CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-674/S-012 & NDA 50-675/S-015

ADMINISTRATIVE DOCUMENTS

ENVIRONMENTAL ASSESSMENT
CLAIM FOR CATEGORICAL EXCLUSION

As cited at 21 CFR 25.15(d), an environmental assessment (EA) is not required if it is stated that the action requested qualifies for a categorical exclusion and, to the applicant's knowledge, no extraordinary circumstances exist.

An Environmental Assessment dated February 7, 1992 covering cefpodoxime proxetil as VANTIN Tablets (NDA 50-674) and VANTIN for Oral Suspension (NDA 50-675) was submitted to the Division of Anti-Infective Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration on February 12, 1992 and resubmitted on June 30, July 2, and July 14, 1992 to comply with FOI status.

These NDAs were approved on August 7, 1992, and the FDA wrote a finding of no significant impact (FONSI) on this EA dated August 12, 1992.

On June 18, 1996, the FDA provided clearance to market VANTIN for Oral Suspension and VANTIN Tablets under a new shortened dosing regime for tonsillitis and pharyngitis.

Under the new daily dosing regimen for pharyngitis and tonsillitis, doctors can prescribe 5 mg/kg of VANTIN for Oral Suspension twice daily for a treatment period of five to ten days. VANTIN for Oral Suspension's former dosing regimen for pharyngitis and tonsillitis was 5 mg/kg twice daily for ten days.

CATEGORICAL EXCLUSION

Pharmacia & Upjohn Company's supplement to NDA #50-675 qualifies for a categorical exclusion based on Sec. 25.31(a). Action on this supplemental NDA does not increase the use of the active moiety.

EXTRAORDINARY CIRCUMSTANCES

To P&U's knowledge, no extraordinary circumstances, as specified in 21 CFR 25.21, exist in connection with action on this NDA.

DEBARMENT CERTIFICATION FOR NDA 50-674 and NDA 50-675

Vantin (cefpodoxime proxetil) Supplemental NDA for the treatment of sinusitis

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Edward L. Patt

January 7, 1998

Ed L. Patt
Manager
Regulatory Compliance

Date

ITEM 13 & 14

PATENT CERTIFICATION/EXCLUSIVITY

1.	Active ingredient(s)	cefpodoxime proxetil
2.	Strength(s)	50 mg per 5 mL 100 mg per 5 mL
3.	Tradename	VANTIN® Oral Suspension
4.	Dosage Form Route of Administration	Oral Suspension
5.	Applicant Firm Name	Pharmacia & Upjohn Trading Corporation
6.	NDA Number	50-675
7.	Approval Date	August 7, 1992 (original NDA)
8.	Exclusivity-date first ANDA could be approved and length of exclusivity period.	December 4, 2001, or the date of any patent extension, whichever last occurs.
9.	Applicable patent numbers and expiration date of each.	4,486,425 (December 4, 2001) 4,409,215 (October 11, 2000)

EXCLUSIVITY SUMMARY FOR NDA # 50-674/S-012 50-675/S-015 SUPPL #_____

Trade Name Vantin Tablets & Oral Suspension Generic Name cefpodoxime proxetil

Applicant Name Pharmacia & Upjohn HFD # 520

Approval Date If Known November 20, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1 1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than

clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

_____ 11/20/98

Signature Date

Title: Project Manager

/S/

_____ 11/20/98

Signature of Office/ Date
Division Director

cc:
Original NDA 50-674, 50-675
HFD-520/Division File
HFD-520/CSO/B. Duvall-Miller
HFD-93/Mary Ann Holovac

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 50-674 50-675 Supplement # 012 015 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Vantin (cefpodoxime proxetil) Action: (AP) AE NA

Applicant Pharmacia & Upjohn Therapeutic Class cephalosporin

Indication(s) previously approved LRTI, uncomp. gonorrhea, ano-rectal infections, SSSI, UTI, AOM, Phar/tons.
Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application acute maxillary sinusitis (For supplemen answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

✓ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager 11/20/98
Signature of Preparer and Title Date

cc: Orig (NDA)/PLA/PMA # 50-674, 50-675
HFD-520 /Div File
(NDA)/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

