CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-168

CSO LABELING REVIEW(S)

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

ANDA Number: 76-168 Date of Submission: January 11, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   As addressed in the last deficiency letter, pending resolution of the Citizen Petition filed on September 18, 2001, regarding Oxycontin® (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg, we defer labeling comments specifically associated with your proposed 160 mg tablets.

2. CONTAINER – 100s

   a. We note that you did not respond to our comment "Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06." in the last deficiency letter. Please respond.

   b. We note that you submitted your draft container labels for the 80 mg strength only. Please include your proposal for the 160 mg strength in your next submission if you are still seeking for the approval of 160 mg tablets.

3. PATIENT INFORMATION LEAFLET

   a. Please submit you proposal for this labeling piece to be in accordance with the attached patient information leaflet approved on January 15, 2002 for the reference listed drug, Oxycontin Controlled Release Tablets . In addition, describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets you will supply for each container size and how these leaflets will be supplied for dispensing to the patients.

   b. Please ensure that the full text of this patient information is also reprinted at the end of the insert labeling. In addition, this patient information must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

4. INSERT

   a. DESCRIPTION

      As we addressed in the last deficiency letter, we note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.,* [redacted]. Please revise and/or comment.

   b. DRUG ABUSE AND ADDICTION - Include the following subsection immediately following the "Respiratory Depression" subsection.

      Head Injury

      Oxycodone may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure ahs been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone

may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

c. PRECAUTIONS

See comment (a) under PATIENT INFORMATION LEAFLET

d. DOSAGE AND ADMINISTRATION

i. General Principles - Sixth paragraph, second sentence:

...allows the oxycodone tablets to be... [rather than "

ii. Initiation of Therapy - Item #1 following the paragraph "Oxycodone...side effects.".

...estimates (see Table 4 below), multiply... [rather than "

e. HOW SUPPLIED

See comment (b) under PATIENT INFORMATION LEAFLET.

Please revise your labels and labeling, as instructed above and submit in draft. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

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

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.

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

Attachment: A copy of Patient Information Leaflet approved for Oxycontin Controlled Release Tablets

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (a) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.

3. It is NOT a subject of a USP monograph.

4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). See comment under DESCRIPTION.

6. Patent Data

020553	**001**	**4861598**	**AUG 29,2006**
020553	**001**	**4970075**	**NOV 13,2007**
020553	**001**	**5266331**	**FEB 05,2008**
020553	**001**	**5508042**	**APR 16,2013**
020553	**001**	**5549912**	**FEB 05,2008**
020553	**001**	**5656295**	**FEB 05,2008**

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATINETS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has bee carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. Refer to the general comment. The following is the e-mail correspondences in this regard (1/28/02).

   Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

10. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

11. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s for both strengths

12. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

13. SCORING – Both RLD and ANDA unscored.

14. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, [illegible] cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

15. RLD employees a specific delivery form of "[illegible] tablet. ANDA proposes [illegible] tablets. The sponsor did not include any specific information associated with the " [illegible] tablet.

16. Teva is the manufacturer of this drug product.

Date of Review: November 1, 2001 **Date of Submission: January 11, 2001**

Primary Reviewer: Chan Park **Date:** 2/1/02

Team Leader: Charlie Hoppes **Date:** 2/1/02

cc:

ANDA: 76-168
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: 76-168 Date of Submission: May 8, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   Include the phrase "[see USP]" in the storage temperature statement.

2. CONTAINER – 100s

   a. See GENERAL COMMENT above.

   b. We encourage the increase of prominence for the statements "Swallow tablets whole. Do not crush or chew." by printing in bold face type or any other means.

   c. Please assure that the controlled substances symbol appear clear and large enough. We refer you to 21 CFR 1302.04 for guidance.

   d. Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06.

