to be safe and effective in the treatment of gastrointestinal motility symptoms, such as diarrhea, cramping, and bloating.

Pamine and Pamine Forte are associated with numerous risks, as described in the “Warnings,” “Precautions,” and “Adverse Reactions” sections of the PI. These risks include:

- Diarrhea: The “Warnings” section of the PI states, “Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.”
- Drowsiness or blurred vision: The “Warnings” section of the PI states, “Methscopolamine bromide may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.”
- Use in elderly and in all patients with autonomic neuropathy, hepatic or renal disease, or ulcerative colitis: The “Precautions” section of the PI states, “large doses may suppress intestinal motility to the point of producing a paralytic ileus and for this reason precipitate or aggravate ‘toxic megacolon,’ a serious complication of the disease.”
- CNS: The “Adverse Reactions” section of the PI states, “Headaches, nervousness, mental confusion, drowsiness, dizziness” have been observed.
- Special Senses: The “Adverse Reactions” section of the PI states, “Blurred vision, dilatation of the pupil, cycloplegia, increased ocular tension, loss of taste” have been observed.
- Gastrointestinal: The “Adverse Reactions” section of the PI states, “Nausea, vomiting, constipation, bloated feeling” have been observed.

According to the "Pharmacokinetics" section of the PI, "Methscopolamine bromide has limited ability to cross the blood-brain barrier."

Unsubstantiated Effectiveness Claims

The professional sales aid, patient brochure, and website suggest that Pamine and Pamine Forte are effective in treating gastrointestinal motility symptoms and in improving patients’ control of their lives. For example, the professional sales aid for Pamine states:

- “Do Your Patients’ Lives Revolve Around Gastrointestinal Motility Symptoms?”
- “I wish I could just have a good time without constantly worrying about whether my pain and diarrhea will let me have a good day or not.”
- “At 35, I feel so isolated from the world. I find myself accepting invitations less and less because of my nearly uncontrollable diarrhea.”
- “Diarrhea and abdominal pain affect my life constantly. I can’t count on regularly attending any of my activities.”

- “About three years ago, my life just fell apart. I started getting episodes of severe abdominal pain and bloating with diarrhea. Now, I miss several days of work each month, which is putting my job in jeopardy.”
- “Demonstrated Effective Relief of Painful Motility Symptoms”
- “Inhibits discomfort caused by bloating, diarrhea and cramps, improving patients’ control of their lives.”
- “Relieves pain of functional gastrointestinal symptoms.”
- “In the Pamine® group, 63% of patients achieved a spasm-free experience or minimal spasms compared to 30% in the control group.”
- “Because of my diarrhea and cramps, I wouldn’t wish my life on anyone.”
- “With pain, bloating and diarrhea, I feel like I have no control over my life.”
- “I am hardly ever on time because I have to revisit the bathroom so many times.”
- “I don’t even have fun anymore – I have had to curtail activities like golfing, tennis and vacations because my bowel is so unpredictable.”

The patient brochure asks the following questions, suggesting that such conditions can be effectively treated with Pamine Forte:

- “Do you suffer from
 - Abdominal pain?
 - Cramping?
 - Diarrhea?
 - Bloating and Gas?”

The patient brochure also states:

- “If you are suffering from abdominal pain and cramping, diarrhea, bloating and gas, it is often hard to maintain a normal lifestyle. Work attendance can suffer, leisure activities may be curtailed and vacations can become something to dread.”
- “Now that I’m free of abdominal pain, my work performance has really improved!”
- “It’s wonderful to enjoy a day without worrying about a flare-up of pain and diarrhea”
- “Finally I can enjoy a social life without severe abdominal pain getting in the way.”

