CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50675_S14

ADMINISTRATIVE DOCUMENTS

DEBARMENT CERTIFICATION FOR NDA 50-675

Vantin Oral Suspension (NDA 50-675) Supplement: 5-Day Regimen for Otitis Media

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.

Ed L. Patt

12/17/97

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 # 50-675 SUPPL #014 _____

Trade Name Vantin_____ Generic Name cefpodoxime proxetil
Applicant Name Pharmacia & Upjohn HFD- 520

Approval Date August 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 questions about the submission.

   a) Is it an original NDA?

   YES /___/ NO /_x__/

   b) Is it an effectiveness supplement?

   YES /_x__/ NO /___/

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

   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 /_x__/ 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 /_x__/

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

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?

YES /___/ NO /_x__/

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 /_x__/

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 /_x__/

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 /_x__/

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study #

Investigation #4, Study #

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 /__/
Investigation #3	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:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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 /__/
Investigation #3	YES /___/	NO /__/

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

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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"):

Investigation #_, Study # _____

Investigation #2, Study # _____

Investigation #3, Study #

Investigation #4, Study #

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: _____

_____

_____

_____

Signature /S/ Date 11/20/98
Title: Lloyd Mcmeyer

Signature of Division Director /S/ Date 11/20/98

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

(NDA)/PLA/PMA # 50-675/S-[illegible] Supplement # 014 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 CAP AECB 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 5 day otitis media regimen (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 # 50-675/S014
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)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 13, 1998

FROM: Beth Duvall-Miller, Project Manager

SUBJECT: Vantin labeling; 50-675/S-014

TO: Rebecca Tong
Regulatory Manager, Regulatory Affairs
Pharmacia & Upjohn

(via facsimile and FedEx)

Becky,

Attached is the basis for our argument for excluding penicillin-resistant strains of *Streptococcus pneumoniae* from the labeling based on Dr. Fred Marsik's review. I have sent the referenced articles by FedEx as well as a copy of Dr. Marsik's review and this memorandum.

The revised labeling should be revised to read:

- Under Aerobic Gram-positive microorganisms in the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section, the label should read:

  "*Streptococcus pneumoniae* (excluding penicillin-resistant strains)"

- Under Acute otitis media in the **INDICATIONS AND USAGE** section, the label should read:

  "Acute otitis media caused by *Streptococcus pneumoniae* (excluding penicillin-resistant strains), *Streptococcus pyogenes*, *Haemophilus influenzae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains)."

cc:
Original NDA 50-675/S-014
HFD-520/Division files
HFD-520/CSO/B. Duvall-Miller 11/13/98
HFD-520/MO/R. Viraraghavan
HFD-520/Micro/F. Marsik
drafted: bdm/November 13, 1998/M:\MEMOS\50675.014

MEMORANDUM OF TELECON

DATE: Tuesday, November 10, 1998

APPLICATION NUMBER: NDA 50-675/SE2-014; Vantin® (cefpodoxime proxetil) Oral Suspension

BETWEEN:

Name: Ms. Rebecca Tong, Regulatory Manager
Dr. Charles Wajszczuk, Medical Monitor
Mr. Gary Zurenko, Microbiologist
Dr. Steven Francom, Biostatistician
Mr. David Kempe, Product Manager
Ms. Susan Speziale, Project Manager
Ms. Nelia Masiques, Regulatory Labeling Manager
Phone: (616) 833-0286
Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Roopa Viraraghavan, Medical Officer
Dr. Janice Soreth, Medical Team Leader
Dr. Fred Marsik, Microbiologist
Dr. Al Sheldon, Microbiology Team Leader
Dr. Gary Chikami, Division Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Vantin® labeling negotiations

Pharmacia & Upjohn (P&U) submitted supplemental new drug application 50-675/S-014 for the 5-day treatment of acute otitis media on December 22, 1998. Previous negotiations of labeling for this application include facsimiles dated September 22, 1998 (FDA), October 6, 1998 (FDA), October 21, 1998 (P&U), November 6, 1998 (FDA), and November 9, 1998. The November 6, 1998 facsimile was the result of an internal labeling meeting held November 5, 1998 which summarized labeling changes necessary for approval of 50-675/S-014, excluding final changes to the Microbiology subsection which was pending review of P&U's October 21, 1998 submission. P&U faxed labeling on November 9, 1998 which agreed to all changes outlined in the FDA facsimile dated November 6, 1998. This telecon was held to discuss unresolved labeling in the Microbiology subsection.

FDA agreed with P&U's MIC interpretive criteria for *Streptococcus pneumoniae* but wondered why no disk diffusion data was included in the label. P&U responded that they had included this language in June 1998 but the NCCLS did not want to evaluate such data until all anti-microbial compounds were tested. This data is to be presented at the January 1999 NCCLS meeting. FDA and P&U agreed that this data could be included in the label at a later date by means of a labeling

supplement.

