

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-089

CHEMISTRY REVIEW(S)

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO.# 1

2. ANDA # 65-089

3. NAME AND ADDRESS OF APPLICANT:

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS OF SUBMISSION:

RLD: Augmentin® Powder for reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml (NDA 50-725, Smithkline Beecham).

Patent Certification Exemption: p. 12
RLD Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml is subject to the exemption provisions of Section 125 (d) (2) of Title 1 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

Exclusivity Statement: p. 13
No listed exclusivities for the reference drug product, Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml.

5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amoxicillin and Clavulanate Potassium for Oral Suspension USP

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Teva
04-12-2001 Submission of ANDA
05-11-2001 New Correspondence
07-10-2001 Telephone Amendment

FDA:
05-07-2001 Telephone conversation
05-29-2001 Acknowledgment (accept for filing)
07-06-2001 Telephone conversation

10. PHARMACOLOGICAL CATEGORY:

As on 356 h

11. Rx or OTC: R

12. RELATED IND/NDA/DMF(s):

See #37 under this review

13. DOSAGE FORM: Powder for Oral Suspension

14. STRENGTH:

200mg/28.5mg/5ml and 400mg/57mg/5ml

15. CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:

Amoxicillin

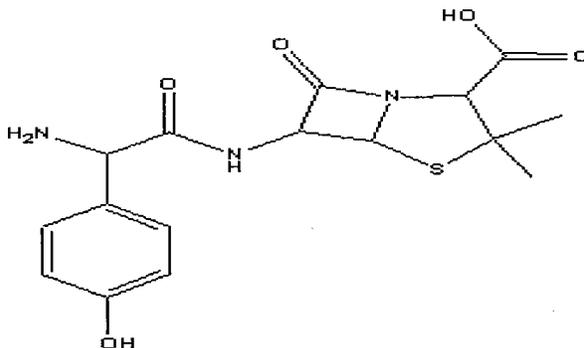
Chemical name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate [2S-[2 α , 5 α , 6 β (s*)]]-

Molecular weight: 419.45

Chemical Formula: C₁₆H₁₉N₃O₅S.3H₂O

CAS#: [61336-70-7]

Structure:



Clavulanate Potassium:

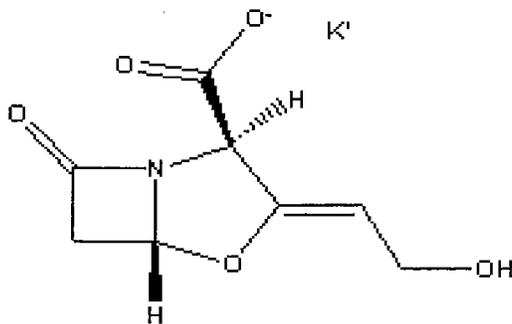
Chemical name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2 α , 3Z, 5 α)]

Molecular weight: 237.25

Chemical Formula: C₈H₈KNO₅

CAS#: 61177-45-5

Structure:



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

- EERs (issued on 5/29/01): Pending.
- Bio-review: Pending
- Labeling review: Finished (6/25/01, deficiencies)
- Micro: N/A
- Major CMC deficiencies listed under #38 in this review.
- DMF ———: inadequate; DMF ———: adequate

18. CONCLUSIONS AND RECOMMENDATIONS:

Not approvable (NA/Major)

19. REVIEWER: Yanping Pan DATE COMPLETED: 8/10/01

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CHEM REVIEW #1

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO.# 2

2. ANDA # 65-089.

3. NAME AND ADDRESS OF APPLICANT:

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS OF SUBMISSION:

RLD: Augmentin® Powder for reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml (NDA 50-725, Smithkline Beecham).

Patent Certification Exemption: p. 12

RLD Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml is subject to the exemption provisions of Section 125 (d) (2) of Title 1 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

Exclusivity Statement: p. 13

No listed exclusivities for the reference drug product, Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml.

