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February 27, 2006

BY E-MAIL

Division of Dockets Management
Food and Drug Administration
5360 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 2005P-0472/CP1
Comments on Opposition to Pediatric Waiver Request for Ramipril Tablets

Dear Sir or Madam:

We are submitting these comments in opposition to the Pediatric Waiver Request which was submitted on November 15, 2005 by Pharmaceutical Patent Attorneys, LLC ("Petitioner") in connection with the above-cited petition (the "Waiver Request"). 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, we ask that the requested waiver be denied.

2005P-0472 C1

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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, FDA has specifically identified Ramipril (among other ACE inhibitors) as a drug for which additional information may provide benefit in pediatric patients, and therefore requested Altace's sponsor King Pharmaceuticals, Inc. to perform pediatric studies.[1]

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 fails to identify, much less offer any evidence to support, any basis for FDA to grant the requested waiver under the criteria prescribed by PREA.

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1 See Lachman Consulting Services, Inc., Pediatric Waiver Request, Docket No. 05P-0460/CP1 at 2 (Nov. 15, 2005).

2 See FDA, Draft Guidance For Industry, How to Comply with the Pediatric Research Equity Act (September 2005), 9-11.

Instead, Petitioner merely asserts that it "believes" a pediatric assessment is not required for a change in dosage form from capsule to tablet if the "dosing regimen" remains unchanged, or, alternatively, that it is entitled to the a waiver because "FDA has waived and deferred the pediatric assessments for the reference listed drug." Waiver Request at 4-5. Neither of those assertions is correct, and the requested waiver must be denied on both factual and legal grounds.

To begin with, as the Waiver Request itself recognizes, PREA expressly requires a pediatric assessment to be performed for a proposed change in dosage form unless waived by FDA. A change from a capsule to a tablet is clearly such a change, and is routinely treated as such by FDA. Once the PREA requirements are triggered by a proposed change, FDA may only grant a waiver based on evidence that the statutory criteria are satisfied. Petitioner's request provides no such evidence, and therefore must be denied.

Petitioner also is flatly incorrect in asserting that its proposed product merits a PREA waiver because FDA has previously waived pediatric studies on the reference listed drug, Altace. In fact, the waiver cited in Petitioner's Waiver Request applied only to a single, then-new indication (for reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes) which is explicitly limited in Altace's labeling to use "in patients 55 years or older." By contrast, FDA has requested, and Altace's sponsor has performed, pediatric studies for one or more of Altace's other approved indications (all of which Petitioner apparently intends to include in its own product labeling). Additionally, the fact that Altace's sponsor is performing such studies would provide no basis for granting a waiver to any other party in the absence of approved pediatric labeling for Altace.[3]

Finally, 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

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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).

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 that the proposed product would be unsafe or ineffective in all pediatric populations, or that it would not likely to be used in a substantial number of pediatric patients. The requested change from capsule to tablet form is likely to offer a meaningful benefit to pediatric patients, who often find capsules difficult to swallow. Additionally, 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, the option of splitting tablets could provide needed flexibility in dosing for pediatric patients.[4] A PREA waiver clearly cannot be granted under these circumstances.

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

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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.