N-50-674
DF

MEMORANDUM OF MULTIPLE TELECONS

DATES: April 22, 1998
May 1, 1998
May 13, 1998

APPLICATIONS:

NDA 50-674/S-012 Vantin (cefpodoxime proxetil) Tablets
NDA 50-675/S-015 Vantin (cefpodoxime proxetil) Oral Suspension

BETWEEN:

Pharmacia Upjohn Corporation

Ms. Rebecca Tong	Regulatory Manager
Dr. Charles Wajszchuk	Medical Monitor
Dr. Bruce Peel	Clinical Trial Specialist
Mr. Robert Schaser	Biostatistician
Lynn Sikkenga	Programmer
Mr.Gary Zurenko	Microbiologist

(See Attached for List)
Phone: 616-833-0286

FDA --Division of Anti-Infective Drug Products, HFD-520

Dr. Janice Soreth	Clinical Team Leader
Dr. Holli Hamilton	Clinical Reviewer
Dr. Cheryl Mc Donald	Clinical Reviewer
Dr. Joel Jang	Biostatistician
Mr. Carmen DeBellas	Project Manager

SUBJECT: Review – Indication of Sinusitis

April 22, 1998

Dr. Hamilton requested any gram stains of sinus aspirates or any microbiological quantitative data for study 108 be provided to support a claim against or Staphylococcus aureus. These would be of value for reviewing the indication. She also stated that the Agency has rejected Staphylococcus aureus cultures in sinusitis without quantitation and that mixed cultures (those containing bacteria other than S. aureus) were of little value in sinusitis reviews. She also questioned whether the cultures for study 108 performed quantitatively.

Upjohn replied quantitative data for 0045 was taken but not used for outcome evaluation and semiquantitative cultures were collected for 108.

Dr. Hamilton also requested a list of those clinically evaluable patients without pathogens be provided so that clinical cure rates could be calculated and compared with 109, the clinical only study.

Dr Jaing had numerous questions regarding inconsistencies in naming variables in the different studies, data sets and in text summaries.

It was agreed a list of Dr. Jaing's questions and that some case report forms for study 109 would also be would be faxed to the sponsor.

May 1, 1998

The Sponsor phoned to update the Clinical and Statistical Reviewer on the procedure used to collect and handle sinus specimens. For study 108, they received reports on 85 evaluable patients and confirmed specimens in 84 of them were obtained via sinus punctures as per protocol.

The quantitative microbiology data from the central laboratory will be faxed after this teleconference.

Dr. Hamilton stated that quantitative culture data and gramstains are needed a claim of Staphylcoccocus aureus. She also mentioned that patients who had previous ENT surgery should be excluded due to possible colonization of Staphylococcus aureus. She also repeated the required numbers of the three organisms (S. pneumoniae, H. influenzae, and M. catarralis) for approval of this indication.

The Statisticians will send Dr. Jiang the datasets for study 108 and 109 containing information clarifying the inconsistencies in the datasets.

May 13, 1998

Dr. Hamilton asked that we hold this teleconference to update the Sponsor concerning the review of the Staphylcococcus aureus patients in protocol 108. After reviewing 91 patients who had attained an aspirate, had a pure Staph aureus culture, a smear of PMN's, and quantitative +4 and Semi quantitative 3 or +4, only three patients were acceptable. (#'S 59, 51, and 82).

Dr. Wajszcuk inquired about patient

Dr. Hamilton accepted bringing the total number of acceptable patients to 4. Patient is really patient , who is already acceptable.

There was some discussion of a few more patients but the number of acceptable patients did not increase.

Dr. Hamilton did repeat that the Agency has been asking that Sponsor try to get at least 20-25 evaluable patients with Staph. aureus to support the claim. Combining data for the same microorganism from other indications has not been done to date. The problems related to this general recommendation were discussed.

