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August 26th, 2005

Regulatory Affairs
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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION - ANDA SUITABILITY

Dear Sir or Madam:

This petition is submitted in quadruplicate under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(j)(2)(C) and 21 CFR 910.20 and §10.30, and 21 CFR §314.93, to request the Commissioner of Food and Drug Administration to make a determination that an abbreviated new drug application (ANDA) may be submitted for Losartan Potassium Oral Solution.

A. Action Requested

Morton Grove Pharmaceuticals, Inc. (MGP) requests that the Commissioner of Food and Drug Administration declare that Losartan Potassium Solution for oral administration is suitable for submission as an ANDA. The reference listed drug product upon which this petition is based is Losartan Potassium oral tablets, available in strengths of 25mg, 50mg and 100mg. The brand name of the product is **Cozaar** manufactured by **Merck**. Since **Cozaar**, with strength 100mg is the designated RLD upon which this petition is based, the petition requests a change in dosage form from tablets to oral solution of 10 mg/ml from that of the RLD product.

B. Statement of Grounds

Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act provides for submission of an ANDA for a new drug that differs in dosage form from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application, pursuant to

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21 CFR 314.93. In accordance with 21 CFR 314.93(b), this petition seeks a change in dosage form from that of the reference listed drug product from a tablet to an oral solution. The need for an oral solution dosage form is that it serves as a viable alternative for patients—particularly the elderly—who have problems swallowing the tablet dosage form.

The proposed drug product will differ only in dosage form. The indications, dosage recommendations, strengths and route of administration, are the same as those included in approved labeling of the listed drug. See labeling for RLD **Cozaar**, Attachment 1; proposed labeling for MGP's Losartan Potassium Oral Solution, Attachment 2.

The dosage strengths of the two products for dosage administration are the same. **Cozaar** is supplied in tablets containing 25mg, 50mg and 100mg of Losartan Potassium. The Losartan potassium Solution is provided in solution which contains 10mg/mL of Losartan Potassium in 4 oz and 6 oz bottles. The solution is dispensed in the same dosage amounts as the RLD tablet dosages.

Accordingly, the proposed change in dosage form from Losartan tablets to Losartan oral solution raises no questions regarding the safety and efficacy of the proposed products. The indication remains unchanged and the proposed labeling will be the same as that of the approved labeling of the listed drug except for the Description (inactive ingredients), How Supplied (dosage form and amounts), and Product Distributor. See Attachment 2. Thus, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness.

The proposed product Losartan Oral Solution is intended to meet the 90% confidence limit when compared to the RLD **Cozaar** tablets (100mg) in a comparative *In vivo* Bioavailability study.

The approved labeling for the listed drug is provided in Attachment 1. The proposed package insert for Losartan Potassium Solution is provided in Attachment 2. A copy of the appropriate page from the electronic Approved Drug Products with Therapeutic Equivalence Evaluations 24th Edition (commonly referred to as the Electronic



Orange Book) showing the listing of the reference-listed drug product upon which this petition is based is included in Attachment 3.

C. Pediatric Waiver Request

In December of 2003, Congress passed the Pediatric Research Equity Act that amended the Federal Food, Drug and Cosmetic Act to provide the Agency authority to require drug firms to study certain drugs in pediatric patients, if the Agency felt that such study would provide beneficial health data for that patient population.

In the Pediatric Rule, issued by the FDA in the Federal Register on December 2, 1998, 63 FR 66632 and codified in FDA's regulations at 21 CFR 314.55(c)(2)(i), (ii), and (iii), a waiver of pediatric studies may be granted upon a showing of any of the following:

the drug

1. does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients;
2. is not likely to be used in a substantial number of pediatric patients;

The petitioner hereby requests that a waiver from the conduct of pediatric studies be granted for the approval of this petition to permit subsequent ANDA filing. The basis for this request is detailed below.

The Reference listed drug (RLD) product for Losartan Potassium, **Cozaar**, is currently available in a conventional immediate release tablet. The labeling of the RLD has comprehensive instructions for pediatric dosing in pediatric patients. The label of the product **Cozaar** carries the instruction for the preparation of the suspension (Oral Liquid dosage form). Pediatric studies have been conducted on Losartan Potassium and Merck has been granted 6 months of exclusivity for the patents for **Cozaar** tablets and other products containing Losartan Potassium that are listed in the Orange book. The current label of Merck's **Cozaar** has the following information on the clinical study conducted in pediatric patients. The Label has mention of the pediatric studies carried out by the administration of the Oral Liquid Dosage form.



Pediatric Hypertension

The antihypertensive effect of losartan was studied in one trial enrolling 177 hypertensive pediatric patients aged 6 to 16 years old. Children who weighed <50 kg received 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥50 kg received 5, 50 or 100 mg of losartan daily. Children in the lowest dose group were given losartan in a suspension formulation (see DOSAGE AND ADMINISTRATION,) Preparation of Suspension). The majority of the children had hypertension associated with renal and urogenital disease. The sitting diastolic blood pressure (SiDBP) on entry into the study was higher than the 95th percentile level for the patient's age, gender, and height. At the end of three weeks, losartan reduced systolic and diastolic blood pressure, measured at trough, in a dose-dependent manner. Overall, the two higher doses (25 to 50 mg in patients <50 kg; 50 to 100 mg in patients ≥50 kg) reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used (2.5 mg in patients <50 kg; 5 mg in patients ≥50 kg). The lowest dose, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomized to continue losartan at the two higher doses or to placebo after 3 weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients randomized to continuing losartan. When the low dose of losartan was randomly withdrawn, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan, again suggesting that the lowest dose did not have significant antihypertensive efficacy. Overall, no significant differences in the overall antihypertensive effect of losartan were detected when the patients were analyzed according to age (<, ≥12 years old) or gender. While blood pressure was reduced in all racial subgroups examined, too few non-White patients were enrolled to compare the dose-response of losartan in the non-White subgroup

The requirements for the conduct of the pediatric studies were fulfilled by the innovator, therefore there should be no need to repeat such studies or engage in additional studies for the product proposed by this petition. The change in dosage form to an oral solution from an immediate release tablet provides a more convenient dosage form for patients who do not want to take or cannot take a tablet product. The



proposed change in dosage form does not represent a meaningful therapeutic benefit over existing therapies and would likely to be used only for those patients for whom treatment is currently indicated in the labeling.

D. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 525.31.

E. Economic Impact

According to 21 CFR §10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

F. Certification

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner (MGP), which is unfavorable to the petition.

Sincerely,



Chang Lee MD, MSHA, DrPH
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Attachments:

- 1. Labeling for the Innovator (Cozaar Tablets)**
- 2. Labeling for the Generic product (Losartan Potassium Solution)**
- 3. Approved Drug Products with Therapeutic Equivalence Evaluations 24th Edition (electronic)**

cc: LT Arianne Camphire (Office of Generic Drugs)

