

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-856

CHEMISTRY REVIEW(S)



1/16/09

CMC Memo to File

To:	NDA
Date	16 Jan 2009
Sponsor:	Takeda
Drug:	Uloric (febuxostat)
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall "acceptable" recommendation given on Jan 16, 2009 of the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 21-856 be approved.

HFD-/Division File
HFD-170
HFD-170/M. Sullivan

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

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/s/

Olen Stephens
1/16/2009 01:55:28 PM
ENV ASSESSMENT
Approval Recommendation

Ali Al-Hakim
1/16/2009 02:00:24 PM
CHEMIST

1/6/09



NDA 21-856

**Uloric
(febuxostat tablets)**

TAP Pharmaceutical Products Inc.

Olen M. Stephens

Review Chemist

**Office of New Drug Quality Assessment
Pre-Marketing Division I, Branch II
for the
Division of Anesthesia, Analgesia and
Rheumatology Products**



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A. Labeling & Package Insert	7

APPEARS THIS WAY
ON ORIGINAL



Chemistry Review Data Sheet

1. NDA 21-856
2. REVIEW #: 4
3. REVIEW DATE: 18-Dec-2008
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	14-Dec-2004
Amendment (BC) (control of excipients and comparability protocol for DP scale-up)	28-Jan-2005
Amendment (BL)	30-Mar-2005
Amendment (SU) (stability and labeling update)	14-Apr-2005
Amendment (BZ) (dissolution response)	02-Jun-2005
Amendment (BC) (drug substance critical steps comparability protocol for DS equipment)	30-Jun-2005
Amendment (BZ) (revised dissolution method and acceptance criteria)	19-Jul-2005
Amendment (BC) (commitment to revise drug product specification and stability protocol)	12-Aug-2005
Amendment (BC) (revised _____ testing and stability protocol – placed in CTD sections)	22-Aug-2005
Amendment (BC) (degradation product method and validation)	31-Aug-2005
Amendment (BC) (container closure system response)	12-Sep-2005
Amendment (BZ) (revised DP stability protocol and specification including dissolution method and validation)	16-Sep-2005
Resubmission (AZ)	17-Feb-2006

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (AZ)	17-Jul-2008
Amendment (BC) (labeling changes)	28-Oct-2008

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 N. Field Drive
Lake Forest, IL 60045
Representative: Binita Kwankin, Assistant Director, Regulatory
Affairs
Telephone: (847) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Uloric
- b) Non-Proprietary Name (USAN): febuxostat tablets
- c) Code Name/# (ONDC only): TMX-67, TEI-6720, A-319198.0
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 40 mg and 80 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

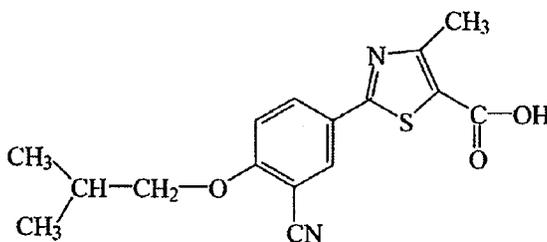
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____ SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid



C₁₆H₁₆N₂O₃S

MW 316.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	IV	/		1	Adequate	8/22/05	
	III		4	N/A		*	
	III		3 & 4	Adequate	12/7/04	*	
	III		4	N/A		*	
	III		4	N/A		*	
	III		4	N/A		*	
	III		4	N/A		*	
	III		4	N/A		*	
	III		4	N/A		*	
	III		3 & 4	Adequate	6/16/08 for	*	

b(4)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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*See page 78 of Review #1 under container closure system for details.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,229	RMX-67

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	20-Oct-2008	Cruz Concepcion
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
OPDRA	The proposed proprietary name Uloric is acceptable	6/2/06	Tina Tezky (DMETS)
EA	Categorical exclusion		
Microbiology	N/A		



II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Response to FDA Discipline Review Letter Dated June 14, 2006

The Agency's comments are in bold.

The Applicant's response is in normal font.

[Redacted content]

b(4)

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Olen Stephens
1/6/2009 10:15:11 AM
ENV ASSESSMENT
Revised Labeling Review

Ali Al-Hakim
1/6/2009 12:57:40 PM
CHEMIST

10/31/08



NDA 21-856

**Uloric
(febuxostat tablets)**

TAP Pharmaceutical Products Inc.

Olen M. Stephens

Review Chemist

**Office of New Drug Quality Assessment
Pre-Marketing Division I, Branch II
for the
Division of Anesthesia, Analgesia and
Rheumatology Products**



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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	Error! Bookmark not defined.
S DRUG SUBSTANCE [Name, Manufacturer]	Error! Bookmark not defined.
P DRUG PRODUCT [Name, Dosage form].....	Error! Bookmark not defined.
A APPENDICES	Error! Bookmark not defined.
R REGIONAL INFORMATION	Error! Bookmark not defined.
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	Error! Bookmark not defined.
A. Labeling & Package Insert	Error! Bookmark not defined.
B. Environmental Assessment Or Claim Of Categorical Exclusion ...	Error! Bookmark not defined.
III. List Of Deficiencies To Be Communicated.....	Error! Bookmark not defined.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (AZ)	17-Jul-2008

