CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-687/S004, 007, 008, 009, 010, 011, 012
50-688/S006, 008, 009, 010, 011, 012, 013

PROJECT MANAGEMENT REVIEW

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JAN 5 2000

Division of Anti-Infective Drug Products

PROJECT MANAGEMENT REVIEW
OF DRAFT LABELING

Application Number: NDAs 50-687/S-004, S-007, S-008, S-009, S-010, S-011, S-012; 50-688/S-006, S-008, S-009, S-010, S-011, S-012, S-013

Name of Drug: Banan® (cefpodoxime proxetil tablets) Tablets and Banan® (cefpodoxime proxetil for oral suspension) Granules for Oral Suspension

Sponsor: Sankyo U.S.A. Corporation

Material Reviewed

Submission Dates: February 26, 1999 (50-687/S-004 and 50-688/S-006), April 9, 1999 (50-687/S-007 and 50-688/S-008), April 16, 1999 (50-687/S-008 and 50-688/S-009), April 23, 1999 (50-687/S-009 and 50-688/S-010), April 26, 1999 (50-687/S-010 and 50-688/S-011), April 27, 1999 (50-687/S-011 and 50-688/S-012), and May 5, 1999 (50-687/S-012 and 50-688/S-013).

Receipt Dates: March 2, 1999 (50-687/S-004 and 50-688/S-006), April 12, 1999 (50-687/S-007 and 50-688/S-008), April 19, 1999 (50-687/S-008 and 50-688/S-009), April 26, 1999 (50-687/S-009 and 50-688/S-010), April 28, 1999 (50-687/S-010 and 50-688/S-011), April 29, 1999 (50-687/S-011 and 50-688/S-012), and May 6, 1999 (50-687/S-012 and 50-688/S-013).

Background and Summary Description:

Sankyo U.S.A. Corporation submitted labeling and efficacy supplements for Banan® (cefpodoxime proxetil) Tablets and Granules for Oral Suspension to bring Banan® NDAs current with Vantin™ NDAs 50-674 (tablets) and 50-675 (granules for oral suspension). The series of supplements reviewed herein correspond to approved Vantin supplements as shown in Table 1 below. Sankyo does not currently market Banan Tablets or Banan Granules for Oral Suspension.

Review

This review consists of two labeling comparisons: 1) The draft labeling for all Banan supplements was compared to the approved labeling (or approved FPL) for the corresponding Vantin supplements as shown in Table 1. The original Vantin reviews, reviewers, and approval dates are also listed in Table 1; and 2) A line by line labeling review was done comparing Vantin FPL for 50-675/S-013, acknowledged May 14, 1998, to the draft labeling submitted herein for 50-687/S-012 and 50-688/S-013 on May 5, 1999.

A letter of authorization for information contained in Vantin NDAs 50-674 and 50-675 was submitted by Sankyo on February 25, 1999.

Table 1: Banan Supplements Versus Corresponding Approved Vantin Supplements

	Banan Supp # (Submission Date)	*Summary of Labeling Changes*	*Corresponding Vantin Supp #*	*Vantin Supp Approval Date*	*Vantin Supp Reviewer and Date*
A	50-687/SE8-004* 50-688/SE8-006 (2/26/99)	Updated numbers in Geriatric Use and AR sections, revised Ceph Class labeling	50-674/S-003 50-675/S-006	AP: 11/2/93	DeBellas /Lizambri 10/27/93
B	50-687/SE1-007* 50-688/SE1-008 (4/9/99)	*H. influenzae* (including beta-lactamase producing strains) under CAP & AECB	50-674/S-007 50-675/S-009	AE: 9/13/95 AP: 3/14/96	Blank 4/4/95 DeBellas (FPL) 2/20/96
C	50-687/SLR-008 50-688/SLR-009 (4/16/99)	Revisions to Post-Marketing Experience, Cephalosporin Class labeling, & D&A sections	50-674/S-008 50-675/S-010	AP: 3/14/96	Eckert/Hamilton 12/7/95
D	50-687/SLR-009 50-688/SLR-010 (4/23/99)	Addition of serum-sickness like reactions to Post Marketing Experience	50-674/S-009 50-675/S-011	AP: 9/28/95	Alexander 8/24/95
E	50-687/SE2-010* 50-688/SE2-011 (4/26/99)	Revised dosage regimens for Phar/Tons, updated Clinical Trials subsection of AR, & PK info	50-674/S-005 50-675/S-008	AP: 5/7/96	Hamilton 5/3/96 Colangelo 4/29/96 Silliman 2/26/96 DeBellas (FPL) 4/17/97
F	50-687/SE2-011* 50-688/SE2-012 (4/27/99)	Revisions to Pediatric Use, D&A, and Clinical Studies (AOM QD)	50-674/S-010 50-675/S-003	AP: 2/7/96 AR: 6/16/95	DeBellas (S-010) 2/1/96 Lizambri (S-003) 3/3/95
G	50-687/SLR-012 50-688/SLR-013 (5/5/99)	Addition of new fill sizes; 50 ml, 75 ml, in 100 ml bottles	50-675/S-012 50-675/S-013	AP: 12/9/96 AP: 4/29/97 AR: 5/14/98	Timper 12/4/96, 8/24/99 DeBellas (FPL) 4/7/98