FDA questioned why P&U had struck out FDA's proposed parenthetic statement "(penicillin-susceptible strains only)" that follows the listing of *S. pneumoniae* in the Microbiology subsection of the label. P&U responded that in the absence of interpretive criteria they felt that the unqualified listing of *S. pneumoniae* was acceptable given that most active cephalosporin labeling does not include such language. FDA noted that the literature indicates that the activity of cefpodoxime is diminished against penicillin-resistant *S. pneumoniae*. In fact, the literature shows that the MIC of cefpodoxime against penicillin-resistant *S. pneumoniae* is >2.0 mg/mL. This makes these organisms resistant to cefpodoxime. The FDA agreed to provide P&U with literature describing the activity of cefpodoxime against penicillin-resistant *S. pneumoniae*. The FDA agreed that the literature supports the *in-vitro* activity of cefpodoxime against *S. pneumoniae* isolates that are intermediate in their susceptibility to penicillin. Therefore, the FDA proposed adding "(excluding penicillin-resistant strains)" to the label to replace "(penicillin-susceptible strains only)". P&U agreed to consider this proposal after reviewing the literature that the FDA promised to provide. P&U indicated that they did not have any information for *in-vitro* susceptibility test results on the penicillin susceptibility of the *S. pneumoniae* isolates mentioned in NDAs 50-674 and 50-675 because they did not test penicillin against *S. pneumoniae* isolates.

Action Items:

1. FDA to provide P&U with literature data regarding cefpodoxime activity versus penicillin-intermediate and -resistant strains of *S. pneumoniae*.
2. P&U to consider labeling addition of "(excluding penicillin-resistant strains)" next to *Streptococcus pneumoniae* in Microbiology subsection and in the INDICATIONS AND USAGE section under Acute otitis media.
3. FDA and P&U to follow-up by next week for tentative action on application by end of week (11/20/98).

/S/

Beth Duvall-Miller
Project Manager

MEMORANDUM OF TELECON

DATE: Thursday, May 14, 1998

APPLICATION NUMBER: NDA 50-675/S-014; Vantin (cefpodoxime proxetil) Oral Suspension

BETWEEN:

Name: Dr. Charles Wajszcuk, Medical Monitor
Dr. Steven Francom, Statistician
Ms. Rebecca Tong, Regulatory Manager
Phone: (616) 833-0286
Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Joel Jiang, Statistician
Dr. Roopa Viraraghavan, Medical Officer
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: SAS variables and patients with recurrent otitis media

The FDA requested this teleconference in order to discuss the following issues regarding their review of the supplemental application for Vantin for the treatment of acute otitis media:

1. The medical officer review considers patients with perforations of the tympanic membrane ≤48 hours and having isolates of one of the four causative organism as microbiologically and clinically evaluable. However, Dr. Viraraghavan and Dr. Jiang could not locate the SAS variables that would easily identify these patients. Therefore, the FDA asked Pharmacia & Upjohn what the SAS variable is that describes this data set.

   Discussion: After several exchanges of references to tables in the submission, it was determined that the information Dr. Jiang was looking for regarding the SAS variables that would identify patients with perforations was available for his review.

2. Dr. Viraraghavan wants to look at patients with recurrent otitis media. Dr. Viraraghavan stated that the standard definition of recurrent otitis media is as follows: 1) patients less than 1 year of age who have 3 or more episodes per year period; or 2) patients greater than 1 year of age who have 4 or more episodes per year over a 2 year period. Therefore, the FDA requested what information was available on patients with recurrent otitis media.

   Discussion: Dr. Viraraghavan commented that if the subset of patients with recurrent otitis media is small, these patients will be excluded from the analysis. However, if this

group of patients is large, the FDA will perform a subset analysis of these patients. Dr. Viraraghavan commented that the "HISTDESC" data set includes some information but does not provide enough detail to show the number of episodes of otitis media. Pharmacia & Upjohn responded that the only information available would have been included in the case report form (CRF) under the "comments" section. No history of previous episodes of otitis media were collected on the CRFs as an individual variable; any information regarding previous episodes would have been included verbatim as a comment. Pharmacia & Upjohn agreed to look at the CRFs and identify cases of recurrent otitis media that are apparent from the comments section of the CRF.

/S/

Beth Duvall-Miller
Project Manager

cc:
Original NDA 50-675/S-014
HFD-520/Div. File
HFD-520/CSO/~~C. DeBellas~~ B. Duvall Miller
HFD-520/MO/R. Viraraghavan
HFD-520/Stats/J. Jiang

Concurrence only:
HFD-520/SCSO/J. Bona 10/28/98
HFD-725/Stats/J. Jiang 10/28/98
HFD-520/MO/R. Viraraghavan 11/3/98

Drafted: bdm/May 21, 1998/M:\TELECON\N50675.1
Initials r/d:
Final: bdm 10/28/98

TELECON