/S/

Carmen DeBellas
Project Manager

cc: Original NDA 50-674/S-012 and NDA 50-675/S-015
HFD-520/Div. File
HFD-520/DeBellas
Hfd-520/Hamilton
HFD-520/

TELECON

TO: Carmen Debellas

SUBJECT: NDA 50-674

DATE: September 22, 1998

FROM: Frederic J. Marsik, Ph.D., Microbiologist

Carmen,

I have the following questions and need the indicated information from Pharmacia and Upjohn Trading Company in regard to the indicated NDA.

1. Why doesn't the proposed labeling include the interpretive MIC breakpoints and disc diffusion zone diameters as well as the quality control criteria for both MIC and disc diffusion testing for *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus* spp., and *Neisseria gonorrhoeae* indicated in the recent NCCLS document [a.]?
2. Does Pharmacia and Upjohn have the data to support the interpretive and quality control criteria in the NCCLS document for these organisms?
3. Did Pharmacia and Upjohn present this data to the NCCLS? If so when?
4. How many of the isolates of *Streptococcus pneumoniae* in the "acute maxillary sinusitis" studies were either penicillin-resistant or intermediate in their resistance to penicillin?
5. What information does the company have concerning the activity of cefpodoxime against penicillin-resistant *S. pneumoniae* and those *S. pneumoniae* that show intermediate-resistance to penicillin?

a. NCCLS. Performance standards for antimicrobial susceptibility testing: Eighth informational supplement. NCCLS document M100-S* [ISBN 1-56238-337-x]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1989.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-674/S-012 & NDA 50-675/S-015

CORRESPONDENCE

Pharmacia & Upjohn

Office of:
Rebecca K. Tong, M.S.
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-0286
Facsimile No. (616) 833-8237

August 21, 1996

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

Attn: Mr. Carmen DeBellas

GENERAL CORRESPONDENCE

RE: TELECONFERENCE REQUEST

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

Dear Mr. DeBellas:

We would like to arrange a teleconference with you to discuss a future NDA supplement for VANTIN® Tablets for the treatment of Acute Maxillary Sinusitis.

For the sinusitis indication, we plan to submit three studies:

Protocol M/1140/0045 is an observer-blind, comparative pilot study against Augmentin with sinus aspiration. The final report has been issued and submitted to IND

This study is ongoing and has approximately 100 available patients.

Protocol M/1140/0109 is an adequate well controlled study to compare the efficacy and safety of VANTIN® with Lorabid. Enrollment of this study is completed and data cleanup is in progress.

The purpose of this meeting is to seek your clarification of the Anti-Infective Drug Products Points to Consider (October, 1992) and to review our data presentation plan for the sinusitis supplement.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

Based on our past experience with your division on other anti-infective products, we are planning to handle the data in the following manner:

1. 100 evaluable patients will be included in Protocol 0108, the open labeled study.

2. In order to obtain the M. catarrhalis claim, all 15 patients with M. catarrhalis will be coming from the open labeled study. However, the pilot study also has one M. catarrhalis. For future general reference, is it possible to add this one from the pilot study to the total required 15?

3. In the open label study, if a patient has more than one pathogen, each pathogen can be counted toward the required totals.

4. The X-ray and ultrasound data will be presented in the Technical Report and data presentation will not be repeated in the ISE.

5. The ISE will include data of evalulable patients; the technical report will also include non-evaluable and intent-to-treat patient data.

6. Vital signs and laboratory test data will be presented in the Technical Report and will not be repeated in the ISS.

7. Dropouts due to drug related medical events will be included in the ISS.

Meeting participants from our company will be:

Dr. Hendrik deKoning-Gans, Director, Regulatory Affairs
Dr. Paul, D. Eleftheriou, Medical Monitor
Mr. Robert J. Schaser, Statistician
Ms. Sue C. Speziale, Project Manager
Ms. Rebecca K. Tong, Regulatory Manager

Since March of this year, we have contacted the Agency numerous times to request clarifications for items 1, 2 and 3. Because your guidance is very critical to the continuation of the ongoing open labeled study, we are requesting that this meeting be scheduled next week.

