

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 65-089**

**LABELING REVIEW(S)**

E123 All  
Chambersia.

REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH

ANDA Number: 65-089

Date of Submission: April 12, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP,  
400 mg/5 mL (57 mg\*/5 mL) and 200 mg/5 mL (28.5 mg\*/5mL)  
\*(clavulanate acid equivalent)

Labeling Deficiencies:

1. CONTAINER: Amoxicillin and Clavulanate Potassium for Oral Suspension USP,  
400 mg/5 mL (57 mg\*/5 mL) and 200 mg/5 mL (28.5 mg\*/5mL)  
\*(clavulanate acid equivalent)
  - a. We note that in your manufacturing facility statement you identify Novopharm Limited located in Ontario, Canada as the manufacturer and Teva Pharmaceuticals USA as the distributor. This information is not consistent with your container label. Please revise and/or comment. We refer you to 21 CFR 201.1(5) and (6).
  - b. We encourage the inclusion of the potassium content, per 5 mL to be consistent with your DESCRIPTION section.
  - c. When printing final print, please assure that your container labels are differentiated by using different colors, boxing and/or some other means.
  - d. Delete the text, "—————" on the front panel.

2. INSERT

a. DESCRIPTION

Revise as follows:

- i. Revise the last sentence of the first two paragraphs to read, "... and has the following structural formula:".
- ii. Prior to your list of inactive ingredients add the following statement.  
  
After reconstitution each teaspoonful (5 mL) of suspension will contain \_\_\_ mg or \_\_\_ mg amoxicillin as the trihydrate and \_\_\_ mg or \_\_\_ mg clavulanic acid as the potassium salt. If you prefer you may use separate sentences for each strength.
- iii. Relocate the last two sentences "... 0. \_\_\_ mEq potassium" to immediately follow the statement in 4(a)(i).

b. CLINICAL PHARMACOLOGY

We acknowledge that you omitted text for the chewable tablet dosage form and for suspension concentrations that are not proposed by this application. However, we

request that you retain this text to be consistent with the reference listed drug insert labeling.

c. INDICATIONS AND USAGE

... potassium for oral suspension is indicated...

d. PRECAUTIONS

i. Drug/Laboratory Test Interactions

Revise the last sentence of the first paragraph to read, "... Clinistix®) be used".

ii. Pediatric Use

Revise to read, "... may be delayed. Dosing of amoxicillin and ..."

e. DOSAGE AND ADMINISTRATION (Administration)

i. See comment under CLINICAL PHARMACOLOGY.

ii. First sentence

Reconstituted amoxicillin and ...

f. HOW SUPPLIED

i. Include the color of your drug product in your physical description statement. We refer you to 21 CFR 201.57 (k)(3).

ii. We encourage inclusion of the NDC numbers in this section.

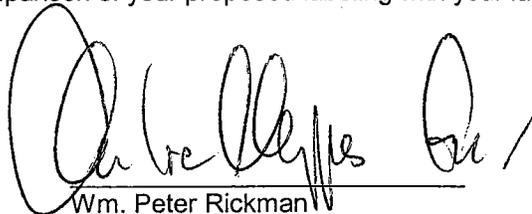
iii. Please refer to comment 1(a) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

[http://www.fda.gov/cder/ogd/rld/labeling\\_review\\_branch.html](http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html)

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman  
Acting Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:

Has this been verified by the MIS system for the NDA? Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	

<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.	X*		
<b>Inactive Ingredients:</b> (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**APPEARS THIS WAY  
ON ORIGINAL**

**NOTES/QUESTIONS TO THE CHEMIST:**

1. DESCRIPTION section:

The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

2. The firm recommends dispensing their drug product in the original container. Are the firm's containers "tightly closed and moisture-proof?"

3. Has firm submitted stability data to support "refrigeration storage up to 10 days" after reconstitution?

4. DOSAGE AND ADMINISTRATION/Directions for Mixing Oral Suspension section:

- The volume of water required for reconstitution differs from the reference listed drug. Has the firm submitted data to support the "volume of water specified for reconstitution"?