3. INSERT

   a. GENERAL

      i. Please note that the insert labeling for the reference listed drug, OxyContin® was last approved on July 18, 2001. Please revise your insert labeling in accordance with the attached OxyContin® insert labeling. In addition, we have the following comments.

      ii. It is preferable to use the term "mcg" rather than ' — throughout the text.

      iii. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.

      iv. Revise to read "mL" rather than ″— throughout the text.

      v. Italicize the terms *in vivo* throughout the text.

      vi. We believe that the information regarding dose proportionality for all strengths should be included in your insert labeling including the tables.

   b. DESCRIPTION

      i. ...4,5-Epoxy14 - ... [note upper case "E" per USP 24]

ii. Revise the molecular weight to read "351.82" per USP 24.

iii. We note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.*, [redacted]. Please revise and/or comment.

iv. Last paragraph, last sentence – Revise to read:

Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal...

c. CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism

This is a subsection heading. Please reduce the prominence so that it is differentiated from section headings.

d. INDICATIONS AND USAGE

...tablets are an extended-release oral... [add "extended-release"]

e. HOW SUPPLIED

See GENERAL COMMENT above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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

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.

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

Attachment: A copy of last approved innovator's insert labeling

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (d) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022). The insert labeling was last approved on July 18, 2001.

2. It is NOT a subject of a USP monograph.

3. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be inconsistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2.

5. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

6. The innovator markets 10, 20, 40, 80, and 160 mg strengths whereas the sponsor proposed only 80 mg strength. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATINETS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo).

7. Since two tablets of 80 mg can be administered in lieu of one 160 mg tablet, we will retain any specific information pertaining to the 160 mg tablet.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

   ANDA: CRT, See general comment.

9. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

10. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s.

11 The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951.

12. SCORING – Both RLD and ANDA unscored.

13. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s CRC. — cap) with Liner (p.3893, B .1.2)

14. RLD employees a specific delivery form of "— tablet. ANDA proposes ' — tablets. The sponsor did not include any specific information associated with the "— tablet.

15. Teva is the manufacturer of this drug product.

Date of Review: August 1, 2001 **Date of Submission: May 8, 2001**

Primary Reviewer: Chan Park 8/2/01 **Date:**

Team Leader: Charlie Hoppes 8/2/01 **Date:**

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ANDA: 76-168
DUP/DIVISION FILE
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Review

(This review supersedes the one prepared on 8/1/01)
EVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168 Date of Submission: May 8, 2001 and July 25, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   Include the phrase "[see USP]" in the storage temperature statement.

2. CONTAINER – 100s

   a. See GENERAL COMMENT above.

   b. We encourage the increase of prominence for the statements "Swallow tablets whole. Do not crush or chew." by printing in bold face type or any other means.

   c. Please assure that the controlled substances symbol appear clear and large enough. We refer you to 21 CFR 1302.04 for guidance.

   d. Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06.

   e. We encourage you to differentiate your drug products of different strengths by using boxing, contrasting colors, and/or some other means.

3. INSERT

   a. GENERAL

      i. Please note that the insert labeling for the reference listed drug, OxyContin® was last approved on July 18, 2001. Please revise your insert labeling in accordance with the attached OxyContin® insert labeling. In addition, we have the following comments.

      ii. It is preferable to use the term "mcg" rather than "— throughout the text.

      iii. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.

      iv. Revise to read "mL" rather than "— throughout the text.

      v. Italicize the terms *in vivo* throughout the text.

      vi. We believe that the information regarding dose proportionality for all strengths should be included in your insert labeling including the tables.

b. DESCRIPTION

i. ...4,5-Epoxy14 - ... [note upper case "E" per USP 24]

ii. Revise the molecular weight to read "351.82" per USP 24.

iii. We note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.,* ' Please revise and/or comment.

iv. Last paragraph, last sentence – Revise to read:

Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal...

c. CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism

This is a subsection heading. Please reduce the prominence so that it is differentiated from section headings.

d. INDICATIONS AND USAGE

...tablets are an extended-release oral... [add "extended-release"]

e. HOW SUPPLIED

See GENERAL COMMENT above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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

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.