Please contact Rebecca K. Tong at (616) 833-0286 as soon as the meeting date is available. Please send mail correspondence to mail stop 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Rebecca K. Tong

Rebecca K. Tong
Regulatory Manager
Regulatory Affairs

RKT:mls

UPJOHN TRADING CORPORATION
A DIVISION OF THE UPJOHN COMPANY
Kalamazoo, Michigan 49001, U.S.A. • Telex 224426-UINTI KMZ • Cable: UPJOHN

Office of:
Rebecca K. Tong, M.S.
Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-0286
Facsimile No. (616) 833-8237

September 27, 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 - 9/23/96
Teleconference for Sinusitis Indication

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

Dear Sir/Madam:

On September 23 a teleconference was held with Dr. Janice Soreth (Group Leader), Dr. Roopa Viraraghavan (Medical Reviewer) and Mr. Carmen DeBellas (Project Manager), Anti-Infective Division of the FDA. Participants from Pharmacia & Upjohn were: Dr. Paul Eleftheriou, Dr. Hendrik deKoning-Gans, Mr. Robert Schaser, and Rebecca Tong.

The purpose of this meeting was to seek the Agency's guidance for the Sinusitis Supplement to be submitted in 1997. A memo listed seven items requiring FDA's input was sent to Mr. DeBellas on August 21, 1996 (General Correspondence-Teleconference Request from Rebecca Tong, attached); recommendations from Dr. Soreth are summarized as follows:

1. 100 evaluable patients from the open labeled study (Protocol 0108) is consistent with the Anti-Infective Points to Consider and acceptable to the FDA. Of the 100 patients, 25 evaluable with H. influenza, 25 evaluable with S. pneumonia and 15 evaluable with M. catarrhalis are needed for the Sinusitis indication.

2. In order to obtain the required number of patients with the above pathogens, it is acceptable to pool patients from different studies provided the protocol design, study conduct, and the method of sinus aspirate collection are comparable.

   Dr. Soreth referred us to an Anti-Infective Advisory Committee meeting held in November 1994 that discussed the sinusitis indication and the use of endoscope vs. sinus puncture for specimen collection.

   Post meeting note: During the meeting we misinformed Dr. Soreth that the sinus samples of our studies were collected via endoscope. Instead, procedures for sinus specimen collection in Protocols 0045 (pilot study) and 0108 (open labeled) are described as follows: "After local anesthesia, puncture of the maxillary sinus beneath the inferior turbinate will be performed and an aspirate obtained for quantitative culture of aerobes and anaerobes".

3. If a patient has more than one of the above mentioned pathogens, each pathogen can be counted toward the required totals.

4. X-ray and ultrasound data need not be repeated in the ISE if they are included in the study report and the Case Report Form tabulations.

5. It is acceptable to include the evaluable patients in the ISE; the study report will include the non-evaluable and the intent-to-treat patients as well.

6. It is acceptable to present vital signs and laboratory data in the final report only and not repeat them in the ISS.

7. In the ISS, all medical events related dropouts regardless of attribution will be presented. In addition, dropouts assessed as drug related will also be presented separately.

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

Sincerely,

UPJOHN TRADING COMPANY

Rebecca K. Tong
Regulatory Manager
Regulatory Affairs

RKT:jss:92796

UPJOHN TRADING CORPORATION
A DIVISION OF THE UPJOHN COMPANY
Kalamazoo, Michigan 49001, U.S.A. • Telex 224426-UINTI KMZ • Cable: UPJOHN

Office of:
Rebecca K. Tong, M.S.
Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-0286
Facsimile No. (616) 833-8237

December 30, 1996

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

Attention: Mr. Carmen DeBellas

GENERAL CORRESPONDENCE

Sinusitis Indication

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

Dear Mr. DeBellas:

As indicated in our September 23, 1996 telephone conference, we are planning to submit an NDA supplement in 1997 for VANTIN® for the treatment of Acute Maxillary Sinusitis. For this indication, we will include three studies:

Protocol M/1140/0045 is an observer-blind, comparative pilot study against Augmentin with sinus aspiration (via maxillary sinus puncture). The final report has been issued and submitted to IND

There are two *M. catarrhalis* patients in this study, one clinical cure and one clinical improvement.