5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amoxicillin and Clavulanate Potassium for Oral Suspension USP

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Teva
04-12-2001 Submission of ANDA
05-11-2001 New Correspondence
07-10-2001 Telephone Amendment
06-17-2002 Minor Amendment

FDA:

05-07-2001 Telephone conversation
05-29-2001 Acknowledgment (accept for filing)
07-06-2001 Telephone conversation

09-27-2001 Chemistry review #1
04-01-2002 Revised Dissolution testing recommendation

10. **PHARMACOLOGICAL CATEGORY:**

As on 356 h

11. **Rx or OTC:** R

12. **RELATED IND/NDA/DMF(s):**

See #37 under this review

13. **DOSAGE FORM:** Powder for Oral Suspension

14. **STRENGTH:**

200mg/28.5ml and 400mg/57ml

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:**

Amoxicillin

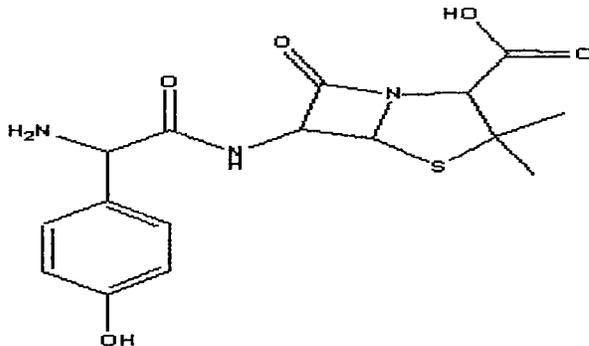
Chemical name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate [2S-[2 α , 5 α , 6 β (s*)]]-

Molecular weight: 419.45

Chemical Formula: C₁₆H₁₉N₃O₅S.3H₂O

CAS#: [61336-70-7]

Structure:



Clavulanate Potassium:

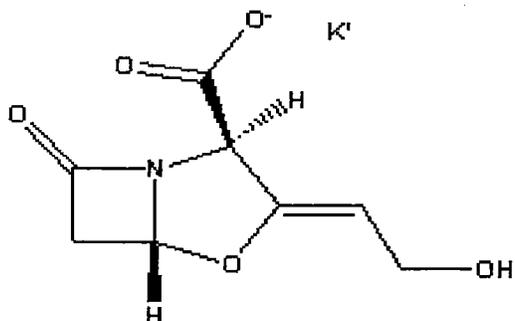
Chemical name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2 α , 3Z, 5 α)]

Molecular weight: 237.25

Chemical Formula: C₈H₈KNO₅

CAS#: 61177-45-5

Structure:



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

- EERs (issued on 5/29/01): Pending.
- Bio-review: satisfactory (4/9/02)
- Labeling review: Finished (6/25/01, deficiencies)
- Micro: N/A
- DMF _____: adequate (information request); DMF _____: adequate

18. CONCLUSIONS AND RECOMMENDATIONS:

Not Approvable- _____ required (major)

19. REVIEWER: Yanping Pan DATE COMPLETED: 7/17/02

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO. # 3

2. ANDA # 65-089

3. NAME AND ADDRESS OF APPLICANT:

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS OF SUBMISSION:

RLD: Augmentin® Powder for reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml (NDA 50-725, Smithkline Beecham).

Patent Certification Exemption: p. 12

RLD Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml is subject to the exemption provisions of Section 125 (d) (2) of Title 1 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

Exclusivity Statement: p. 13

No listed exclusivities for the reference drug product, Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml.

5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amoxicillin and Clavulanate Potassium for Oral Suspension USP

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Teva	
04-12-2001	Submission of ANDA
05-11-2001	New Correspondence
07-10-2001	Telephone Amendment
06-17-2002	Minor Amendment
02-28-2003	Major Amendment (subject this review)

<u>FDA:</u>	
05-07-2001	Telephone conversation

05-29-2001 Acknowledgment (accept for filing)
07-06-2001 Telephone conversation
09-27-2001 Chemistry review #1
04-01-2002 Revised Dissolution testing recommendation
07-17-2002 Chemistry review #2