- Has the firm submitted data to support the accuracy of the final concentrations, 200 mg/5 mL of amoxicillin and 28.5 mg of clavulanic acid as the potassium salt and 400 mg/5 mL of amoxicillin and 57 mg of clavulanic acid as the potassium salt in 100 mL bottles?

5. CONTAINER LABELS

The firm indicates that their 200 mg/5 mL drug product contains 0.67 mg phenylalanine and that their 400 mg/5 mL drug product contains 1.12 mg phenylalanine. Do you concur?

**APPEARS THIS WAY  
ON ORIGINAL**

**FOR THE RECORD:**

1. Reference Listed drug: Augmentin (amoxicillin/clavulante potassium) powder for oral suspension and chewable tablets/NDA 50-564. Current insert approved 2/11/98.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.  
[B1.2, p. 604]

3. Manufacturing Facility:

Manufactured by:  
Novopharm Limited  
Ontario, Canada

Distributed by:  
Teva Pharmaceuticals USA  
Sellersville, PA  
[B1.2, p. 6195]

4. Container/Closure:

Round, natural color, HDPE bottles with CRC  
[Vol. B1.3, p. 6524, 6687]

5. Package Size:

NDA – Bottles of 50 mL, 75 mL and 100 mL  
ANDA – Bottles of \_\_\_\_\_ and 100 mL

6. Patent/Exclusivity: None

7. Storage/Dispense:

USP – Preserve in tight containers, at controlled room temperature.  
NDA – Store tablets at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

ANDA - Store \_\_\_\_\_. Dispense in original container. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

Date of Review: 6/8/01

Date of Submission: April 12, 2001

*Jacqueline Council, Pharm.D.*

6-25-01

Primary Reviewer:  
Jacqueline Council, Pharm.D.

Date:

Team Leader:

*[Signature]*

*6/8/01*  
Date

cc: ANDA: 65-089  
DUP/DIVISION FILE  
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Review

**APPEARS THIS WAY  
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH

ANDA Number: 65-089                      Dates of Submission: June 17, 2002 and February 28, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP,  
400 mg/5 mL/(57 mg\*/5 mL) and 200 mg/5 mL/(28.5 mg\*/5mL)  
\*(clavulanate acid equivalent)

Labeling Deficiencies:

1. CONTAINER 100 mL

Replace the statements \_\_\_\_\_ and \_\_\_\_\_ with the following statements:

"Store reconstituted suspension under refrigeration." and "Discard unused suspension after 10 days."

2. INSERT

a. TITLE

Delete the strength from the title.

b. DESCRIPTION

i. Second paragraph, last sentence - Delete the excess space between the word "potassium" and the chemical name.

ii. Third paragraph - "hypromellose" rather than ' \_\_\_\_\_

c. PRECAUTIONS

Labor and Delivery - Add the following as the last sentence: "... necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin and clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates."

d. ADVERSE REACTIONS

i. Hypersensitivity Reactions, first sentence - "... (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis and an occasional ..."

ii. Add the following as the last subsection in the ADVERSE REACTIONS section:

*Miscellaneous:* Tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing.

e. OVERDOSAGE

Revise the first sentence as follows: "Following overdosage, patients have experienced primarily gastrointestinal ..."

f. DOSAGE AND ADMINISTRATION (Administration)

Dosage, Adults, second paragraph - "amoxicillin 250 mg and clavulanate potassium tablet" [three instances]

g. HOW SUPPLIED

First paragraph, last sentence - "... in bottles of 100 mL."

h. CLINICAL STUDIES

Add the following paragraph to the end of this section:

The incidence of diarrhea<sup>†††</sup> was significantly lower in patients in the q12h treatment group compared to patients who received the q8h regimen (14.3% and 34.3%, respectively). In addition, the number of patients with either severe diarrhea or who were withdrawn with diarrhea was significantly lower in the q12h treatment group (3.1% and 7.6% for the q12h/10 day and q8h/10 day, respectively). In the q12h treatment group, 3 patients (1.0%) were withdrawn with an allergic reaction, while 1 patient (0.3%) in the q8h group was withdrawn for this reason. The number of patients with a candidal infection of the diaper area was 3.8% and 6.2% for the q12h and q8h groups, respectively.