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 N. Field Drive
Lake Forest, IL 60045
Representative: Binita Kwankin, Assistant Director, Regulatory
Affairs
Telephone: (847) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

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- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

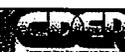
12. STRENGTH/POTENCY: 40 mg and 80 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

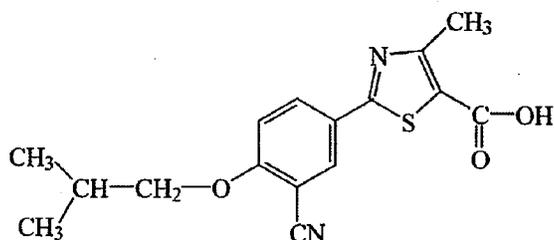
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid



C₁₆H₁₆N₂O₃S

MW 316.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
b(4)	IV	[Redacted]	[Redacted]	1	Adequate	8/22/05	
	III			4	N/A		*
	III			3 & 4	Adequate	12/7/04	*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			3 & 4	Adequate	6/16/08 for	*



CHEMISTRY REVIEW



Chemistry Review Data Sheet

*See page 78 of Review #1 under container closure system for details.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,229	RMX-67

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
OPDRA	The proposed proprietary name Uloric is acceptable	6/2/06	Tina Tezky (DMETS)
EA	Categorical exclusion		
Microbiology	N/A		



The Chemistry Review for NDA 21-856

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an "Acceptable" Office of Compliance recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

(No changes to the drug substance sections in the current submission.)

The USAN and INN name for the active pharmaceutical ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance characterization, manufacturing and controls was provided in the original NDA and has been previously reviewed. The drug substance is produced as _____ which is consistently manufactured by _____

b(4)

Febuxostat solubility is highly pH dependent. At $\text{pH} \leq 5.5$ solubility is minimal _____ ng/mL , and exceeds _____ mg/mL in pH 6.8 phosphate buffer.

Febuxostat is stable _____ for 36 months at $25^\circ\text{C}/60\% \text{RH}$ and 6 months at $40^\circ\text{C}/75\% \text{RH}$. Furthermore, stress testing at 70°C , in packages ranging in protective properties, showed no change _____. The stability data show no increase in impurities, nor trends in other attributes, and therefore support the proposed retest period of _____

b(4)

(2) Drug Product

The drug product is an immediate release film-coated tablet containing febuxostat in two strengths: 40 mg and 80 mg. Except for the color (Opadry II, Green



CHEMISTRY REVIEW



Executive Summary Section

coating the tablets, all the excipients are pharmacopeial (USP/NF). Critical parameters in the manufacturing process were identified as:

The 40 mg tablets are packaged in 30, 90, and 500 count bottles and 100 count blisters (10 cards x 10 tablets). The 80 mg tablets are packaged in 30, 100, and 1000 count bottles and 3 and 100 count blisters (10 cards x 10 tablets). The two dosage forms are:

b(4)

The proposed expiration date of 60 months is supported by real time stability data in both commercial packaging configurations.

B. Description of How the Drug Product is Intended to be Used

Febuxostat tablets will be dispensed by prescription only for the management of hyperuricemia in patients with gout. The recommended dose is 40 mg or 80 mg QD

b(4)

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and the drug product have been communicated to the applicant during the previous review cycles and have been sufficiently addressed and resolved, except for the discriminatory ability of the proposed dissolution method, for the two strengths (see CMC reviews #1 and #2). In the current resubmission, the dissolution method and acceptance criterion have been amended to conditions that can discriminate between the 40 mg and 80 mg tablets by changing the pH of the media used in the method. The new method validation has been reviewed and deemed adequate.

All labeling comments from review #1 have been conveyed to the applicant in the Agency 6/14/06 "Approvable" letter. New labeling has been re-submitted.

There are no changes in the manufacturing facilities for febuxostat. The Office of Compliance found all the facilities used in the manufacture and control of the drug substance and drug product acceptable on 8/1/05 (Chemistry Review #1), and on 6/14/06 (Chemistry Review #2). The facilities have been resubmitted for re-evaluation to the Office of compliance and are pending inspection.



III. Administrative

- A. Reviewer's Signature:** electronically signed in DFS
Olen M. Stephens
- B. Endorsement Block:** electronically signed in DFS
- C. CC Block:** entered electronically in DFS

9 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/  
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Olen Stephens  
10/30/2008 01:51:46 PM  
ENV ASSESSMENT

Ali Al-Hakim  
10/31/2008 09:51:08 AM  
CHEMIST

**NDA 21-856**

**Uloric  
(febuxostat tablets)**

**TAP Pharmaceutical Products Inc.**

**Sue-Ching Lin**

**Review Chemist**

**Office of New Drug Quality Assessment  
Pre-Marketing Division III, Branch V  
for  
Division of Anesthesia, Analgesia, and  
Rheumatology Products**



