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APPLICATION NUMBER:

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CORRESPONDENCE

UPJOHN TRADING CORPORATION

A DIVISION OF THE UPJOHN COMPANY

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December 12, 1996

Division of Anti-Infective Drug Products, HFD-520
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

GENERAL CORRESPONDENCE
Memo of Understanding - 12/3/96
Teleconference for Otitis Media 5-day dosing

NDA 50-674	NDA 50-675
VANTIN® Tablets	VANTIN® Oral Suspension
(cefpodoxime proxetil)	(cefpodoxime proxetil oral suspension)

Dear Sir/Madam:

A teleconference with the FDA was held on December 3, 1996, to discuss an NDA supplement for Vantin 5-day dosing for the treatment of Otitis Media. FDA participants were: Dr. Janice Soreth (Group Leader), Dr. Roopa Viraraghavan (Medical Reviewer) and Mr. Carmen DeBellas (Project Manager). Participants from Pharmacia & Upjohn were: Dr. Marie Borin, Dr. Hendrik deKoning-Gans, Dr. Paul Eleftheriou, Dr. Steven Francom, Ms. Kathy Kupka, Mr. Jim Timm, Dr. Gary Zurenko, and Rebecca Tong.

The purpose of this meeting was to seek the Agency's agreement on the format, content, and data presentation plan of the supplemental NDA. Dr. Soreth started the meeting by informing us that: 1) Clinical study requirements for shortened dosing duration of anti-infectives have evolved over the last few years; currently, the Agency is asking sponsors to conduct a study comparing the efficacy and safety of the short vs

the long dosing duration (ie, Vantin 5-day vs Vantin 10-day). 2) Cefixime is not the best first line therapy for Streptococcus pneumonia.

Dr. Soreth acknowledged that the studies we have conducted for the 5-day regimen for otitis will support registration as previously agreed by the Agency (telephone contact report between Dr. G.W. Powley and Mr. Carmen DeBellas on December 1993 and minutes of September 8, 1995 teleconference). However, to enhance the review process, Dr. Soreth recommended that we include the following data from the 10-day otitis studies of the original NDA (submitted in 1991):

- Synopsis of the otitis 10-day studies.
- Enrollment details of the otitis 10-day study including number of patients enrolled, evaluable, dropout, and lost to follow-up.
- In the ISE, side-by-side display of clinical and bacteriological cure rates, overall and by pathogen, of the 5-day and the 10-day studies.
- In the ISS, side-by-side tabular safety summary by body system of the 5-day and the 10-day studies.

The meeting continued with presentations of clinical, statistics, and NDA outline overviews. Discussion following the overviews is summarized as follows:

- The NDA supplement will not include an item 7 (microbiology) due to the lack of new data. Bacteriological data from protocol 0098 studies A and B will be included in item 8.
- Data analysis deviation (from the protocol analysis plan) could be handled by either submitting an information amendment or providing a justification in the NDA.
- Electronic text files and selected (by the FDA statistician) SAS data sets will be submitted with the sNDA.
- Item 12 will include Case Report Forms of patients who died during the study and patients who did not complete the study because of medical events.

Please contact Rebecca K. Tong at (616) 833-0286 if you have any questions on the above meeting summary. Please send written correspondence to mail stop 0636-298-113.

Sincerely,

UPJOHN TRADING COMPANY

Rebecca K. Tong
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September 20, 1995

Division of Anti-Infective Drug Products, HFD-520
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Food and Drug Administration
5600 Fishers Lane
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Attention: Carmen DeBellas, Project Manger

Re: NDA 50-675
VANTIN® Oral Suspension
(cefpodoxime proxetil oral suspension)

Dear Mr. DeBellas:

A teleconference with FDA was held on September 8, 1995, to discuss registration options for VANTIN® Oral Suspension for the treatment of otitis media using a 5-day dosing schedule. FDA was represented by Dr. Renata Albrecht, Supervisory Medical Reviewer, and Carmen DeBellas, Consumer Safety Officer; Upjohn participants included D.C. Beuving, T.H. Oliphant, S.C. Speziale, J.A. Timm, and E.W. Yankee. Prior to the teleconference Upjohn's proposal was provided to Dr. Albrecht.

To begin the teleconference, E.W. Yankee reviewed past discussions regarding this indication, the current status of the clinical trials, and our proposed registration strategy. In December of 1993, an agreement with FDA was reached whereby Upjohn would conduct two identical studies comparing the safety and efficacy of VANTIN given for 5-days with those of cefixime given for 10-days. Tympanocentesis would be performed on each patient at study entry, thereby allowing microbiological evaluation of each patient. It was determined that each study would need 224 evaluable patients to provide the power necessary to allow adequate statistical comparison of the two treatment arms. The estimated numbers of evaluable patients in the two studies is currently 192 and 131.

The FDA's Points to Consider document, which outlines registration requirements for otitis media and other bacterial diseases, states that two studies are recommended, one adequate and well controlled study designed to assess clinical efficacy, and a second smaller and open labeled study to assess microbiological efficacy. Based on these stated requirements, the need to complete two fully powered studies, each with microbiological evaluation endpoints, was questioned. Under the proposal presented to

Dr. Albrecht, the two studies in progress would be combined to meet the need for an adequate and well controlled study. This one large study could also be used to provide the data sought by the second study recommended in the Points to Consider since microbiological evaluation is performed on all patients who participate.

Dr. Albrecht pointed out that the Points to Consider allows room for interpretation. In the time since this document issued in 1992, it has become policy with the Anti-Infective Division at FDA to regard the recommendations provided in this document as adequate when the antibiotic under evaluation is to be given for a standard course of therapy, i.e. 10 days for the treatment of otitis media. When the duration of therapy is shortened, the Division requires two adequate and well controlled studies to demonstrate efficacy.

A counter proposal was presented whereby the registration package would contain one larger, fully powered study and a second smaller confirmatory study with less statistical power. Dr. Albrecht indicated this package would be difficult to approve, but suggested we could meet the registration requirements if one of the studies provided only clinical efficacy data with the second providing both microbiological and clinical efficacy data. While this option will be examined, it is unlikely that the number of clinically evaluable patients will be much larger than the number of microbiologically evaluable patients due to study entry criteria.

E.W. Yankee stated that a protocol will be submitted to FDA shortly which will meet our Phase IV requirement for comparison of twice daily and once daily dosing for the treatment of otitis media. Dr. Albrecht was asked if a similar Phase IV study will be needed to compare 10-days and 5-days of therapy for this disease. She indicated that completion of two adequate and well controlled studies prior to approval will prove the safety and efficacy of the shortened dosing duration, eliminating the need for such a comparison study.

If you should have further questions on the above information, please contact Peter J. DiRoma at (616) 329-8070.

Very truly yours,

THE UPJOHN COMPANY

Peter D. Rome

Hendrik J. de Koning Gans, MD
Regulatory Liaison

HJD:PJD:seh