<sup>†††</sup>Diarrhea was defined as either: (a) three or more watery or four or more loose/watery stools in one day, OR (b) two watery stools per day or three loose/watery stools per day for two consecutive days.

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 100 mL

*Satisfactory in FPL as of June 17, 2002 submission [vol 2.1].*

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Augmentin-400 For Oral Suspension

NDA Number: 50-725

NDA Drug Name: Augmentin (amoxicillin/clavulanate potassium) For Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 5-12-03 (S-017)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

<b>Established Name</b>	<b>Yes</b>	<b>No</b>	<b>N.A.</b>
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	x		
Is this name different than that used in the Orange Book?		x	
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO.		X	
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
<b>Inactive Ingredients:</b> (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

#### NOTES/QUESTIONS TO THE CHEMIST:

1. DESCRIPTION section:

The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

Yes

2. The firm recommends dispensing their drug product in the original container. Are the firm's containers "tightly closed and moisture-proof?"

Yes

3. Has firm submitted stability data to support "refrigeration storage up to 10 days" after reconstitution?

Yes

4. DOSAGE AND ADMINISTRATION/Directions for Mixing Oral Suspension section:

- The volume of water required for reconstitution differs from the reference listed drug. Has the firm submitted data to support the "volume of water specified for reconstitution"?
- Has the firm submitted data to support the accuracy of the final concentrations, 200 mg/5 mL of amoxicillin and 28.5 mg of clavulanic acid as the potassium salt and 400 mg/5 mL of amoxicillin and 57 mg of clavulanic acid as the potassium salt in 100 mL bottles?

NO

Yes

5. CONTAINER LABELS

The firm indicates that their 200 mg/5 mL drug product contains 0.67 mg phenylalanine per 5 mL and that their 400 mg/5 mL drug product contains 1.12 mg phenylalanine per 5 mL. Do you concur?

Yes

FOR THE RECORD:

1. Reference Listed drug: Augmentin (amoxicillin/clavulante potassium) powder for oral suspension and chewable tablets/NDA 50-725. Current insert approved 5/12/03. The firm has added the information regarding antibacterial resistance at the beginning of the PI after the title as well as in the INDICATIONS AND USAGE and PRECAUTIONS (two places) sections of the insert. The added text can be found in 21 CFR 201.24
2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements. [B1.2, p. 604]
3. Manufacturing Facility: [B1.2, p. 6195]  
  
Manufactured by: Novopharm Limited Ontario, Canada  
Distributed by: Teva Pharmaceuticals USA Sellersville, PA
4. Container/Closure:  
  
Round, natural color, HDPE bottles with CRC [Vol. B1.3, p. 6524, 6687]
5. Package Size:  
  
NDA – Bottles of 50 mL, 75 mL and 100 mL  
ANDA – Bottles of 100 mL\*  
\*(Originally the firm submitted draft labels for the \_\_\_\_\_ sizes but subsequent submissions contained only the 100 mL size and the others were removed from the submitted PI - per chemist R Adams the firm's \_\_\_\_\_ container sizes failed \_\_\_\_\_ stability tests so the firm withdrew them.)
6. Patent/Exclusivity: None
7. Storage/Dispense:  
  
USP – Preserve in tight containers, at controlled room temperature.  
NDA – Store tablets and dry powder at or below 25°C (77°F). Dispense in original containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.  
ANDA - Store \_\_\_\_\_, Keep tightly closed. Shake well before using. \_\_\_\_\_
8. The very last paragraph of the RLD insert was omitted from the generic labeling intentionally by the labeling reviewer because it is not accurate:  
  
"It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed at q12h, versus suspensions dosed q8h, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The q12h oral suspensions are sweetened with aspartame only."  
  
This applicant's drug product does have mannitol as well as aspartame and sodium saccharin so the above comments do not apply.
9. The strengths of the products are not listed in the Title of the insert for Augmentin and so the decision was made to not require the generics to include it. There are two different inserts from two generics in the folder for this drug product; one has the strength in the title of the PI but only of the amoxicillin [LEK] and the other has no strength at all in its title [GENEVA].

