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Docket No. 2004P-0339/CP1

VIA FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Refuse to File an ANDA for the Combination Drug Amlodipine Besylate-Benazepril Hydrochloride (amlodipine-benazepril)

Dr. Reddy's Laboratories Response to July 28, 2004 Citizen Petition Submitted on Behalf of Frommer Lawrence & Haug LLP

On behalf of Dr. Reddy's Laboratories ("Dr. Reddy's"), we submit this response to the above referenced Citizen Petition, submitted by the law firm Frommer, Lawrence & Haug LLP, presumably on behalf of Novartis, the manufacturer of Lotrel® (amlodipine-benazepril) ("Frommer Citizen Petition"). Frommer's July 28, 2004 Citizen Petition, FDA Docket No. 2004P-03339/CP1, requests that the Food and Drug Administration ("FDA") refuse to file any ANDA for the combination drug amlodipine besylate-benazepril hydrochloride unless the application contains both fasted and fed segments of a drug study demonstrating bioequivalence.

Frommer's Citizen Petition contends that FDA requires that bioequivalence studies for all orally-administered immediate release drug products be conducted under both fasted and fed conditions unless the product falls within one of three exempted categories. Frommer contends that none of these exceptions apply for an ANDA for amlodipine besylate-benazepril hydrochloride citing Lotrel as the referenced listed drug ("RLD").

As the following discussion will demonstrate, Frommer's petition is wholly without merit and should be denied. Frommer's Citizen Petition is both misleading and seeks to impart conditions on generic applicants that have not been required of the brand company. Upon review of the relevant facts and materials, it is clear that fed studies should not be required for any

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ANDA for amlodipine-benazepril which references Lotrel, prior to acceptance for filing or as a condition of the ANDA approval process.

I. While FDA Recommends That Food Effect Bioequivalence Studies Be Conducted Under Certain Circumstances, Amlodipine-Benazepril ANDAs Meet A Relevant Exemption.

The Federal Food, Drug, and Cosmetic Act (“FDCA”) requires that an ANDA contain “information to show that the new drug is bioequivalent to the listed drug...” 21 U.S.C. § 355(j)(2)(A)(iv). *See also* 21 CFR § 314.94(a)(7) & 320.1(e). A generic drug is considered to be bioequivalent to the RLD if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses...

21 U.S.C. § 355(j)(8)(B)(i). *See also* 21 CFR § 320.1(e).

Frommer’s Citizen Petition states that “FDA requires that bioequivalence studies for all orally-administered immediate release drug products be conducted under both fasted and fed conditions” citing to FDA’s Guidance Document on Food-Effect Bioavailability and Bioequivalence Studies (“Bioequivalence Guidance”). Citizen Petition at 2 (emphasis added). Yet Frommer’s choice of words is misleading. A correct reading of the Guidance reveals the following:

In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products....

Bioequivalence Guidance at 3 (emphasis added). Thus, FDA does not require, but merely recommends a fed bioequivalence study under certain circumstances. As noted below, this is not Frommer’s only selective use of disclosing relevant information.

Though the Bioequivalence Guidance notes that FDA generally recommends a bioequivalence study under fed conditions for all orally administered immediate-release drug products, it notes the following exceptions:

- When both test product and the RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) ... , or
- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or

- When the RLD label does not make any statements about the effect of food absorption or administration.

See Bioequivalence Guidance at 3. Frommer argues that none of the three exemptions noted above apply here. First the petition states that “Benazapril is not a BCS Class I drug substance, [and that] the labeling of LOTREL® does not recommend administration on an empty stomach....” Citizen Petition at 2. Finally, and most importantly, Frommer argues that the Lotrel labeling “contains a statement that the absorption of the individual active drug substances is not influenced by the presence of food in the gastrointestinal tract.” Citizen Petition at 2. On this basis, Frommer argues that an ANDA referencing Lotrel does not meet any of the exceptions and that therefore FDA should reject for filing any ANDA not containing bioequivalence data under both fasted and fed situations. However as discussed below, this argument is wholly without merit and omits one critical fact.

II. Frommer Fails To Disclose That The Labeling For Lotrel Specifically States That Food Effects On Absorption From Lotrel Have Not Been Studied

As noted above, the Frommer Petition argues that the “Lotrel labeling contains a statement that the absorption of the individual active drug substances is not influenced by the presence of food in the gastrointestinal tract,” and that on this basis, fed bioequivalence studies should be required. Citizen Petition at 2. Although the Petition paraphrases the labeling, it is worth quoting the actual language from which Frommer summarizes:

The rate and extent of absorption of benazepril and amlodipine from Lotrel are not significantly different, respectively, from the rate and absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract...

However, despite signing a certificate which represents that “all representative data and information known to Petitioner which are unfavorable to the Petition” have been included, Frommer omits any mention of the statement which immediately follows the above labeling statement:

food effects on absorption from Lotrel have not been studied.

See Lotrel package insert attached to Citizen Petition (emphasis added).

Thus, a review of the labeling makes it clear that food effects have not been studied on Lotrel and that the only basis for this statement is information derived from studies on the individual tablets (i.e., benazepril and amlodipine). The Citizen Petition’s failure to note this crucial fact and that the Petition is nevertheless requesting generic applicants to conduct studies not performed on the brand product is striking and indicative of the true motive behind the petition, delay of generic competition. Given the fact that food effects on Lotrel have not been

studied, there is no reasonable basis to require ANDA applicants using Lotrel as the RLD to conduct such studies.

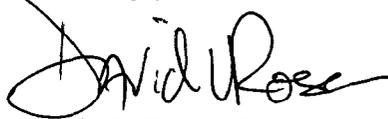
III. Case Law Demonstrates That It Is Arbitrary And Capricious To Treat Similarly Situated Parties Differently

Courts have ruled that agencies must “treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.” *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997), citing *Independent Petroleum Association of America v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996). “If an agency treats similarly situated parties differently, its action is arbitrary and capricious and violation of the APA.” *See id.*, citing *Allegan Inc. v. Shalala*, 6 Food and Drug Rep. 389, 391, No. 94-1223 (D.D.C. Nov. 10, 1994).

Here, it is clear that Novartis, the innovator, has not conducted studies which measure the influence of Lotrel on the presence of food in the gastrointestinal tract. Nevertheless, Frommer’s Citizen Petition requests that FDA require generic ANDA applicants seeking approval for an identical product conduct studies not performed by the innovator. This is a textbook definition of unequal treatment. Thus, it is both arbitrary and capricious for FDA to require a generic amlodipine-benazepril applicant to conduct studies to demonstrate an effect that the innovator has not.

Given these facts, Frommer’s Citizen Petition should be denied. Frommer’s unmerited attempt is merely one of a host of brand companies’ efforts to delay generic competition and should therefore be denied.

Sincerely yours,



David L. Rosen, B.S. Pharm., J.D.

cc: Timothy Wheeler
Dr. Reddy’s Corporation

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