# Chemistry Review Data Sheet

1. NDA 21-856
2. REVIEW #: 2
3. REVIEW DATE: 14-July-2006
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

| Submissions Reviewed in Chemistry Review #1                                                                  | Document Date |
|--------------------------------------------------------------------------------------------------------------|---------------|
| Original Submission                                                                                          | 14-Dec-2004   |
| Amendment (BC) (control of excipients and comparability protocol for DP scale-up)                            | 28-Jan-2005   |
| Amendment (BL)                                                                                               | 30-Mar-2005   |
| Amendment (SU) (stability and labeling update)                                                               | 14-Apr-2005   |
| Amendment (BZ) (dissolution response)                                                                        | 02-Jun-2005   |
| Amendment (BC) (drug substance critical steps comparability protocol for DS equipment)                       | 30-Jun-2005   |
| Amendment (BZ) (revised dissolution method and acceptance criteria)                                          | 19-Jul-2005   |
| Amendment (BC) (commitment to revise drug product specification and stability protocol)                      | 12-Aug-2005   |
| Amendment (BC) (revised <del>_____</del> testing and stability protocol—placed in CTD sections)              | 22-Aug-2005   |
| Amendment (BC) (degradation product method and validation)                                                   | 31-Aug-2005   |
| Amendment (BC) (container closure system response)                                                           | 12-Sep-2005   |
| Amendment (BC) (revised DP stability protocol and specification including dissolution method and validation) | 16-Sep-2005   |

b(4)

6. SUBMISSION(S) BEING REVIEWED:

| Subject of this Review | Document Date |
|------------------------|---------------|
| Resubmission (AZ)      | 17-Feb-2006   |



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.  
Address: 675 N. Field Drive  
Lake Forest, IL 60045  
Representative: Binita Kwankin, Assistant Director, Regulatory Affairs  
Telephone: ( 847 ) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Uloric
- b) Non-Proprietary Name: febuxostat tablets
- c) Code Name/# (ONDQA only): TMX-67, TEI-6720
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1 (new molecular entity)
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

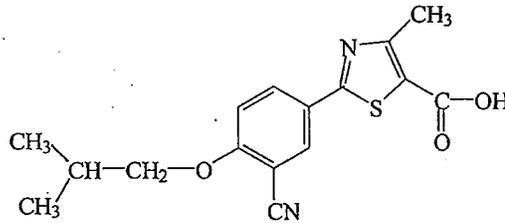
Not a SPOTS product

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S

MW 316.37

**17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS    |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|-------------|
|       | IV   | /      | /               | 1                 | Adequate            | 8/22/05               |             |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 3 & 4             | Adequate            | 12/7/04               | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 4                 | N/A                 |                       | *           |
|       | III  |        |                 | 3 & 4             | Adequate            |                       | 6/13/02 for |

\*See page 78 of Review #1 under \_\_\_\_\_ for details.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| IND      | 58,229             | TMX-67      |

**18. STATUS:**

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                                     | DATE    | REVIEWER           |
|-------------------------------|----------------------------------------------------|---------|--------------------|
| Biometrics                    | N/A                                                |         |                    |
| EES                           | Acceptable                                         | 6/14/06 | J. D. Ambrogio     |
| Pharm/Tox                     | N/A                                                |         |                    |
| Biopharm                      | N/A                                                | N/A     |                    |
| LNC                           | N/A                                                |         |                    |
| Methods Validation            | N/A, according to the current ONDQA policy         |         |                    |
| Office of Drug Safety         | The proposed proprietary name Uloric is acceptable | 6/2/06  | Tina Tezky (DMETS) |
| EA                            | Categorical exclusion (see Review #1)              |         |                    |
| Microbiology                  | N/A                                                |         |                    |



# The Chemistry Review for NDA 21-856

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, this NDA is recommended for approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

The active ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance was provided in the NDA. The drug substance is produced as \_\_\_\_\_, is consistently manufactured by controlling \_\_\_\_\_.

b(4)

Solubility of febuxostat is highly pH dependent. Up to pH 5.5, the solubility is minimal (\_\_\_\_ mg/mL), while in pH 6.8 phosphate buffer, solubility exceeds \_\_\_\_\_ mg/mL.

Febuxostat was shown to be stable for \_\_\_\_\_ 36 months at 25°C/60%RH and 6 months at 40°C/75% RH in the commercial container (\_\_\_\_). Furthermore, stress testing at up to 70°C, in packages ranging in protective properties, showed no change (\_\_\_\_). The submitted stability data, which also show no increase in impurities, support the proposed retest period of \_\_\_\_\_.

b(4)



## CHEMISTRY REVIEW



### Executive Summary Section

#### (2) Drug Product

The drug product is an immediate release tablet containing febuxostat in two strengths: 80 mg and 120 mg. With the exception of the color (Opadry II, Green), used in coating tablets, all the excipients are USP/NF materials. The critical parameters in the manufacturing process were identified as \_\_\_\_\_ The tablets are packaged in \_\_\_\_\_ bottles and blisters.

b(4)

#### B. Description of How the Drug Product is Intended to be Used

Febuxostat tablets will be dispensed by prescription only. The drug product is indicated for the management of hyperuricemia in patients with gout. The recommended dose is \_\_\_\_\_

b(4)

The submitted drug product stability data include long-term stability data for 18 months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. The supportive data include 18 months of data for febuxostat 20 mg and 12 months of data for 40 mg tablets. The supportive lots were manufactured using the same formulation as the proposed commercial product. The stability data support the proposed \_\_\_\_\_ expiration period for the drug product stored at controlled room temperature.

b(4)

#### C. Basis for Approvability or Not-Approval Recommendation

As stated in the executive summary of chemistry review #1 of this NDA, the only pending CMC issue was related to the drug product dissolution method and acceptance criteria. The deficiency was included in the FDA 10/14/05 "approvable" letter. In response, the applicant revised the dissolution method and acceptance criteria as requested by the FDA. The response is adequate.