10. In the DOSAGE AND ADMINISTRATION - Adults subsection - the second and third paragraphs discussing tablets vs. chewable tablets were retained because it was felt that they provided useful information. The ~~\_\_\_\_\_~~ application does not have these paragraphs but the ~~\_\_\_\_\_~~ application does.
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Date of Review: 11-6-03

Dates of Submission: 6-17-02 and 2-28-03

Primary Reviewer: Adolph Vezza

Date:

11/6/03

Team Leader: Lillie Golson

Date:

11/6/03

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cc: ANDA: 65-089  
DUP/DIVISION FILE  
HFD-613/AVezza/LGolson (no cc)  
aev/11/6/03[V:\FIRMSNZ\TEVA\LTRS&REV\65089NA2.L  
Review

APPEARS THIS WAY  
ON ORIGINAL

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 65-089

Dates of Submission: February 24, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP,  
400 mg/57\* mg per 5 mL) and 200 mg/28.5\* mg per 5 mL)  
\*(the potassium salt of clavulanic acid)

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Labeling Deficiencies:

1. CONTAINER: 100 mL
  - a. Front panel

When printing the established name, use the same size print for the "active ingredients" and the text "for Oral Suspension".
  - b. Revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature]."
2. INSERT:
  - a. GENERAL COMMENTS
    - i. We note that your insert labeling is not consistent with regards to including the strength of both active ingredients of your drug product. Your insert labeling should include the strength of both active ingredients throughout the text. Please revise accordingly.
    - ii. Delete the terminal zero, "57" instead of "57.0".
  - b. DESCRIPTION
    - i. Revise the first sentence to read, "... Potassium for oral suspension is ...".
    - ii. Revise the first sentence of the last paragraph to read, "...contains 200 mg amoxicillin as the trihydrate and 28.5 mg clavulanic acid as the potassium salt or 400 mg amoxicillin as the trihydrate and 57 mg clavulanic acid as the potassium".
  - c. CLINICAL PHARMACOLOGY/Table

Dose

Revise "400" to read "400 mg".

d. DOSAGE AND ADMINISTRATION

i. Dosage/Pediatric Patients/Neonates and infants aged < 12 weeks (3 months)

Revise the first sentence to read, "... potassium oral suspension is ...".

ii. Administration

Revise the first sentence to read, "... potassium oral suspension may be ...".

e. HOW SUPPLIED

See comment 1 (b) under CONTAINER.

f. CLINICAL STUDIES

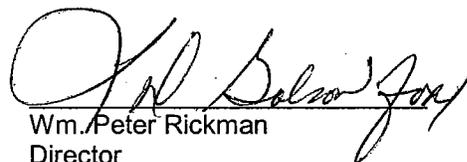
Add the following paragraph as the third paragraph,

It is not know if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed q12h, versus suspensions dosed q8h, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The q12h oral suspensions are sweetened with aspartame only.

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

-----Page Break-----

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100 mL

Satisfactory in FPL as of submission [Vol=].

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Augmentin For Oral Suspension

NDA Number: 50-725

NDA Drug Name: Augmentin (amoxicillin/clavulanate potassium) For Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 5-12-03 (S-017)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD side-by-sides

Other Comments:

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	x		
Is this name different than that used in the Orange Book?		x	
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO.		X	
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP		X	

guidelines)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
<b>Inactive Ingredients:</b> (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

APPEARS THIS WAY  
ON ORIGINAL

**NOTES/QUESTIONS TO THE CHEMIST:**

1. DESCRIPTION section:

The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

2. The firm recommends dispensing their drug product in the original container. Are the firm's containers "tightly closed and moisture-proof?"

3. Has firm submitted stability data to support "refrigeration storage up to 10 days" after reconstitution?

4. DOSAGE AND ADMINISTRATION/Directions for Mixing Oral Suspension section:

- The volume of water required for reconstitution differs from the reference listed drug. Has the firm submitted data to support the "volume of water specified for reconstitution"?
- Has the firm submitted data to support the accuracy of the final concentrations, 200 mg/5 mL of amoxicillin and 28.5 mg of clavulanic acid as the potassium salt and 400 mg/5 mL of amoxicillin and 57 mg of clavulanic acid as the potassium salt in 100 mL bottles?

