

**ARNOLD & PORTER**

555 TWELFTH STREET, N.W.  
WASHINGTON, D.C. 20004-1206

(202) 942-5000  
FACSIMILE: (202) 942-5999

NEW YORK  
DENVER  
LOS ANGELES  
LONDON

DONALD O. BEERS  
(202) 942-5012  
INTERNET: Donald\_Beers@aporter.com

10 16 '00 NOV -1 09:29

October 30, 2000

Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane  
Room 10-61  
Rockville, MD 20857

Re: Docket No. 00P-1550, Citizen Petition relating to Cefuroxime Axetil

Dear Sir or Madam:

In support of our September 29, 2000 citizen petition on behalf of Glaxo Wellcome Inc. (hereafter the "petition"), we enclose three supplemental exhibits.

First, please find enclosed as Exhibit N a recently obtained copy of an international patent application, submitted by a potential manufacturer of a generic version of cefuroxime axetil. The patent application was submitted by Ranbaxy Laboratories Limited ("Ranbaxy") and "relates to a process of mixing of crystalline cefuroxime axetil with amorphous cefuroxime axetil for the preparation of a bioavailable oral dosage form comprising of amorphous cefuroxime axetil containing from 7 to 25% crystalline cefuroxime axetil." Process for the Preparation of a Bioavailable Oral Dosage Form of Cefuroxime Axetil, International Patent Application Number PCT/IB00/00292, International Publication Date, September 28, 2000, p. 1 lines 7 - 10.

00P-1550

SUP1

ARNOLD & PORTER

Dockets Management Branch  
October 30, 2000  
Page 2

In the patent application itself, Ranbaxy admits that crystalline cefuroxime axetil is inferior to amorphous for therapeutic use:

Crystalline cefuroxime axetil, however, does not exhibit adequate bioavailability upon oral administration. It is important that cephalosporin compounds for oral administration should be in a form which provides high bioavailability whereby absorption into the blood stream is maximized and the amount of antibiotic remaining in the gastro-intestinal tract is minimized. Any antibiotic which is not absorbed will be therapeutically ineffective and by remaining in the gastrointestinal tract may cause side effects. An amorphous form of cefuroxime axetil which has high bioavailability has been described in U.S. Patent No. 4,562,181.

*Id.*, p. 1, line 17 to p. 2, line 5.

The patent application is for a process that, the application says, "allows the use of the cheaper and more commercially viable method of solvent precipitation of preparing predominantly amorphous cefuroxime axetil, which may contain up to 10% crystallinity." *Id.*, p., 3. lines 17-19. The patent application contends that combinations of amorphous and crystalline product containing from 7 to 25% crystalline cefuroxime axetil "exhibited similar bioavailability profile as the tablets composed of pure amorphous cefuroxime axetil." *Id.*, p. 3, lines 12-14.

ARNOLD & PORTER

Dockets Management Branch  
October 30, 2000  
Page 3

As pointed out in the petition, we believe that FDA should conclude that a mixture containing crystalline cefuroxime axetil is not the same "active ingredient" as totally amorphous cefuroxime axetil, even if the requirement that the product be amorphous had not been specified in the USP monograph. It is so specified, however, and in light of the effective monograph terms, it would be inappropriate for FDA to conclude that an active ingredient that does not satisfy that monograph is the "same" active ingredient as an active ingredient that does meet that current monograph. Certainly, consistent with FDA law and precedent, FDA should not approve a product that does not comply with a monograph specification on the assumption, which may not in fact be correct, that the monograph will eventually be changed. Our understanding is that the USP intends to deliberate carefully upon the published proposal, taking full advantage of the opportunity to study additional information and views that may be submitted through the comment process, and only then will reach a final conclusion about the advisability of making the proposed change.

As noted, we believe that statements made by Ranbaxy in the enclosed patent application reinforce the legal and scientific imperatives to limit pharmaceutical formulations of cefuroxime axetil strictly to the amorphous form. Even if FDA were to consider a formulation containing some proportion of crystalline material, the patent application is highly instructive in that it highlights likely sources of manufacturing variability, and the attendant need to establish appropriate specifications to assure batch-

ARNOLD & PORTER

Dockets Management Branch  
October 30, 2000  
Page 4

to-batch consistency in solid state form. Specifically, in acknowledging that solvent precipitation (drug substance preparation) and wet granulation (drug product preparation) would introduce some amount of crystalline material, *id.*, p.3, lines 5-7 and 14-20, but seeking nonetheless to justify the use of such steps, the application underscores the role that drug substance and drug product specifications must play in assuring batch-to-batch consistency in the relative proportions of crystalline and amorphous material, as well as the underlying proportions of the various crystalline forms. *See* petition pp. 11-13. We accordingly ask that the patent application be reviewed in the context of FDA's consideration of the petition.

We also enclose, for the sake of completeness, materials describing two clinical pharmacology studies that may have a bearing on the issues raised in the petition. Other clinical pharmacology studies relevant to the issues were discussed in the original petition and included as Exhibits G–J. In one of these additional studies<sup>1</sup>, involving six subjects, three different 250 mg dosages of cefuroxime (given as cefuroxime axetil) were administered, all as suspensions: one of the “A” crystalline isomer, one of the “B” crystalline isomer, and a 50:50 mixture of the two. Two subjects took the mixture a week after taking one of the single crystalline isomers, whereas the other four subjects took

---

<sup>1</sup> Report No. HVT/77/14, “Human Volunteer Trial to Investigate the Oral Absorption of Isomers A and B of Cefuroxime E47 Ester” (1977). (A copy of this Report is attached as Exhibit O.)

ARNOLD & PORTER

Dockets Management Branch  
October 30, 2000  
Page 5

each of the single crystalline isomers a week apart. As measured by average 24-hour urinary recoveries, the distinctly more soluble B isomer was absorbed the best (37%), the A isomer the worst (21%), and the mixture to an intermediate degree (32%). In the other study<sup>2</sup>, a four-way cross-over design, 12 volunteers took 250 mg doses of cefuroxime (given as cefuroxime axetil) on successive days, as suspensions, in the following mixtures, expressed as the ratio of A to B crystalline isomers: 60:40, 50:50, 40:60, and 30:70. When the proportion of isomer A (the least soluble) in the mixture exceeded 50%, absorption of cefuroxime axetil, as measured by average 12-hour urinary recoveries, decreased as compared to the other formulations. In this study, increasing the proportion of isomer B to greater than 50% did not improve absorption.

Sincerely,



Donald O. Beers  
David E. Korn

---

<sup>2</sup> Report No. HVT/80/27, "Human Volunteer Trial to Investigate the Urinary Recovery of Cefuroxime After Single Oral Doses of 250mg Cefuroxime as E.47 ester in Four Different Isomer Ratios" (1980). (A copy of this Report is attached as Exhibit P.)