Protocol M/1140/0109 is an adequate well controlled study to compare the efficacy and safety of VANTIN® with Lorabid. The outcome of this study is based on clinical evaluation only, no bacteriological data is collected. Enrollment of this study is complete and the study report is in progress.

Protocol M/1140/0108 is an open-label study to establish clinical cure as well as pathogens eradication with sinus aspiration (via maxillary sinus puncture). This study started in January 1995 and has enrolled 448 patients with approximately 110 evaluables. Currently we have eleven *M. catarrhalis* patients: 6 clinical cures and 5 clinical improvements; we also have two non-evaluables.

In the sinusitis supplement, we intend to combine the *M. catarrhalis* patients from protocols 0045 and 0108 (total 13 patients) as agreed by the Agency in the September 23 teleconference. In order to obtain more *M. catarrhalis* patients, protocol 0108 is being continued after we have obtained 100 evaluable patients. However, since April 16, 1996 we have enrolled 78 patients but with no additional *M. catarrhalis* identified. Based on this success rate, it probably will take one more year to obtain two additional *M. catarrhalis* patients to meet the total 15 required by the Anti-Infective Points to Consider.

The definition of clinical success for protocols 045 and 0108 is either clinical cure or clinical improvement; according to the protocol these patients are not required to have a second sinus puncture. For the bacteriological analysis, clinical success presumes pathogens eradication which in this case will result in a 13/13 eradication rate or 100% cured. If two more *M. catarrhalis* would be found in future enrolled patients, and if we assume that these two additional patients would be failures, the end result would be 13/15 or 87% presumed bacteriological eradication. Does the Agency agree that the addition of two more *M. catarrhalis* cases, even if they would be failures, would not change the conclusion that VANTIN® is effective in the treatment of sinusitis caused by *M. catarrhalis*? Does the Agency also agree that we can file with the present 13 cases and it would give us (confirmed by your review of our sNDA) the claim for *M. catarrhalis* in sinusitis?

Thank you in advance for you reply and looking forward to hearing from you. Please contact Rebecca K. Tong at (616) 833-0286 if you have any questions. Please send mail correspondence to mail stop 0636-298-113.

Sincerely,

UPJOHN TRADING COMPANY

Rebecca K. Tong
Regulatory Manager
Regulatory Affairs

RKT:jss:123096

Desk Copies: Dr. Janice Soreth
Dr. Roopa Viraraghavan
Mr. Carmen DeBellas

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Office of:
Rebecca K. Tong, M.S.
Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-0286
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February 12, 1997

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

Attention: Mr. Carmen DeBellas

GENERAL CORRESPONDENCE

Sinusitis Indication - Memo of Understanding

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

Dear Mr. DeBellas:

Thank you for your telephone call of February 12, 1997. This is to confirm that the medical reviewer has reviewed our letter dated December 30, 1996 (General Correspondence, Sinusitis Indication). It is understood that the Agency agreed that we may file the NDA supplement with thirteen *M. catarrhalis* patients, and this is also sufficient for the *M. catarrhalis* claim in sinusitis (confirmed by your review and approval of our sNDA).

Please contact Rebecca K. Tong at (616) 833-0286 if you have any questions. Please address written correspondence to mailstop 0636-298-113.

Sincerely,

UPJOHN TRADING COMPANY

Rebecca K. Tong
Regulatory Manager
Regulatory Affairs

RKT:jss:021297

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Office of:
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December 2, 1997

Ms. Duvall Miller
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

Sinusitis Indication - NDA Supplement

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

Dear Ms. Duvall Miller:

Reference is made to our telephone discussion of December 1,1997 regarding the VANTIN (cefpodoxime proxetil) Sinusitis NDA Supplement.

It is agreed that the Integrated Safety Summary of this supplement will include safety data from the sinusitis studies (one pilot, one adequate well controlled and one open-label). The incidence percentages for the "ADVERSE REACTIONS" section of the package insert will be provided to the Agency at a later day prior to the finalization of the proposed insert.

If you have any questions regarding the contents of this submission, please contact me at (616) 833-0286. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Rebecca K. Tong, M.S.
Regulatory Manager
U.S. Regulatory Affairs

RKT:crdt
Attachment