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February 27, 2006

BY E-MAIL

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 2005P-0460/CP1
Comments in Opposition to Pediatric Waiver Request for Ramipril Tablets

Dear Sir or Madam:

We are submitting these comments in opposition to the above Pediatric Waiver Request (the "Waiver Request") submitted on November 15, 2005 by Lachman Consulting Services, Inc. ("Petitioner"). Petitioner seeks a determination that an abbreviated new drug application (ANDA) may be submitted for a change in dosage form from capsules to tablets, based on the reference listed drug Altace (Ramipril Capsules, 1.25 mg., 2.5 mg., 5 mg., and 10 mg.) (NDA 19-901), and requests a waiver of the requirement to perform pediatric studies as required by the Pediatric Research Equity Act ("PREA"). For the reasons detailed in the discussion that follows, there is no basis to support the pediatric waiver and we respectfully request that the waiver be denied.

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Discussion

Ramipril, the drug for which Petitioner seeks a pediatric waiver, is an angiotensin converting enzyme ("ACE") inhibitor which is indicated for: (1) reduction in risk of myocardial infarction, stroke and death from cardiovascular causes in patients 55 years or older; (2) treatment of hypertension (alone or in combination with thiazide diuretics); and (3) treatment of heart failure post myocardial infarction. As stated in the labeling of the proposed reference listed drug, Altace, safety and effectiveness in pediatric patients have not been established. However, ACE inhibitors are routinely used in substantial numbers of pediatric cardiac patients. Indeed, as recognized in the Waiver Request, FDA has specifically identified Ramipril (among other ACE inhibitors) as a drug for which additional information may provide benefit in pediatric patients, and requested Altace's sponsor King Pharmaceuticals, Inc. to perform pediatric studies.[1] According to public statements by King Pharmaceuticals, such a study has been undertaken.

Under the Federal Food, Drug, and Cosmetic Act ("FDCA") as amended by the PREA (FDCA § 505B(a)(1)), a person who submits an application under section 505 of the Act for a new dosage form of a drug must conduct studies adequate to evaluate the proposed product's safety and effectiveness and to establish appropriate dosing in all relevant pediatric populations, unless FDA waives the requirement. In order to obtain a waiver under the statute, a petitioner must show that: necessary studies are impossible or highly impracticable; there is evidence strongly suggesting the product would be ineffective or unsafe in all pediatric age groups; or the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric populations and is not likely to be used in a substantial number of pediatric patients. FDA has made it clear that the burden of establishing eligibility for a waiver is on the requester, and that all such requests must specify the particular statutory basis for a waiver and provide supporting evidence that a waiver is appropriate under the circumstances.[2] If a change from an approved drug proposed in an ANDA suitability petition triggers the need for pediatric clinical studies under PREA (as would a change in dosage form), and FDA does not waive the requirement, the proposed product will not be eligible to be approved in an ANDA and the suitability petition must be denied.

The Waiver Request included in the ANDA Suitability Petition fails to identify, much less offer any evidence to support, any basis for FDA to grant the requested waiver

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1 Id. at 2.

2 See FDA, Draft Guidance For Industry, How to Comply with the Pediatric Research Equity Act (September 2005), 9-11.

under the criteria prescribed by PREA. Instead, the Petitioner merely asserts that a waiver "should be granted" because FDA-requested pediatric studies on Ramipril and other ACE activities have been or are being conducted by other parties, and "it is not likely that duplication of studies . . . will add anything to the knowledge base for pediatric patients[.]" FDA must and routinely has refused to grant PREA waivers in the absence of evidence that the statutory criteria are satisfied, notwithstanding other parties' ongoing pediatric studies, and it should certainly do so again in this case.[3]

Furthermore, FDA has an ample basis to conclude that none of the statutory waiver criteria applies to the drug product at issue. Given the established use of Ramipril and other ACE inhibitors in pediatric patients, as well as FDA's prior determination that additional information on Ramipril may produce benefits for the pediatric population, there certainly is no reason to think that either the proposed product would be unsafe or ineffective in all pediatric populations, or that it is not likely to be used in a substantial number of pediatric patients. Finally, the requested change in dosage form is specifically intended "to provide a more convenient dosage form for those patients that find it difficult to swallow capsules or who prefer a tablet dosage form." Such a change is at least as likely to increase convenience for children as it is for adults, and may in fact be especially desirable for children in cases where tablet-splitting could provide desired flexibility in dosing. This may especially be true for Ramipril, given that children appear to be especially sensitive to the effects of ACE inhibitors and therefore may require lower starting doses and more precise titration than adults.[4] A PREA waiver clearly cannot be granted under these circumstances.

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3 See, e.g. Letter to Lachman Consulting Services from Gary Buehler, 2004P-0405/PDN1 (July 28, 2005) at 2 and note 1 (petition refused because it "offered no basis, and the Agency finds none, for concluding that any of these [PREA-specified waiver] circumstances exist", notwithstanding argument that FDA had already requested pediatric studies on the reference listed drug); Letter to Bedford Laboratories from Gary Buehler, 2004P-0085/PDN1 at 2 and note 1 (refusing pediatric waiver on grounds petition failed to assert a statutory basis and FDA found that none applied, notwithstanding arguments based on innovator's pediatric studies and exclusivity status).

4 See, e.g. Li, J.S. et al., Is the Extrapolated Adult Dose of Fosinapril Safe and Effective in Treating Hypertensive Children? (abstract available at http://hyper.ahajournals.org/cgi/content/abstract/44/3/289.

Conclusion

Although Petitioner's proposed product clearly is subject to PREA, Petitioner's Waiver Request offers no basis for FDA to grant a waiver under the applicable statutory criteria, and in fact no such basis exists. We therefore request that FDA deny Petitioner's Waiver Request and, accordingly, also determine that Petitioner's proposed product is not suitable for submission under an ANDA.

Respectfully submitted,

Robert A. Dormer

RAD/tee