5. CONTAINER LABELS

The firm indicates that their 200 mg/ 28.5 per 5 mL drug product contains 0.67 mg phenylalanine per 5 mL and that their 400 mg/57 mg per 5 mL drug product contains 1.12 mg phenylalanine per 5 mL. Do you concur?

**NOTE/QUESTION TO THE CHEMIST:**

1. In the firm's February 24, 2004 amendment the amount of water for required for suspension was revised to read, "92 mL" and "87 mL". Is this revision accurate?

Jackie,

Here are the answers to your questions:

1. Clavanate comes *Streptomyces clavuligerus*.
2. The firm's containers are "tightly closed and moisture-proof".
3. The firm routinely tests the constituted product after 10 days of refrigerated storage as part of the stability study.
4. Yes.
5. Phenylalanine comes from aspartame. The numbers are correct.
6. Yes.

Yanping

**APPEARS THIS WAY  
ON ORIGINAL**

**FOR THE RECORD:** [Portions from previous reviewer]

1. Reference Listed drug: Augmentin (amoxicillin/clavulante potassium) powder for oral suspension and chewable tablets/NDA 50-725. Current insert approved 5/12/03. The firm has added the information regarding antibacterial resistance at the beginning of the PI after the title as well as in the INDICATIONS AND USAGE and PRECAUTIONS (two places) sections of the insert. The added text can be found in 21 CFR 201.24
2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements. [B1.2, p. 604]
3. Manufacturing Facility: [B1.2, p. 6195]  
  
Manufactured by: Novopharm Limited Ontario, Canada  
Distributed by: Teva Pharmaceuticals USA Sellersville, PA
4. Container/Closure:  
  
Round, natural color, HDPE bottles with CRC [Vol. B1.3, p. 6524, 6687]
5. Package Size:  
  
NDA – Bottles of 50 mL, 75 mL and 100 mL  
ANDA – Bottles of 100 mL\*  
\*(Originally the firm submitted draft labels for the \_\_\_\_\_ sizes but subsequent submissions contained only the 100 mL size and the others were removed from the submitted PI - per chemist R Adams the firm's \_\_\_\_\_ container sizes failed accelerated stability tests so the firm withdrew them.)
6. Patent/Exclusivity: None
7. Storage/Dispense:  
  
USP – Preserve in tight containers, at controlled room temperature.  
NDA – Store tablets and dry powder at or below 25°C (77°F). Dispense in original containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.  
ANDA - Store \_\_\_\_\_ . Keep tightly closed. Shake well before using. \_\_\_\_\_
8. The very last paragraph of the RLD insert was omitted from the generic labeling intentionally by the previous labeling reviewer because it is not accurate:  
  
"It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed at q12h, versus suspensions dosed q8h, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The q12h oral suspensions are sweetened with aspartame only."  
  
This applicant's drug product does have mannitol as well as aspartame and sodium saccharin so the above comments do not apply.
9. In the DOSAGE AND ADMINISTRATION - Adults subsection - the second and third paragraphs discussing tablets vs. chewable tablets were retained because it was felt that they provided useful information.

APPEARS THIS WAY  
ON ORIGINAL

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Date of Review: 3/12/04

Dates of Submission: 2/24/04

Primary Reviewer: *Jacqueline Council, Pharm.D.*  
Jacqueline Council, Pharm.D.

Date: *3-28-04*

Team Leader: Captain Lillie Golson



Date: 3/24/04

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cc: ANDA: 65-089  
DUP/DIVISION FILE  
HFD-613/JCouncil/LGolson (no cc)  
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Review

**APPROVAL SUMMARY**  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

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ANDA Number: 65-089  
Dates of Submission: April 23, 2004  
Applicant's Name: Teva Pharmaceuticals USA  
Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP,  
400 mg/57\* mg per 5 mL) and 200 mg/28.5\* mg per 5 mL)  
\*(the potassium salt of clavulanic acid)

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**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 400 mg/57 mg per 5 mL and 200 mg/28.5 mg per 5 mL -100 mL

Satisfactory as of the April 23, 2004 submission [Vol. Temp.].