Comparison of Vantin approved labeling and proposed Banan labeling noted the following discrepancies:

1. For 50-687/S-004 and 50-688/S-006 submitted February 26, 1999: In the Geriatric Use subsection of the PRECAUTIONS section of the label, the number "3038" should be revised to read "3338" to describe the number of patients.

   Reviewer comment: The sponsor should update the Banan label as described.

2. For 50-687/S-011 and 50-688/S-012 submitted April 27, 1999: In the ADVERSE REACTIONS section under Granules for Oral Suspension (Multiple dose), the sentence that appears above Incidence greater than 1% should read "Adverse events thought possibly- or probably- related to cefpodoxime proxetil for oral suspension in multiple dose clinical trials ([redacted] cefpodoxime-treated patients) were:".

   Reviewer comment: This revision was approved in corresponding Vantin supplements 50-675/S-003 on June 16, 1995. The sponsor should update the Banan label as described.

3. For 50-687/S-011 and 50-688/S-012 submitted April 27, 1999: Under Acute Otitis Media Studies in the CLINICAL TRIALS section, the eradication rate for *H. influenzae* listed under Cefpodoxime proxetil 10 mg/kg Q 24h x 10 d should be "36/56 (64%)".

   Reviewer comment: The sponsor should update the Banan label as described.

4. For 50-687/S-011 and 50-688/S-012 submitted April 27, 1999: Under Acute Otitis Media Studies in the CLINICAL TRIALS section, the eradication rate for *S. pneumoniae* listed under Comparator (versus Cefpodoxime proxetil 10 mg/kg Q 24h x 10 d) should be "21/38 (55%)".

   Reviewer comment: The sponsor should update theBanan label as described.

Line by line comparison of Vantin FPL for 50-675/S-013, acknowledged May 14, 1998, to the draft labeling submitted herein for 50-687/S-012 and 50-688/S-013 on May 5, 1999 noted the following discrepancies:

5. In the Effects of Food subsection of the CLINICAL PHARMACOLOGY section of the label, the second sentence should read "Following a 200 mg tablet dose taken with food ...".

   Reviewer comment: The sponsor should update the Banan label as described.

6. In the INDICATIONS AND USAGE section, the word "Acute" should be deleted from the Community-acquired pneumonia indication header.

Reviewer comment: The sponsor should update the Banan label as described.

7. In the **INDICATIONS AND USAGE** section under **Community-acquired pneumonia**, *H. influenzae* is qualified by "(including beta-lactamase-producing strains)".

Reviewer comment: This revision is included in 50-687/S-007 and 50-688/S-008, submitted April 9, 1999, and approved in corresponding Vantin supplements 50-674/S-007 and 50-675/S-009, and is therefore acceptable.

8. Under the **NOTE** within the **Uncomplicated urinary tract infections (cystitis)** indication in the **INDICATIONS AND USAGE** section, the end of the sentence should read " ... some classes of approved agents".

Reviewer comment: The sponsor should update the Banan label as described.

9. In the first sentence of the third paragraph of the **WARNINGS** section, "*C. difficile*" is misspelled.

Reviewer comment: The sponsor should update the Banan label as described.

10. In the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section, the third sentence should read "No untoward effects on fertility or reproduction ...".

Reviewer comment: The sponsor should update the Banan label as described.

11. In the **Geriatrics Use** section of the **PRECAUTIONS** section, the number of patients in multiple-dose clinical studies should be 3338 (not 3038).

Reviewer comment: This typographical error was also noted in #1 above. The sponsor should update the Banan label as described.

12. Under **Film Coated Tablets (Multiple dose)** in the **ADVERSE REACTIONS** section, the fifth sentence should read "The percentage of cefpodoxime proxetil-treated patients ...".

Reviewer comment: The sponsor should update the Banan label as described.

13. Under **Granules for Oral Suspension (Multiple dose)** in the **ADVERSE REACTIONS** section, the sentence preceding the header **Incidence Greater Than 1%** should read "Adverse events thought possibly- or probably- related to cefpodoxime proxetil for oral suspension ...".

Reviewer comment: This typographical error was also noted in #2 above. This revision was approved in corresponding Vantin supplements 50-675/S-003 on June 16, 1995. The sponsor should update the Banan label as described.