All the labeling comments from review #1 have been conveyed to the applicant in the 6/14/06 letter.

All the facilities used in the manufacture and control of the drug substance and drug product were found to be acceptable by the Office of Compliance on 8/1/05, as indicated in Chemistry Review #1. Establishment evaluation was requested again for this resubmission. The Office of Compliance issued an "acceptable" recommendation again on 6/14/06 for all the sites used in the manufacture and control of the drug substance and drug product.



Executive Summary Section

**III. Administrative**

- A. **Reviewer's Signature:** electronically signed in DFS  
Sue-Ching Lin
- B. **Endorsement Block:** electronically signed in DFS  
Ravi Harapanhalli
- C. **CC Block:** entered electronically in DFS

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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Sue Ching Lin  
7/17/2006 11:54:39 AM  
CHEMIST

Ravi Harapanhalli  
7/18/2006 02:54:07 PM  
CHEMIST



b(4)

Drug substance packaging is adequate, and stability studies support a retest. The stability protocol and commitment are adequate.

**Conclusion**

Drug substance is satisfactory.

The Uloric drug product is a film coated immediate release tablet of 80 and 120 mg manufactured at Abbott Laboratories, Abbott Park, IL (CFN# 1415939).

The formulation is as follows

| Strength                              |           |               | 80 mg     | 120 mg    |
|---------------------------------------|-----------|---------------|-----------|-----------|
| Component                             | Reference | Function      | mg/tablet | mg/tablet |
| febuxostat                            | In-house  | Active        | 80.00     | 120.00    |
| Lactose, Monohydrate, Powder, Regular | NF        | /             | /         | /         |
| Cellulose, Microcrystalline,          | NF        | /             | /         | /         |
| Hydroxypropyl Cellulose               | NF        | /             | /         | /         |
| Croscarmellose Sodium                 | NF        | /             | /         | /         |
| Silicon Dioxide                       | NF        | /             | /         | /         |
| Magnesium Stearate                    | NF        | /             | /         | /         |
| <b>Total Core Tablets</b>             |           |               |           |           |
| <b>Color Coating</b>                  |           |               |           |           |
| Opadry II, Green,                     | In-house  | Color coating |           |           |
| <b>Total Coated Tablets</b>           |           |               | 520.84    | 769.23    |

b(4)

Note that 3 different formulations were used through the phase I – II trials, but the differences are not considered to be significant with respect to performance attributes.

The manufacturing method is a conventional

Batch size is with comparability protocol to increase batch size to Controls of critical processes are considered adequate. The specification is considered adequate after addition of individual specified and total degradation product

b(4)

tests and acceptance criteria. The \_\_\_\_\_ testing will on a "skip-lot" basis and then if there is shown to be no need for the testing it will be "sun-set". The dissolution method and acceptance criteria are yet to be fully agreed upon. The firm is requested to revise the acceptance criteria to  $Q=$  — at  $t=15$  min.

b(4)

Room temperature stability data for all presentations and strengths were provided through 18 months. These data, along with supportive data are considered adequate to support a \_\_\_\_\_ tentative expiry. The stability protocol (matrix design) and commitment are acceptable following revisions in accord with FDA recommendations.

b(4)

All associated DMFs are acceptable

The overall Compliance recommendation is pending as of 11-JUL-2005.

**Overall Conclusion**

From a CMC perspective the application is recommended for an approvable action.

Eric P. Duffy, PhD  
Director, DNDC II/ONDC

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Eric Duffy  
10/12/2005 11:12:40 AM  
CHEMIST

**NDA 21-856**

**Uloric  
(febuxostat tablets)**

**TAP Pharmaceutical Products Inc.**

**Sue-Ching Lin**

**Review Chemist**

**Division of Anesthesia, Analgesia, and  
Rheumatology Products**



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# CHEMISTRY REVIEW



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**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. NDA 21-856
2. REVIEW #: 1
3. REVIEW DATE: 19-Sep-2005
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u>                              | <u>Document Date</u> |
|--------------------------------------------------------|----------------------|
| CMC Pre-NDA meeting (IND 58,229)                       | 20-May-2004          |
| Amendment 59 (IND 58,229) for stability bracket design | 12-Feb-2002          |
| CMC meeting (IND 58,229) for starting materials        | 09-Aug-2001          |