Professional Package Insert Labeling:

Satisfactory as of the April 23, 2004 submission (Insert code: Rev.E 4/2004)[Vol. Temp.].

Revisions needed post-approval:

1. INSERT

a. GENERAL COMMENTS

Your application uses the established name throughout the text, not a proprietary name, therefore as previously requested revise your insert labeling to include the strength of both active ingredients.

b. CLINICAL STUDIES

Add the following as the last sentence of the last paragraph, "The presence of mannitol or aspartame in the drug product may contribute to a different diarrhea profile".

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Augmentin For Oral Suspension

NDA Number: 50-725

NDA Drug Name: Augmentin (amoxicillin/clavulanate potassium) For Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 5-12-03 (S-017)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD side-by-sides

Other Comments:

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

<b>Established Name</b>	<b>Yes</b>	<b>No</b>	<b>N.A.</b>
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	x		
Is this name different than that used in the Orange Book?		x	
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO.		X	
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
<b>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</b>			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X

<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**APPEARS THIS WAY  
ON ORIGINAL**

**NOTES/QUESTIONS TO THE CHEMIST:**

1. DESCRIPTION section:

The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

2. The firm recommends dispensing their drug product in the original container. Are the firm's containers "tightly closed and moisture-proof"?

3. Has firm submitted stability data to support "refrigeration storage up to 10 days" after reconstitution?

4. DOSAGE AND ADMINISTRATION/Directions for Mixing Oral Suspension section:

- The volume of water required for reconstitution differs from the reference listed drug. Has the firm submitted data to support the "volume of water specified for reconstitution"?
- Has the firm submitted data to support the accuracy of the final concentrations, 200 mg/5 mL of amoxicillin and 28.5 mg of clavulanic acid as the potassium salt and 400 mg/5 mL of amoxicillin and 57 mg of clavulanic acid as the potassium salt in 100 mL bottles?

5. CONTAINER LABELS

The firm indicates that their 200 mg/ 28.5 per 5 mL drug product contains 0.67 mg phenylalanine per 5 mL and that their 400 mg/57 mg per 5 mL drug product contains 1.12 mg phenylalanine per 5 mL. Do you concur?

**NOTE/QUESTION TO THE CHEMIST:**

1. In the firm's February 24, 2004 amendment the amount of water for required for suspension was revised to read, "92 mL" and "87 mL". Is this revision accurate?

**CHEMIST RESPONSE:**

Here are the answers to your questions:

1. Clavanate comes *Streptomyces clavuligerus*.
2. The firm's containers are "tightly closed and moisture-proof".
3. The firm routinely tests the constituted product after 10 days of refrigerated storage as part of the stability study.
4. Yes.
5. Phenylalanine comes from aspartame. The numbers are correct.
6. Yes.

[Y.P.]

**FOR THE RECORD:** [Portions from previous reviewer]

1. Reference Listed drug: Augmentin (amoxicillin/clavulante potassium) powder for oral suspension and chewable tablets/NDA 50-725. Current insert approved 5/12/03. The firm has added the information regarding antibacterial resistance at the beginning of the PI after the TITLE as well as in the INDICATIONS AND USAGE and PRECAUTIONS (two places) sections of the insert. The added text can be found in 21 CFR 201.24

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements. [B1.2, p. 604]

3. Manufacturing Facility: [B1.2, p. 6195]

Manufactured by: Novopharm Limited Ontario, Canada  
Distributed by: Teva Pharmaceuticals USA Sellersville, PA

4. Container/Closure:

Round, natural color, HDPE bottles with CRC [Vol. B1.3, p. 6524, 6687]

5. Package Size:

NDA – Bottles of 50 mL, 75 mL and 100 mL

ANDA – Bottles of 100 mL\*

\*(Originally the firm submitted draft labels for the \_\_\_\_\_ sizes but subsequent submissions contained only the 100 mL size and the others were removed from the submitted PI - per chemist R Adams the firm's \_\_\_\_\_ container sizes failed accelerated stability tests so the firm withdrew them.)