14. Under **Granules for Oral Suspension (Multiple dose)/Incidence less than 1%** in the **ADVERSE REACTIONS** section, the *Psychiatric* subsection should read "Hyperactivity/nervousness".

Reviewer comment: The sponsor should update the Banan label as described.

15. Under **Film Coated Tablets (Single dose)/Incidence less than 1%** in the **ADVERSE REACTIONS** section, "Vaginitis" is misspelled within the *Genital* subsection.

Reviewer comment: The sponsor should update the Banan label as described.

16. Under **Cephalosporin Class Labeling** in the **ADVERSE REACTIONS** section, the word "aplastic" in "aplastic anemia" is misspelled.

Reviewer comment: The sponsor should update the Banan label as described.

17. Under **Cephalosporin Class Labeling** in the **ADVERSE REACTIONS** section, the **Adverse reactions and Abnormal Laboratory Tests** subsection should include serum sickness-like reaction such that it reads: "Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, and pancytopenia".

Reviewer comment: This revision was approved in corresponding Vantin supplements 50-674/S-010 on February 7, 1996. The sponsor should update the Banan label as described

18. Under **Cephalosporin Class Labeling** in the **ADVERSE REACTIONS** section, the last sentence should read "Anticonvulsant therapy ....".

Reviewer comment: The sponsor should update the Banan label as described.

19. Under **FILM-COATED TABLETS** in the **DOSAGE AND ADMINISTRATION** section, the duration for **Pharyngitis and/or tonsillitis** should be revised to read "5 to 10 days".

Reviewer comment: This revision was acknowledged in FPL for corresponding Vantin supplements 50-674/S-005 and 50-675/S-008 on April 17, 1997. The sponsor should update the Banan label as described.

20. Under **GRANULES FOR ORAL SUSPENSION (for adults and children)** in the **DOSAGE AND ADMINISTRATION** section, the duration for **Pharyngitis and/or tonsillitis** should be revised to read "**5 to 10 days**".

Reviewer comment: The sponsor should update the Banan label as described.

21. In the **HOW SUPPLIED** section, the storage conditions for Banan Tablets reads "Store tablets between 15° and 30°C (59° to 86°F)".

Reviewer comment: The stated storage information was approved with the original Banan NDAs on August 7, 1992, and is therefore acceptable.

22. In the **HOW SUPPLIED** section, the storage conditions for Banan for Oral Suspension reads "Store unsuspended granules between 15° and 30°C (59° to 86°F)".

Reviewer comment: The stated storage information was approved with the original Banan NDAs on August 7, 1992, and is therefore acceptable.

23. Under **Acute Otitis Media Studies** in the **CLINICAL TRIALS** section, the first sentence should read "In controlled studies of acute otitis media performed in the United States ...".

Reviewer comment: The sponsor should update the Banan label as described.

24. Under **Acute Otitis Media Studies** in the **CLINICAL TRIALS** section, the eradication rate for *H. influenzae* listed under **Cefpodoxime proxetil 10 mg/kg Q 24h x 10 d** should be "36/56 (64%)".

Reviewer comment: This typographical error was also noted in #3 above. The sponsor should update the Banan label as described.

25. Under **Acute Otitis Media Studies** in the **CLINICAL TRIALS** section, the eradication rate for *S. pneumoniae* listed under **Comparator** (versus Cefpodoxime proxetil 10 mg/kg Q 24h x 10 d) should be "21/38 (55%)".

Reviewer comment: This typographical error was also noted in #4 above. The sponsor should update the Banan label as described.

Additional comments:

26. Section 126 of the Food and Drug Administration Modernization Act of 1997 requires that the label of a drug bear, at a minimum, the symbol "R_x only". Therefore, the statement "**Caution: Federal law prohibits dispensing without prescription**" should be

replaced with "Rx only".

27. Currently, Sankyo does not mark : Banan Tablets or Banan Granules for Oral Suspension. Per Jim Timper's review dated August 24, 1999, Sankyo should submit a comprehensive CMC package before marketing Banan again.

Conclusions

In order to approve all supplements reviewed herein, the sponsor should submit revised draft labeling to 50-687/S-012 and 50-688/S-013 that addresses items # 1-6, 8-20, and 23-26 (see attached facsimile dated November 30, 1999). The sponsor should also be instructed that the revised draft labeling submitted for 50-687/S-012 and 50-688/S-013 shall supersede all other draft labeling submitted for the pending Banan supplements listed in Table 1. In addition, when an action letter is drafted for these supplements, the sponsor should be reminded of #27 above.

/S/

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Project Manager

/S/

R. Grant Hills
Project Manager

Supervisory Comment/Concurrence

/S/

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