



10901

Food and Drug Administration
Rockville MD 20857

OCT 16 2001

WARNING LETTER

Mr. James Ascher, Sr.
President and Chief Executive Officer
B.F. Ascher & Company, Inc.
15501 West 109th Street
Lenexa, Kansas 66219-1381

Ref: 02-HFD-312-01

Dear Mr. Ascher:

This letter concerns *MELAGESIC™ PM CAPLETS* (Melagesic), which is marketed by your firm as a combination drug-dietary supplement product. According to the package labeling, each tablet of Melagesic contains, among other ingredients, 500 mg of acetaminophen and 1.5 mg of melatonin. The product is labeled for use to "Promote[] natural, restful sleep[] and relieve[] pain." The labeling also specifies that Melagesic "combines the pain medicine most recommended by physicians with nature's own sleep enhancer, melatonin. MELAGESIC PM relieves your aches and pains as it helps you promote natural, restful sleep. You awake refreshed and alert with no sleep hangover. MELAGESIC PM is not habit forming." The package label also contains a disclaimer that states, "[w]ith regard to melatonin, these statements have not been evaluated by the Food and Drug Administration. Melatonin is not intended to diagnose, treat, cure or prevent any disease."

As formulated and labeled, Melagesic is a "drug" under section 201(g)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) because it is intended to affect the structure or function of the body (e.g., "relieves pain," "Pain Reliever," and "for the temporary relief of minor aches and pains"). Notwithstanding your attempt to market Melagesic as a combination drug-dietary supplement, the presence of the acetaminophen, with its intended use to relieve pain, renders the entire product a drug. This is true even though the acetaminophen in Melagesic is

combined with another ingredient, melatonin, that separately could be marketed as a dietary supplement. When, as here, a drug and a dietary ingredient are combined into a single product, there is no provision in the Act, as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), that exempts any part of that product from the scope of section 201(g).¹

Under section 201(g) (1) (D) of the Act, the melatonin used in combination with the acetaminophen is also a drug since it is a component of the finished drug product. See Title 21 of the Code of Federal Regulations, Part 210.3(b) (3) [21 CFR 210.3(b) (3)]. Based on the labeling claims made for it (e.g., "sleep enhancer"), melatonin is also an "active" drug ingredient within the meaning of 21 CFR 201.66(b) (2).

Moreover, based on its formulation and labeling, Melagesic is a "new drug" within the meaning of section 201(p) of the Act and 21 CFR 310.3(h) and 21 CFR 338 because Melagesic is not generally recognized as safe and effective for its labeled uses. Melagesic is not subject to the Food and Drug Administration's (FDA's) Over-The-Counter (OTC) Drug Review because no other product formulated with these active ingredients and labeled for these intended uses has ever been commercially marketed, and the agency has never proposed that such a product be included in this Review. In the final monograph for OTC nighttime sleep-aids (21 CFR 338), the agency did state that "combinations of a monograph nighttime sleep-aid and an internal analgesic(s) are exempt from the requirements of the final rule until a final decision on such a combination is issued in a future issue of the Federal Register." See 54 Federal Register 6814 at 6822 (Feb. 14, 1989). (Emphasis added)

¹ In addition, the presence of acetaminophen excludes Melagesic from the definition of a dietary supplement under section 201(ff) (3) (B) of the Act because acetaminophen is a new drug that has been approved under section 505(a). See Pharmanex v. Shalala, 221 F.3d 1151, 1154 (10th Cir. 2000). FDA first approved a New Drug Application for acetaminophen in April 1950, and acetaminophen was not marketed as a food or a dietary supplement before that date. Moreover, Melagesic also is not a dietary supplement within the meaning of section 201(ff) (1) of the Act because it includes acetaminophen, which is an active drug ingredient that is not a dietary ingredient under section 201(ff) (1) (A) - (F).

However, melatonin is not identified as a monograph nighttime sleep-aid active ingredient and, therefore, may not legally be used as such in any OTC nighttime sleep-aid product. See 21 CFR 338.10. Thus, Melagesic violates section 505(a) of the Act because it is a new drug and is not the subject of an approved New Drug Application (NDA).

Melagesic is also misbranded under section 502(f)(1) of the Act because the product lacks adequate directions for use as defined in 21 CFR 201.5, 21 CFR 310.201(a)(1)(vii), and 21 CFR 369.21. Under these regulations, the labeling for an OTC drug product that contains acetaminophen is required to specify the duration of administration and contain specific acetaminophen warnings. The product labeling for Melagesic includes the statement, "Do not take for pain for more than 10 days unless directed by a physician..." but it does not warn consumers about the need to consult a physician before giving acetaminophen drug products to children under three years of age. Moreover, the directions for use do not address the duration of administration for use of the product as a sleep aid.

Melagesic is likewise misbranded under section 502(f)(2) of the Act because its labeling lacks adequate warnings. Melagesic is marketed as an OTC nighttime sleep aid, but its warnings state only that it should not be taken "for pain for more than 10 days unless directed by a physician." (Emphasis added). The labeling does not bear a warning limiting use for sleeplessness. Protracted sleeplessness may be a symptom of a more serious underlying condition. See 21 CFR 338.50(c)(2). Under 21 CFR 310.201(a)(1)(vii) and 21 CFR 369.21, over-the-counter use of acetaminophen for the temporary relief of pain is limited to 10 days unless otherwise directed by a doctor. This is true regardless of the other intended uses for which the acetaminophen product is sold.

Finally, Melagesic is misbranded under section 502(e)(1)(A)(ii) of the Act because its labeling fails to identify melatonin as an active drug ingredient. See 21 CFR 201.10.

The violations described in this letter are not meant to be all-inclusive. It is your responsibility to ensure that all drug products manufactured and distributed by your firm comply with

the Act. Federal agencies are advised of the issuance of all Warning Letters pertaining to drugs and devices so that they may take this information into account when considering the award of contracts. We request that you take action immediately to correct these violations. Failure to do so may result in regulatory action without further notice and may include seizure and/or injunction.

Please respond to this office in writing within fifteen (15) working days of receipt of this letter. Your response should describe the specific actions you will take, or have taken, to correct the violations described above. It should also include an explanation of each step being taken to prevent recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed. Your reply should be directed to Mr. Kevin M. Budich, Compliance Officer, as follows:

Food and Drug Administration
OTC Compliance Team, HFD-312
7520 Standish Place, Room 168
Rockville, Maryland 20855

If you have any questions about the content of this letter, you may contact Mr. Budich at 301-827-7354.

Sincerely,



David J. Horowitz, Esq.
Acting Director
Office of Compliance
Center for Drug Evaluation and Research