



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 18 2005

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Robert W. Pollock
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

Re: Docket No. 2004P-0504/CP1

Dear Mr. Pollock:

This responds to your citizen petition dated November 10, 2004 (Petition), requesting that the Food and Drug Administration (FDA) designate DiaBeta, manufactured for Aventis Pharmaceuticals, as a second reference listed drug for glyburide tablets, 5 mg. At this time, the only reference listed glyburide drug product is Micronase, manufactured by Pharmacia & Upjohn. For the reasons stated below, your petition is granted.

I. BACKGROUND

A. Reference Listed Drugs

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an approved abbreviated new drug application (ANDA). To obtain approval, the ANDA sponsor must show, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product (1) has the same active ingredient(s) in the same strength, (2) has essentially identical labeling, and (3) is bioequivalent.

A listed drug is a new drug product that has an effective approval under section 505(c) of the Act for safety and effectiveness or under section 505(j), that has not been withdrawn or suspended under section 505(e)(1) through (5) or (j)(5) of the Act, and that has not been withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.3). Listed drugs are identified as drugs with an effective approval in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) (§ 314.3). A reference listed drug is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its application (id.).

Our policy on the designation of reference listed drugs is stated in the preamble to the 1992 final rule establishing the requirements for ANDAs (57 FR 17950, April 28, 1992).

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In response to comments asking us to explain how we determine which drugs should be reference listed drugs, we stated:

... FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

57 FR 17950 at 17958.

B. Orange Book Listings for Glyburide Tablets, 5 mg, Products

The Orange Book identifies Micronase (NDA 17-498) and DiaBeta (NDA 17-532) glyburide tablets, 5 mg, as having the same active ingredient, dosage form, strength, and route of administration (i.e., they are pharmaceutical equivalents).¹ Micronase is designated as the reference listed drug for glyburide tablets, 5 mg, and several generic drug products are AB-rated (demonstrated to be bioequivalent) to Micronase. DiaBeta Tablets, 5 mg, are rated BX, meaning that the data reviewed by the Agency are insufficient to determine that there is therapeutic equivalence to the listed drug, Micronase.

II. DISCUSSION

You state that because DiaBeta is not rated as therapeutically equivalent to other approved glyburide products, any ANDA applicant seeking approval of a glyburide tablet in strengths of 1.25 mg, 2.5 mg, or 5 mg must cite Micronase as the reference listed drug, effectively shielding DiaBeta from direct competition. You state that DiaBeta Tablets had total sales of approximately \$4 million in 2003. You state that although this is a relatively small share of the glyburide tablet market, it represents sales that should not be shielded from direct generic competition (Petition at 2).

We have examined the issues presented in your petition and have determined that you have stated grounds establishing that it is in the public interest to allow the submission of ANDAs that cite DiaBeta as the reference listed drug. Therefore, in accordance with the policy stated in the 1992 final rule, we will designate DiaBeta as a second reference listed drug for glyburide tablets, 5 mg.

¹ Orange Book, 24th ed. (2004), at 3-178, 3-179.

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We are aware that the presence of two reference listed drugs in the Orange Book might create the potential for confusion and inappropriate substitution. If we approve any ANDAs for glyburide tablets with DiaBeta as the reference listed drug, we will take appropriate steps to make it clear in the Orange Book that a generic drug product that is therapeutically equivalent to either DiaBeta or Micronase is not therapeutically equivalent to the other.

III. CONCLUSION

For the reasons stated above, your petition is granted.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research