6. SUBMISSION(S) BEING REVIEWED:

| <b>Submission(s) Reviewed</b>                                                                                | <b>Document Date</b> |
|--------------------------------------------------------------------------------------------------------------|----------------------|
| Original Submission                                                                                          | 14-Dec-2004          |
| Amendment (BC) (control of excipients and comparability protocol for DP scale-up)                            | 28-Jan-2005          |
| Amendment (BL)                                                                                               | 30-Mar-2005          |
| Amendment (SU) (stability and labeling update)                                                               | 14-Apr-2005          |
| Amendment (BZ) (dissolution response)                                                                        | 02-Jun-2005          |
| Amendment (BC) (drug substance critical steps comparability protocol for DS equipment)                       | 30-Jun-2005          |
| Amendment (BZ) (revised dissolution method and acceptance criteria)                                          | 19-Jul-2005          |
| Amendment (BC) (commitment to revise drug product specification and stability protocol)                      | 12-Aug-2005          |
| Amendment (BC) (revised _____ testing and stability protocol—placed in CTD sections)                         | 22-Aug-2005          |
| Amendment (BC) (degradation product method and validation)                                                   | 31-Aug-2005          |
| Amendment (BC) (container closure system response)                                                           | 12-Sep-2005          |
| Amendment (BC) (revised DP stability protocol and specification including dissolution method and validation) | 16-Sep-2005          |

b(4)



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.  
Address: 675 N. Field Drive  
Lake Forest, IL 60045  
Representative: Binita Kwankin, Assistant Director, Regulatory Affairs  
Telephone: ( 847 ) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Uloric
- b) Non-Proprietary Name: febuxostat tablets
- c) Code Name/# (ONDC only): TMX-67, TEI-6720
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



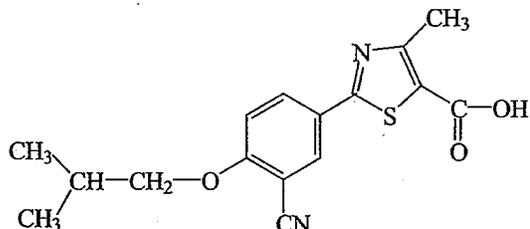
**CHEMISTRY REVIEW**



Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid



$C_{16}H_{16}N_2O_3S$

MW 316.37

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS     |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|--------------|
|       | IV   |        |                 | 1                 | Adequate            | 8/22/05               |              |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 3 & 4             | Adequate            | 12/7/04               | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 4                 | N/A                 |                       | *See page 78 |
|       | III  |        |                 | 3 & 4             | Adequate            | 6/13/02 for           | *See page 78 |

\*See page 78 of this review under \_\_\_\_\_ for details.

<sup>1</sup> Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

b(4)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| IND      | 58,229             | TMX-67      |

### 18. STATUS:

#### ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                                           | DATE                                                   | REVIEWER                                                                            |
|-------------------------------|----------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------|
| Biometrics                    | N/A                                                      |                                                        |                                                                                     |
| EES                           | Acceptable                                               | 8/1/05                                                 | J. D. Ambrogio                                                                      |
| Pharm/Tox                     | N/A                                                      |                                                        |                                                                                     |
| Biopharm                      | Dissolution method and acceptance criteria need revision | See Biopharm review in DFS and page 65 of this review. | Lei Zhang                                                                           |
| LNC                           | N/A                                                      |                                                        |                                                                                     |
| Methods Validation            | N/A, according to the current ONDC policy                |                                                        |                                                                                     |
| Office of Drug Safety         | The proposed proprietary name Uloric is acceptable*.     | 2/25/05 (DMTES) & 8/31/05 (DDMAC)                      | Linda Wisniewski, Dennis Toyer, & Carol Holquist (DMETS)<br>Suzanne Berkman (DDMAC) |
| EA                            | Categorical exclusion (see review)                       |                                                        |                                                                                     |
| Microbiology                  | N/A                                                      |                                                        |                                                                                     |

\* The proposed proprietary name "Uloric" has been consulted to DDMAC (Division of Drug Marketing, Advertising, and Communications) and DMETS (Division of Medication Errors and Technical Support) of the Office of Drug Safety. Both DDMAC and DMETS had no objections to the use of the proposed name, Uloric (refer to the DMETS memo dated 2/25/05 and DDMAC 8/31/05 e-mails in the DFS). However, DDMAC recommended

b(5)

## Executive Summary Section

# The Chemistry Review for NDA 21-856

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is approvable pending satisfactory response to the deficiencies in dissolution method and acceptance criterion.

Please refer to the clinical pharmacology reviewer's recommendation on the analytical procedure and acceptance criterion for the dissolution test. The labeling comments will need to be conveyed to the applicant, if there is a resubmission to this NDA (see the next page under Basis of Approvability).