- “Your doctor may recommend Pamine® Forte 5 mg (methscopolamine bromide) to relieve your symptoms of:
 - Abdominal pain
 - Cramping
 - Diarrhea
 - Bloating and Gas”
- “Pamine® Forte 5 mg is a prescription antispasmodic/anticholinergic that works as follows:
 - 1) Relaxes the muscles of the bowel to help reduce muscle tightness and spasms to relieve pain
 - 2) Relaxes muscles to help reduce bloating and feelings of fullness
 - 3) Reduces intestinal contractions and the secretions in the bowel and may relieve loose bowels and diarrhea
 - 4) Alleviates bowel urgency and lessens the number of bathroom visits”

The website states:

- “Pamine® helps relieve the pain associated with bloating, diarrhea, and cramps by *SLOWING THE MOTION* of the GI tract.”
- "Safe, effective, and time-tested, Pamine® reduces the amount of acid in your stomach, thereby reducing the pain associated with excessive stomach acid."
- "Pamine® is a wise choice for the safe and effective relief of on-going GI tract discomforts."

Moreover, the professional sales aid, patient brochure, and website claim that Pamine and Pamine Forte relieve symptoms of bloating, despite the fact that the “Adverse Reactions” section of the PI states that a “bloating feeling” has been associated with the use of the drugs.

We are not aware of substantial evidence or substantial clinical experience to support any of the preceding claims. If you have data to support the claims, please submit them for review.

Omission of Risk Information

The professional sales aid, patient brochure, and website are false or misleading because they present effectiveness claims for Pamine and Pamine Forte but fail to provide any risk information about the drugs. As described above, Pamine and Pamine Forte are associated with many risks.

The professional sales aid is accompanied by the PI, and the website provides a link to the PI (although not from the page containing the effectiveness claims reproduced above). For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any safety or effectiveness claims made in that part.

False or Misleading Safety Claims

The professional sales aid and website state, respectively:

- “Not likely to produce CNS side effects such as
 - lightheadedness
 - blurred vision
 - fatigue/drowsiness
 - dizziness”
- “Does not cross the blood-brain barrier
 - "No Significant CNS Effects
 - Unlike hyoscyamine sulfate, dicyclomine hydrochloride USP”
- “And, unlike some anticholinergics/antispasmodics that contain substances that cross the blood-brain barrier and enter the Central Nervous System (CNS), Pamine® has not been shown to penetrate the blood-brain barrier and has no significant CNS effects. Using Pamine®, therefore, genuinely minimizes the risk of significant central effects such as light-headedness or fatigue.”

These statements suggest that Pamine is not likely to produce central nervous system side effects because it does not penetrate the blood-brain barrier. This is false or misleading. As noted, Pamine is associated with several CNS side effects, including drowsiness, blurred vision, headache, nervousness, mental confusion, and dizziness, and limited ability to cross the blood-brain barrier.

Finally, the professional sales aid states:

- “LACTOSE-FREE to meet the needs of lactose-intolerant patients.”
 - No added gastrointestinal problems
 - Unlike dicyclomine hydrochloride USP or glycopyrrolate USP”

This professional sale aid thus implies that, because Pamine is lactose-free, patients using it will have no added gastrointestinal problems, unlike dicyclomine hydrochloride and glycopyrrolate. FDA is not aware of substantial evidence supporting this claim. Moreover, as noted, Pamine is associated with gastrointestinal side effects, such as nausea, vomiting, constipation, and bloated feeling.

Failure to Submit Under Form FDA 2253

FDA regulations require you to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of a prescription drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. You did not submit the website to DDMAC under cover of Form FDA 2253 as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the professional sales aid, patient brochure, and website misbrand Pamine and Pamine Forte in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. §§ 352(a), (n); § 321(n); 21 CFR 202.1(e)(5). Furthermore, the website was not submitted to DDMAC under cover of Form FDA 2253 at the time of initial dissemination or publication, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Bradley Pharmaceuticals, Inc. immediately cease the dissemination of violative promotional materials for Pamine and Pamine Forte such as those described above. Please submit a written response to this letter on or before November 23, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Pamine and Pamine Forte 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 plan of action to disseminate truthful, non-misleading, and complete information 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, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12413 in addition to the NDA numbers. 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 Pamine and Pamine Forte 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 W. Abrams, R.Ph., MBA
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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