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

Attachment: A copy of last approved innovator's insert labeling

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (d) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022). The insert labeling was last approved on July 18, 2001.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). See comment under DESCRIPTION.
6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

7. The innovator markets 10, 20, 40, 80, and 160 mg strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATINETS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo).
8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted

between 15oC (59oF) and 30oC (86oF).

ANDA: CRT, See general comment.

9. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

10. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s for both strengths

11 The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

12. SCORING – Both RLD and ANDA unscored.

13. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, —cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

14. RLD employees a specific delivery form of "—tablet. ANDA proposes —tablets. The sponsor did not include any specific information associated with the "—tablet.

15. Teva is the manufacturer of this drug product.

Date of Review: August 9, 2001

Date of Submission: May 8, 2001 & July 25, 2001

Primary Reviewer: Chan Park C Park **Date:** 8/10/01

Team Leader: Charlie Hoppes **Date:** 8/10/01

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ANDA: 76-168
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Review

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

ANDA Number: 76-168 Date of Submission: January 11, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   As addressed in the last deficiency letter, pending resolution of the Citizen Petition filed on September 18, 2001, regarding Oxycontin® (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg, we defer labeling comments specifically associated with your proposed 160 mg tablets.

2. CONTAINER – 100s

   a. We note that you did not respond to our comment "Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06." in the last deficiency letter. Please respond.

   b. We note that you submitted your draft container labels for the 80 mg strength only. Please include your proposal for the 160 mg strength in your next submission if you are still seeking for the approval of 160 mg tablets.

3. PATIENT INFORMATION LEAFLET

   a. Please submit you proposal for this labeling piece to be in accordance with the attached patient information leaflet approved on January 15, 2002 for the reference listed drug, Oxycontin Controlled Release Tablets . In addition, describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets you will supply for each container size and how these leaflets will be supplied for dispensing to the patients.

   b. Please ensure that the full text of this patient information is also reprinted at the end of the insert labeling. In addition, this patient information must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

4. INSERT

   a. DESCRIPTION

      As we addressed in the last deficiency letter, we note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.,* _____ . Please revise and/or comment.

   b. DRUG ABUSE AND ADDICTION - Include the following subsection immediately following the "Respiratory Depression" subsection.

      Head Injury

      Oxycodone may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone

may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

c. PRECAUTIONS

See comment (a) under PATIENT INFORMATION LEAFLET

d. DOSAGE AND ADMINISTRATION

i. General Principles - Sixth paragraph, second sentence:

...allows the oxycodone tablets to be... [rather than "

ii. Initiation of Therapy - Item #1 following the paragraph "Oxycodone...side effects.".

...estimates (see Table 4 below), multiply... [rather than "

e. HOW SUPPLIED

See comment (b) under PATIENT INFORMATION LEAFLET.

Please revise your labels and labeling, as instructed above and submit in draft. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

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

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.

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

Attachment: A copy of Patient Information Leaflet approved for Oxycontin Controlled Release Tablets

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

ANDA Number: 76-168 Date of Submission: May 7, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. CONTAINER – 100s

   a. We encourage the increase of prominence for the statement "for use in opioid tolerant patients".

   b. We encourage you to differentiate your drug products of different strengths by using boxing, contrasting colors, and/or some other means.

2. INSERT

   PRECAUTIONS (Information for Patients/Caregivers) - Revise to read:

   (see **PATIENT INFORMATION** at the end of the package insert)

3. PATIENT INFORMATION - How Should I Take Oxycodone Hydrochloride Extended Release Tablets?

   We believe that your drug product does not contain a specific delivery form of "——— tablet" used by the innovator. Please delete the last bullet and/or comment.

Please revise your labels and labeling, as instructed above. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

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

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.

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

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.

3. It is NOT a subject of a USP monograph.

4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). [redacted] is [redacted] and USP preferred name for [redacted] is Triacetin.