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

The active ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance was provided in the NDA. The drug substance is produced \_\_\_\_\_ as consistently manufactured by controlling \_\_\_\_\_

b(4)

Solubility of febuxostat is highly pH dependent. Up to pH 5.5, the solubility is minimal ( \_\_\_\_\_ mg/mL), while in pH 6.8 phosphate buffer, solubility exceeds \_\_\_\_\_ mg/mL.

b(4)

Febuxostat was shown to be stable for \_\_\_\_\_ for 36 months at 25°C/60%RH and 6 months at 40°C/75% RH in the commercial container \_\_\_\_\_. Furthermore, stress testing at up to 70°C, in packages ranging in protective properties, showed no change \_\_\_\_\_. The submitted stability data, which also show no increase in impurities, support the proposed retest period of \_\_\_\_\_

b(4)



Executive Summary Section

**(2) Drug Product**

The drug product is an immediate release tablet containing febuxostat in two strengths: 80 mg and 120 mg. With the exception of the color (Opadry II, Green) used in coating tablets, all the excipients are USP/NF materials. The critical parameters in the manufacturing process were identified as \_\_\_\_\_ . The tablets are packaged in \_\_\_\_\_ bottles and blisters.

b(4)

**B. Description of How the Drug Product is Intended to be Used**

Febuxostat tablets will be dispensed by prescription only. The drug product is indicated for the management of hyperuricemia in patients with gout. The recommended dose is \_\_\_\_\_

b(4)

The submitted drug product stability data include long-term stability data for 18 months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. The supportive data include 18 months of data for febuxostat 20 mg and 12 months of data for 40 mg tablets. The supportive lots were manufactured using the same formulation as the proposed commercial product. The stability data support the proposed \_\_\_\_\_ expiration period for the drug product stored at controlled room temperature.

b(4)

**C. Basis for Approvability or Not-Approval Recommendation**

The dissolution method and acceptance criterion remained unresolved at the completion of this review, after FDA information request letters, telephone conferences between the applicant and the FDA, and the applicant's revisions in the amendments. Refer to clinical pharmacology review and page 65 of this review for details.

The Division has decided that this NDA will not be approved due to major clinical deficiencies and thus there will be no labeling negotiations with the applicant. However, the labeling comments, as appeared on pages 88 to 90 of this review, will need to be communicated to the applicant if there is a resubmission to this NDA.



Executive Summary Section

**III. Administrative**

- A. Reviewer's Signature:** electronically signed in DFS
- B. Endorsement Block:** electronically signed in DFS
- C. CC Block:** entered electronically in DFS

67 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Sue Ching Lin
9/22/2005 05:12:41 PM
CHEMIST

John Smith
9/22/2005 05:19:28 PM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 21-856

Applicant: TAP Pharmaceutical Products Inc.

Stamp Date: 12/15/04

Drug Name: Uloric (febuxostat) Tablets

IS THE CMC SECTION OF THE APPLICATION FILABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	✓		eCTD format
2	Is the section indexed and paginated adequately?	✓		eCTD format
3	On its face, is the section legible?	✓		eCTD document
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	✓		Module 1, Regional, Forms, 356 H Module 3, Section 3.2.S.2.1 Module 3, Section 3.2.P.3.1
5	Is a statement provided that all facilities are ready for GMP inspection?	✓		Module 1, Regional, Forms, 356 H
6	Has an environmental assessment report or categorical exclusion been provided?	✓		Module 1, Section 1.12.14, categorical exclusion
7	Does the section contain controls for the drug substance?	✓		Module 3, Section 3.2.S.4
8	Does the section contain controls for the drug product?	✓		Module 3, Section 3.2.P.5
9	Has stability data and analysis been provided to support the requested expiration date?	✓		Module 3, Section 3.2.P.8 18-month and 12-month long-term data for 80 mg and 120 mg tablets respectively and 6-month accelerated data on 3 full production batches to support <u> </u> expiration period.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		
11	Have draft container labels been provided?	✓		Module 1, Section 1.14.1.1.
12	Has the draft package insert been provided?	✓		Module 1, Section 1.14.1.3
13	Has an investigational formulations section been provided?	✓		Sections 2.7.1.1, 3.2.P.1, 3.2.P.2.2, and 3.2.P.2.2.1.2. The proposed commercial formulation was used in pivotal and other clinical trials as well as for the registration lots.
14	Is there a Methods Validation package?	✓		Module 3, Section 3.2R
15	Is a separate microbiological section included?			N/A

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Reviewing Chemist: Sue-Ching Lin

Date: 1/21/05

Team Leader: John Smith, Ph.D.

Date: 1/25/05

b(4)

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/s/

Sue Ching Lin
1/25/05 04:54:38 PM
CHEMIST

John Smith
1/26/05 07:14:14 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21856/000	Action Goal:	
Stamp:	15-DEC-2004	District Goal:	19-NOV-2008
Regulatory Due:	18-JAN-2009	Brand Name:	ULORIC (FEBUXOSTAT)
Applicant:	TAKEDA PHARMS NA	Estab. Name:	80/120MG TABLETS
	ONE TAKEDA PKY	Generic Name:	FEBUXOSTAT
	DEERFIELD, IL 60015		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	170	Strength:	40 AND 80 MG TABLET

Application Comment: RESUBMISSION

NOTE THAT THE DRUG SUBSTANCE MANUFACTURING SITE, CFN 1411365 WAS CONFIRMED AS THE CURRENT ACTIVE MANUFACTURING SITE IN THE AMENDMENT SUBMITTED ON 1/14/09. THE BUILDING NUMBER HAS NOT BEEN SPECIFIED AS WAS DISCUSSED IN THE T-CON WITH FIRM AND OC ON 1/13/09. PLEASE UPDATE THE OC RECOMMENDATION FOR THIS SITE. NOTE THAT THE — FACILITY WOULD BE SUBMITTED POST-APPROVAL AS PER AMENDMENT DATED 12/8/08 AND T-CON OF 1/13/09 BETWEEN THE DIVISION, OC AND SPONSOR.