6. Patent/Exclusivity: None

7. Storage/Dispense:

USP – Preserve in tight containers, at controlled room temperature.

NDA – Store tablets and dry powder at or below 25°C (77°F). Dispense in original containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

ANDA - \_\_\_\_\_ Store at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature]. Keep tightly closed. Shake well before using. Must be refrigerated. Discard after 10 days.

8. INSERT LABELING

a. DOSAGE AND ADMINISTRATION/Adults subsection

The second and third paragraphs referencing tablets vs. chewable tablets were retained because it was felt that they provided useful information for Health Care Professionals.

b. CLINICAL STUDIES

In the paragraph below the applicant did not include the last two sentences, since this information pertains to the innovator's drug product. Therefore, ANDAs marketing this drug product should be requested to use the text, "The presence of mannitol or aspartame in the drug product may contribute to a different diarrhea profile".

It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed at q12h, versus suspensions dosed q8h, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The q12h oral suspensions are sweetened with aspartame only.

9. Bioequivalence:

Fasting Bioequivalence study: Amoxicillin and Clavulanate Potassium for Oral Suspension  
400 mg/57per 5 mL for oral suspension

- Amoxicillin

Parameter	ANDA	NDA	Insert [administered at the start of a light meal]
ACU (mcg.hr/mL)	18.3	18.2	17.29
Cmax (mcg/mL)	7.4	7.6	6.94
T ½ (hr)	1.25	1.26	1.3
Tmax	1.21	1.28	1

-Clavulanate potassium/ clavulanic acid

Parameter	ANDA	NDA	Insert [administered at the start of a light meal]
ACUI (mcg.hr/mL)	2.3	2.0	2.34
Cmax (mcg/mL)	1.2	1.1	1.10
T ½ (hr)	1.02	1.01	1
Tmax (hr)	0.96	0.95	1

Non-Fasting Bioequivalence study: Amoxicillin and Clavulanate Potassium for Oral Suspension 400 mg/57 per 5 mL for oral suspension

- Amoxicillin

Parameter	ANDA	NDA	Insert [administered at the start of a light meal]
ACU (mcg.hr/mL)	18.1	17.6	17.29
Cmax (mcg/mL)	5.6	5.2	6.94
T ½ (hr)	1.2	1.2	1.3
Tmax (hr)	2.1	2.1	1

-Clavulanate potassium/ clavulanic acid

Parameter	ANDA	NDA	Insert [administered at the start of a light meal]
ACU (mcg.hr/mL)	1.5	1.5	2.34
Cmax (mcg/mL)	0.677	0.655	1.10
T ½ (hr)	0.89	0.91	1
Tmax (hr)	1.65	1.53	1

- The firm's pharmacokinetic parameters from the fasting and fed bioequivalence studies are comparable to the reference listed drug.
- The firm's pharmacokinetic parameters listed in the insert labeling are comparable to the bioequivalence study results.
- The reported pharmacokinetic parameters from the fasting and fed bioequivalence studies were found to be within acceptable limits by the Division of Bioequivalence.
- The insert labeling indicates that dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. The drug product can be taken without regard to meals. However, the absorption of clavulanate potassium when taken with food is greater relative to the fasted state.
- The fed study pharmacokinetic parameters indicate a slight food effect.
- Biowaiver request for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200mg/ 28.5 mg/5 mL was granted.

APPEARS THIS WAY  
ON ORIGINAL

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Date of Review: 5/5/04

Dates of Submission: 2/23/04

Primary Reviewer: *Jacqueline Council (Handwritten)*  
Jacqueline Council, Pharm.D.

*5-12-04*  
Date:

Team Leader: Captain Lillie Golson

Date: *5/14/04*

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cc: ANDA: 65-089  
DUP/DIVISION FILE  
HFD-613/JCouncil/LGolson (no cc)  
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Review