6. **Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has been carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. Refer to the

general comment. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Parice on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170).". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn form the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). The innovator's labeling for Oxycontin still retains all information on 160 mg strength. Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s for both strengths

14. The sponsor will use the [redacted] manufactured by [redacted] to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, [redacted]cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

18. RLD employs a specific delivery form of "[redacted] tablet. ANDA proposes [redacted] tablets. The sponsor did not include any specific information associated with the "[redacted] tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: June 3, 2002 **Date of Submission: May 7, 2002**

Primary Reviewer: Chan Park C Park **Date:** 6/3/02

Acting Team Leader: Lillie Golson **Date:**

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cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76168na4.LABELING.doc
Review

(This AP summary supersedes the one prepared 8/8/03)

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168 Date of Submission: February 5, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

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 - 100s

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 2)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 3, Rev. 6/03)

PATIENT PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 4, Rev. 6/03)

REVISIONS NEEDED POST-APPROVAL - INSERT (Adverse Reactions)

1. **Table 3:**

   Add "Tablets" to the title of second column to read "Immediate-Release Tablets".

2. Revise the "General" subsection of ADVERSE REACTIONS section to read "pain, *and symptoms associated with either on anaphylactic or anaphylactoid reaction*" as instructed by the Agency. [Add ",*and symptoms associated with either on anaphylactic or anaphylactoid reaction*"]. The sponsor made a commitment to this revision in the amendment dated 2/5/04.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: OxyContin® controlled-release tablets (20-553/S-035).
The insert labeling was last approved on November 20, 2003. The patient information leaflet (S-024) was approved January 15, 2002.

NDA Number: 20-553

NDA Drug Name: OxyCotin® tablets

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:

S-035/November 20, 2003 (package insert)
S-024/January 15, 2002 (patient information leaflet)

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-side comparisons

Other Comments:

The sponsor withdrew the proposal for the 160 mg strength.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-035). The insert labeling was last approved on November 20, 2003. The patient information leaflet (S-024) was approved January 15, 2002.

2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength. **Then, the sponsor withdrew the proposal for the 160 mg strength in the amendment of May 5, 2003.** See FTR 8 & 10 below.

3. It is NOT a subject of a USP monograph.

4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). [redacted] and USP preferred name for [redacted] is Triacetin.

6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Patent Cert	Labeling Impact
020553	004	4861598	AUG 29,2006		IV	No
020553	004	4970075	AUG 29,2006		IV	No
020553	004	5266331	OCT 26,2007		IV	No
020553	004	5508042	APR 16,2013	U-443	IV	No
020553	004	5549912	OCT 26,2007		IV	No
020553	004	5656295	OCT 26,2007	U-443	IV	No

U-443 - Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor initially proposed only 80 mg and 160 mg strengths, but withdrew the 160 mg strength later on. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice in the past. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg has been carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170).". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of

discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn form the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne, Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question – is that a "safety" reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). **The innovator's labeling for Oxycontin still retains all information on 160 mg strength.** Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: Container - Store at controlled room temperature, between 15° and 30°C (59° and 86°F) [see USP].

Insert Labeling - Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). See GENERAL comment above.

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s

14. The sponsor will use the ——, manufactured by —— to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg).

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

    Container – HDPE

    Closure – 100s (CRC, [redacted] cap) with Liner (p.3893, B .1.2)

18. RLD employs a specific delivery form of [redacted] tablet. ANDA proposes [redacted] tablets. The sponsor did not include any specific information associated with the "[redacted]" tablet.

19. Teva is the manufacturer of this drug product.

20. The sponsor proposed one PPI per a bottle of 100 tablets. I called the firm and spoke with Mr. Philip Erickson on this proposal on August 8, 2003. He stated that their proposal is the same as the innovator's.

21. The sponsor is in the process of getting approval for the Risk Management Program. It was submitted per the new drug division to follow the lead of the innovator and is currently under review by the division.

22. OGD will issue an AP letter prior to the implementation of the Risk Management Program. However, OGD will not permit marketing of this drug product until after the implementation of the approved RPM.