PLEASE UPDATE OVERALL OC RECOMMENDATION FOR THE APPLICATION.

NOTE THAT BUILDING — AT THIS ADDRESS PERFORMS DRUG PRODUCT RELEASE AND STABILITY TESTING. (on 15-JAN-2009 by D. CHRISTODOULOU
() 301-796-1342)

b(4)

FDA Contacts:	M. SULLIVAN	(HFD-170)	301-796-1245	, Project Manager
	O. STEPHENS	(HFD-170)	301-796-3901	, Review Chemist
	D. CHRISTODOULOU		301-796-1342	, Team Leader

O all Recommendation: ACCEPTABLE on 16-JAN-2009 by H. KIEL (HFD-323) 301-796-3246
ACCEPTABLE on 14-JUN-2006 by DAMBROGIOJ
ACCEPTABLE on 01-AUG-2005 by DAMBROGIOJ

Establishment: CFN 1411365 FEI 1411365
ABBOTT LABORATORIES
14TH & SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE WILL DO DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY
TESTING OF DRUG SUBSTANCE, RELEASE AND STABILITY TESTING OF DRUG
PRODUCT, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS FOR
DRUG PRODUCT. (on 18-JAN-2005 by S. LIN () 301-796-1403)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
----------------	------	------	------------	-------------------	---------

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC 18-JAN-2005 LINS
 SUBMITTED TO DO 18-JAN-2005 PS DAMBROGIOJ
 ASSIGNED INSPECTION T 27-JUN-2005 PS LJARRELL
 DO RECOMMENDATION 29-JUL-2005 ACCEPTABLE LJARRELL

BASED ON FILE REVIEW

PREVIOUS INSPECTION OF THIS SITE FOR PROFILE CLASS CSN WAS CONDUCTED ON 2/17/04 AND WAS FOUND ACCEPTABLE.

OC RECOMMENDATION 01-AUG-2005 ACCEPTABLE DAMBROGIOJ

DISTRICT RECOMMENDATION

SUBMITTED TO OC 13-JUN-2006 LINS

OC RECOMMENDATION 14-JUN-2006 ACCEPTABLE DAMBROGIOJ

BASED ON PROFILE

SUBMITTED TO OC 06-AUG-2008 ALHAKIMA

SUBMITTED TO DO 07-AUG-2008 GMP FERGUSONS

ASSIGNED INSPECTION T 04-SEP-2008 PS LJARRELL

INSPECTION PERFORMED 30-SEP-2008 30-SEP-2008 LJARRELL

THIS INSPECTION REVEALED FIRM DEMOLISHED THE BUILDINGS WHERE THE API WAS MANUFACTURED.

THEY INTEND TO BUT HAVE NOT UPDATED THE APPLICATION.

INSPECTION SCHEDULED 20-OCT-2008 30-SEP-2008 LJARRELL

b(4)

DO RECOMMENDATION 20-OCT-2008 WITHHOLD LJARRELL

DRUG NOT MADE HERE

SEE COMMENTS UNDER INSPECTION MILESTONE

OC RECOMMENDATION 20-OCT-2008 WITHHOLD CRUZC

DISTRICT RECOMMENDATION

INSPECTION REVEALED FIRM DEMOLISHED THE BUILDINGS WHERE THE API WAS MANUFACTURED. b(4)

FIRM INTENDS TO , BUT HAVE NOT UPDATED THE APPLICATION.

SUBMITTED TO OC 14-JAN-2009 CHRISTODOUL

OC RECOMMENDATION 16-JAN-2009 ACCEPTABLE KIEL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO DO	18-JAN-2005	PS		DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUN-2005	PS		LJARRELL
INSPECTION PERFORMED	29-JUL-2005		29-JUL-2005	LJARRELL

NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483 ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED VAI.

DO RECOMMENDATION	29-JUL-2005		ACCEPTABLE	LJARRELL
			INSPECTION	

INSPECTION CONDUCTED 7/13--29/05.

OC RECOMMENDATION	01-AUG-2005		ACCEPTABLE	DAMBROGIOJ
			DISTRICT RECOMMENDATION	

SUBMITTED TO OC	13-JUN-2006			LINS
-----------------	-------------	--	--	------

OC RECOMMENDATION	14-JUN-2006		ACCEPTABLE	DAMBROGIOJ
			BASED ON PROFILE	

SUBMITTED TO OC	06-AUG-2008			ALHAKIMA
-----------------	-------------	--	--	----------

SUBMITTED TO DO	07-AUG-2008	PS		FERGUSONS
-----------------	-------------	----	--	-----------

ASSIGNED INSPECTION T	04-SEP-2008	PS		LJARRELL
-----------------------	-------------	----	--	----------

INSPECTION PERFORMED	01-NOV-2008		01-NOV-2008	LJARRELL
----------------------	-------------	--	-------------	----------

NO SIGNIFICANT GMP ISSUES FOUND.