10. **PHARMACOLOGICAL CATEGORY:**

As on 356 h

11. **Rx or OTC:** L

12. **RELATED IND/NDA/DMF(s):**

See #37 under this review

13. **DOSAGE FORM:** Powder for Oral Suspension

14. **STRENGTH:**

200mg/28.5mg/5ml and 400mg/57mg/5ml

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:**

Amoxicillin

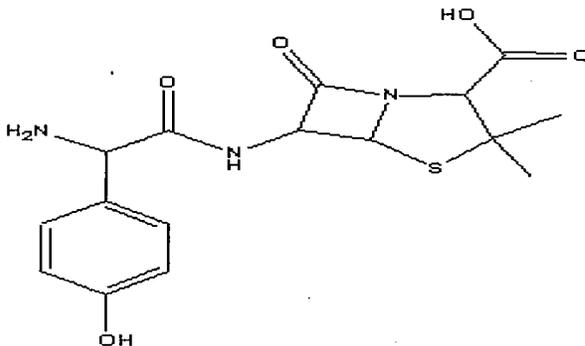
Chemical name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate [2S-[2 α , 5 α , 6 β (s*)]]-

Molecular weight: 419.45

Chemical Formula: C₁₆H₁₉N₃O₅S.3H₂O

CAS#: [61336-70-7]

Structure:



Clavulanate Potassium:

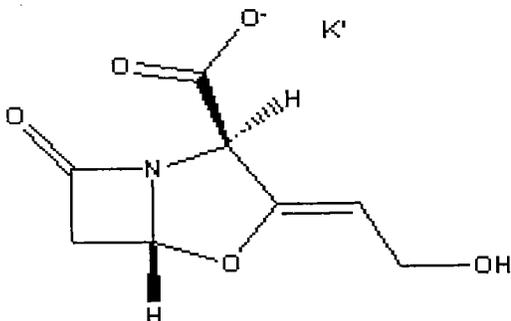
Chemical name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2 α , 3Z, 5 α)]

Molecular weight: 237.25

Chemical Formula: C₈H₈KNO₅

CAS#: 61177-45-5

Structure:



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

- X EERs: acceptable (9/3/02)
- X Bio-review: satisfactory (4/9/02)
- X Labeling review: deficiencies (6/25/01)
- X Micro: N/A

18. CONCLUSIONS AND RECOMMENDATIONS:

Not Approvable (Major)

19. REVIEWER: Yanping Pan

DATE COMPLETED: 6/30/03, revised 7/15/03

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO.# 4

2. ANDA # 65-089

3. NAME AND ADDRESS OF APPLICANT:

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS OF SUBMISSION:

RLD: Augmentin® Powder for reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml (NDA 50-725, Smithkline Beecham).

Patent Certification Exemption: p. 12

RLD Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml is subject to the exemption provisions of Section 125 (d) (2) of Title 1 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

Exclusivity Statement: p. 13

No listed exclusivities for the reference drug product, Augmentin® Powder for Reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml.

5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

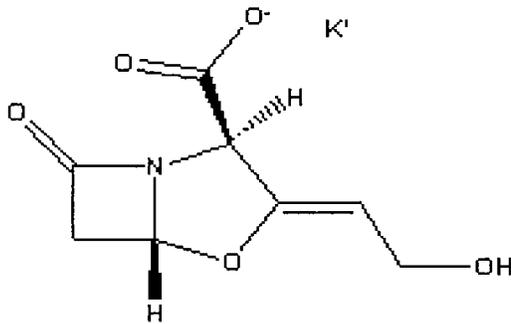
7. NONPROPRIETARY NAME: Amoxicillin and Clavulanate Potassium for Oral Suspension USP

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Teva
04-12-2001 Submission of ANDA
05-11-2001 New Correspondence
07-10-2001 Telephone Amendment
06-17-2002 Minor Amendment
02-28-2003 Major Amendment
10-03-2003 Minor Amendment (subject this review)

[2R-(2 α , 3Z, 5 α)]
Molecular weight: 237.25
Chemical Formula: C₈H₈KNO₅
CAS#: 61177-45-5
Structure:



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

X EERs: acceptable (9/3/02)
X Bio-review: satisfactory (4/9/02)
X Labeling review: deficiencies (11/06/03)
X Micro: N/A

This review covers Minor Amendment dated 10/3/03.

Note:

We issued a Major NA letter to TEVA on July 21, 2003 for this application based on the assumption that the firm would need to _____ to improve the stability of their products.

However, the firm has submitted an amendment dated October 3, 2003, which provides additional _____ stability data on their additional batches submitted in their 2/28/03 amendment. The firm has not _____. Based on this it appears appropriate to reclassify the major Amendment status to the Minor Amendment status.