Date of Review: 2/12/04 **Date of Submission: July 2, 2003 & 2/5/04**

Primary Reviewer: Chan Park Date: 2/12/04

Team Leader: Lillie Golson Date: 2/18/04

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cc:

ANDA: 76-168
DUP/DIVISION FILE
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Review

(NOT FINAL, CITIZEN'S PETITION NEEDS TO BE RESOLVED)
(TENTATIVE APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168 Date of Submission: June 25, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

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

Do you have 12 Final Printed Labels and Labeling? No

CONTAINER LABELS -100s

Satisfactory in **draft** as of 6/25/02 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in **draft** as of 6/25/02 submission

PATIENT PACKAGE INSERT LABELING:

Satisfactory in **draft** as of 6/25/02 submission

REVISIONS NEEDED POST-APPROVAL:

None

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No (Not sure yet)

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

NDA Number: 20-553

NDA Drug Name: Oxycontin®

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:

July 18, 2001/S-022 (Package insert)

January 15, 2002/S-024 (PPI)

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

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.

3. It is NOT a subject of a USP monograph.

4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). [redacted], is [redacted] and USP preferred name for [redacted] is Triacetin.

6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	**001**	**4861598**	**AUG 29,2006**	
020553	**001**	**4970075**	**NOV 13,2007**	
020553	**001**	**5266331**	**FEB 05,2008**	
020553	**001**	**5508042**	**APR 16,2013**	
020553	**001**	**5549912**	**FEB 05,2008**	
020553	**001**	**5656295**	**FEB 05,2008**	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
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5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has been carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R

tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

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Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

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9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

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Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn form the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne, Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question -- is that a "safety"

reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). The innovator's labeling for Oxycontin still retains all information on 160 mg strength. Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s for both strengths

14. The sponsor will use the ———, manufactured by ——— to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, — cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

18. RLD employs a specific delivery form of "— tablet. ANDA proposes ——— tablets. The sponsor did not include any specific information associated with the "— tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: July 22, 2002 **Date of Submission: June 25, 2002**

Primary Reviewer: Chan Park C Park **Date:** 7/31/02

Acting Team Leader: Lillie Golson L D Golson **Date:** 7/31/02

This review supersedes the TAP summary prepared on 7/22/02.

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

ANDA Number: 76-168 Date of Submission: May 5, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   a. We acknowledge that you withdrew your proposal for the 160 mg tablet.

   b. Revise the storage temperature statement to read "Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature]"

   c. Upon further review, we have the following comments on your container labels submitted on June 25, 2002.

      i. See comment (b) above.

      ii. We encourage you to revise to read "Each film-coated tablet contains:". add "film-coated"]

      iii. Revise to read "...Do not break, crush or chew". [add "break"]

2. INSERT

   a. GENERAL

      Replace the term [redacted] appearing in the innovator's labeling with "oxycodone HCl extended-release tablets" rather than "[redacted]" throughout the text of your insert labeling.

   b. TITLE

      Please increase the prominence of the boxed statement.

   c. DESCRIPTION

      Please revise "[redacted] to read "Hypromellose" and include its substitution type and its viscosity type as required by USP. We refer you to USP 26.

   d. CLINICAL PHARMACOLOGY

      i. Delete the subsection heading "[redacted]

      ii. Absorption:

         Revise the first sentence of the second paragraph to read "...20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for...". We believe that it may be beneficial to the health practitioners to include all strengths in the text regarding dose proportionality although you will not be marketing the

160 mg strength. We also refer you to the third paragraph of the "Pharmacokinetics and Metabolism" subsection.

iii. Table 1 - Multiple Dose

10 mg oxycodone hydrochloride extended-release tablets q12h [add "extended-release"]

iv. Include Table 2 as found in the innovator's labeling. Please refer to the comment d(ii) above.

e. DRUG ABUSE AND ADDICTION (Head Injury) - Revise to read:

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

f. ADVERSE REACTIONS - Table 3:

Add "Tablets" to read "...Extended-Release Tablets". [2 instances]

g. HOW SUPPLIED

i. We encourage the Inclusion of the name and place of business and the revision date.

ii. See GENERAL comment above.