DO RECOMMENDATION	07-JAN-2009		ACCEPTABLE	LJARRELL
			INSPECTION	

INSPECTION CONDUCTED 10/29 - 11/5/08.

OC RECOMMENDATION	08-JAN-2009		ACCEPTABLE	FERGUSONS
			DISTRICT RECOMMENDATION	

Estab. Comment: THIS SITE WILL DO DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY
 TESTING OF DRUG SUBSTANCE, RELEASE AND STABILITY TESTING OF DRUG
 PRODUCT, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS FOR
 DRUG PRODUCT. (on 18-JAN-2005 by S. LIN () 301-796-1403)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-JAN-2005				LINS
SUBMITTED TO DO	18-JAN-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUN-2005	PS			LJARRELL
DO RECOMMENDATION	29-JUL-2005			ACCEPTABLE BASED ON FILE REVIEW	LJARRELL
PREVIOUS INSPECTION OF THIS SITE FOR PROFILE CLASS CSN WAS CONDUCTED ON 2/17/04 AND WAS FOUND ACCEPTABLE.					
OC RECOMMENDATION	01-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
SUBMITTED TO OC	13-JUN-2006				LINS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION 14-JUN-2006 ACCEPTABLE DAMBROGIOJ
BASED ON PROFILE

Establishment: CFN 1415939 FEI 1415939
ABBOTT LABORATORIES
100/200 ABBOTT PARK RD
ABBOTT PARK, IL 60064

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

Estab. Comment: THIS SITE WILL DO DRUG PRODUCT MANUFACTURING, PACKAGING, AND TESTING OF
COMPONENETS AND CONTAINER CLOSURE SYSTEMS. (on 18-JAN-2005 by S. LIN ()
301-796-1403)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-JAN-2005				LINS
SUBMITTED TO DO	18-JAN-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUN-2005	PS			LJARRELL
INSPECTION PERFORMED	29-JUL-2005		29-JUL-2005		LJARRELL

NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483
ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED
VAI.

COMMENDATION 29-JUL-2005 ACCEPTABLE LJARRELL
INSPECTION
INSPECTION CONDUCTED 7/13--29/05.
OC RECOMMENDATION 01-AUG-2005 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

SUBMITTED TO OC 13-JUN-2006

LINS

OC RECOMMENDATION 14-JUN-2006

ACCEPTABLE

DAMBROGIOJ

BASED ON PROFILE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21856/000	Action Goal:	
Stamp:	15-DEC-2004	District Goal:	16-AUG-2005
Regulatory Due:	15-OCT-2005	Brand Name:	ULORIC (FEBUXOSTAT)
Applicant:	TAP PHARM	Estab. Name:	80/120MG TABLETS
	675 NORTH FIELD DR	Generic Name:	FEBUXOSTAT
	LAKE FOREST, IL 60045		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	550	Strength:	80 MG & 120 MG

Application Comment:

Contacts: J. DEAN 301-827-2536 , Project Manager
S. LIN (HFD-550) 301-827-2525 , Review Chemist
J. SMITH (HFD-550) 301-827-2529 , Team Leader

Overall Recommendation: ACCEPTABLE on 01-AUG-2005 by J. D AMBROGIO (HFD-322) 301-827-
9049

Establishment: CFN 1411365 FEI 1411365
ABBOTT LABORATORIES
1401 14TH AND SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE

Escab. Comment: THIS SITE WILL DO DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY TESTING OF DRUG SUBSTANCE, RELEASE AND STABILITY TESTING OF DRUG PRODUCT, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS FOR DRUG PRODUCT. (on 18-JAN-2005 by S. LIN (HFD-550) 301-827-2525)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-JAN-2005				LINS
SUBMITTED TO DO	18-JAN-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUN-2005	PS			LJARRELL
DO RECOMMENDATION	29-JUL-2005			ACCEPTABLE BASED ON FILE REVIEW	LJARRELL
PREVIOUS INSPECTION OF THIS SITE FOR PROFILE CLASS CSN WAS CONDUCTED ON 2/17/04 AND WAS FOUND ACCEPTABLE.					
RECOMMENDATION	01-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN 1415939 FEI 1415939
 ABBOTT LABORATORIES
 100/200 ABBOTT PARK RD
 ABBOTT PARK, IL 60064

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

Estab. Comment: THIS SITE WILL DO DRUG PRODUCT MANUFACTURING, PACKAGING, AND TESTING OF
 COMPONENTS AND CONTAINER CLOSURE SYSTEMS. (on 18-JAN-2005 by S. LIN
 (HFD-550) 301-827-2525)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-JAN-2005				LINS
SUBMITTED TO DO	18-JAN-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUN-2005	PS			LJARRELL
INSPECTION PERFORMED	29-JUL-2005		29-JUL-2005		LJARRELL

NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483
 ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED
 VAI.

DO RECOMMENDATION 29-JUL-2005 ACCEPTABLE LJARRELL
 INSPECTION

INSPECTION CONDUCTED 7/13--29/05.

CC RECOMMENDATION 01-AUG-2005 ACCEPTABLE DAMBROGIOJ
 DISTRICT RECOMMENDATION