18. CONCLUSIONS AND RECOMMENDATIONS:

Not Approvable (Telephone)
12/18/03: Converted to Not Approvable - Minor

19. REVIEWER: Yanping Pan DATE COMPLETED: 11/10/03; revised
12/18/03

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO. # 5

2. ANDA # 65-089

3. NAME AND ADDRESS OF APPLICANT:

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS OF SUBMISSION:

RLD: Augmentin® Powder for reconstitution, 200mg/28.5mg/5ml and 400mg/57mg/5 ml (NDA 50-725, Smithkline Beecham).

Patent Certification Exemption: p. 12

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Exclusivity Statement: p. 13

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5. SUPPLEMENT (s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amoxicillin and Clavulanate Potassium for Oral Suspension USP

8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Teva	
04-12-2001	Submission of ANDA
05-11-2001	New Correspondence
07-10-2001	Telephone Amendment
06-17-2002	Minor Amendment
02-28-2003	Major Amendment
10-03-2003	Minor Amendment
02-24-2004	Minor Amendment (subject this review)
04-02-2004	Telephone Amendment (subject this review)

04-23-2004 Labeling amendment

FDA:

05-07-2001 Telephone conversation
05-29-2001 Acknowledgment (accept for filing)
07-06-2001 Telephone conversation
09-27-2001 Chemistry review #1
04-01-2002 Revised Dissolution testing recommendation
07-17-2002 Chemistry review #2
07-15-2003 Chemistry review #3
12-18-2003 Chemistry review #4

10. PHARMACOLOGICAL CATEGORY:

As on 356 h

11. Rx or OTC: RX

12. RELATED IND/NDA/DMF(s):

See #37 under this review

13. DOSAGE FORM: Powder for Oral Suspension

14. STRENGTH:

200mg/28.5mg/5ml and 400mg/57mg/5ml

15. CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:

Amoxicillin

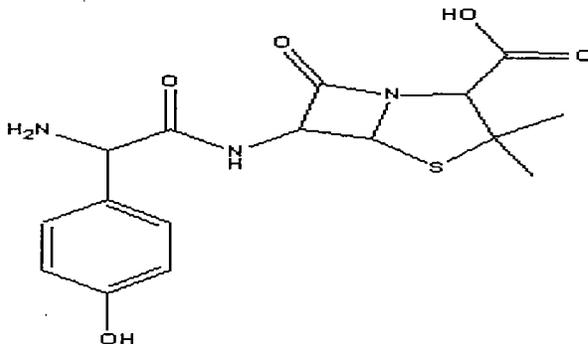
Chemical name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate [2S-[2 α , 5 α , 6 β (s*)]]-

Molecular weight: 419.45

Chemical Formula: C₁₆H₁₉N₃O₅S.3H₂O

CAS#: [61336-70-7]

Structure:



Clavulanate Potassium:

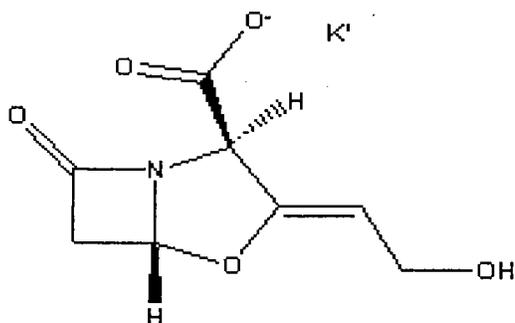
Chemical name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2 α , 3Z, 5 α)]

Molecular weight: 237.25

Chemical Formula: C₈H₈KNO₅

CAS#: 61177-45-5

Structure:



16. RECORDS AND REPORTS: N/A

17. COMMENTS:

- X EERs: acceptable (9/3/02)
- X Bio-review: satisfactory (4/9/02)
- X Labeling review: Acceptable (5/14/04)
- X Micro: N/A

This review covers Minor Amendment dated 2/24/04 and 4/2/04 Telephone Amendment.

18. CONCLUSIONS AND RECOMMENDATIONS:

Approvable

19. REVIEWER: Yanping Pan DATE COMPLETED: 4/7/04; 5/14/04 (as revised after completion of label review)

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CHEM REVIEW #5

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