4. PATIENT INFORMATION LEAFLET

a. Who Should Not ...tablets if - 5th bullet:

Include a disclaimer for Tylex, Tylenol with Codeine, and Vicodin" at the end of the labeling.

b. We encourage the inclusion of the storage temperature statement.

c. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets you will supply for each container of 100 tablets and how these leaflets will be supplied.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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.

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

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength. **Then, the sponsor withdrew the proposal for the 160 mg strength in the amendment of May 5, 2003.** See FTR 8 & 10 below.

3. It is NOT a subject of a USP monograph.

4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). is and USP preferred name for is Triacetin.

6. Patent Data

App I No	Prod No	Patent No	Patent Expiration	Use Code
020553	004	4861598	AUG 29,2006	
020553	004	4970075	AUG 29,2006	
020553	004	5266331	OCT 26,2007	
020553	004	5508042	APR 16,2013	U-443
020553	004	5549912	OCT 26,2007	
020553	004	5656295	OCT 26,2007	U-443

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor initially proposed only 80 mg and 160 mg strengths, but withdrew the 160 mg strength later on. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice in the past. This decision was made at the time or review of ANDA

75-923 (Endo). However, any other specific information associated with other strengths than 80 mg has been carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170).". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn form the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne,

Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question -- is that a "safety" reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). **The innovator's labeling for Oxycontin still retains all information on 160 mg strength.** Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: Container - Store at controlled room temperature, between 15° and 30°C (59° and 86°F) [see USP].

Insert Labeling - Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). See GENERAL comment above.

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s

14. The sponsor will use the [redacted], manufactured by [redacted] to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg).

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, [redacted] cap) with Liner (p.3893, B .1.2)

18. RLD employs a specific delivery form of "[redacted] tablet. ANDA proposes [redacted] tablets. The sponsor did not include any specific information associated with the "[redacted] tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: May 29, 2003 **Date of Submission: June 25, 2002 and May 5, 2003**

Primary Reviewer: Chan Park **Date:** 5/30/03

Team Leader: Lillie Golson **Date:** 5/30/03

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

Superseded by the AP summary prepared on 2/12/04 C Park 2/17/04

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168 Date of Submission: July 2, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

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 - 100s

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 2)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 3, Rev. 6/03)

PATIENT PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 4, Rev. 6/03)

REVISIONS NEEDED POST-APPROVAL - INSERT (Adverse Reactions) - Table 3:

Add "Tablets" to the title of second column to read "Immediate-Release Tablets".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: OxyContin® controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

NDA Number: 20-553

NDA Drug Name: OxyCotin® tablets

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:
S-022 and S-024/July 18, 2001 & January 15, 2002

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-side comparisons

Other Comments:

The sponsor withdrew the proposal for the 160 mg strength.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

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020553	004	5549912	OCT 26,2007	
020553	004	5656295	OCT 26,2007	U-443

U-443 - Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Exclusivity Data

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The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

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Container – HDPE

Closure – 100s (CRC [redacted] cap) with Liner (p.3893, B .1.2)

18. RLD employs a specific delivery form of '[redacted]' tablet. ANDA proposes [redacted] tablets. The sponsor did not include any specific information associated with the "[redacted]" tablet.

19. Teva is the manufacturer of this drug product.

20. The sponsor proposed one PPI per a bottle of 100 tablets. I called the firm and spoke with Mr. Philip Erickson on this proposal on August 8, 2003. He stated that their proposal is the same as the innovator's.

Date of Review: August 8, 2003 **Date of Submission: July 2, 2003**

Primary Reviewer: Chan Park **Date:** 8/12/03

Team Leader: Lillie Golson **Date:** 8/12/03

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cc:

ANDA: 76-168
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Review

APPEARS THIS WAY
ON ORIGINAL