

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213674Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 20, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 213674
Product Name and Strength:	Xtandi (enzalutamide) tablets, 40 mg and 80 mg
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
OSE RCM #:	2019-2337-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 19, 2020 for Xtandi. Division of Oncology 1 (DO1) requested that we review the revised container labels and carton labeling for Xtandi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Gao, T. Label and Labeling Review for Xtandi (NDA 213674). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 19. RCM No.: 2019-2337.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 7, 2020

To: Alice Lee, PharmD
Regulatory Project Manager
Division of Oncology 1 (DO 1)

William Pierce, PharmD, Associate Director for Labeling, DO 1

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xtandi (enzalutamide) tablets, for oral use

NDA: 213674

In response to DO 1's consult request dated December 9, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Xtandi (enzalutamide) tablets, for oral use. OPDP's review of the proposed PI and carton and container labeling was filed May 6, 2020.

OPDP has reviewed the draft PPI received by electronic mail from DO 1 on April 29, 2020 (attached for reference), and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer, PharmD at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 6, 2020

To: Alice Lee, PharmD
Regulatory Project Manager
Division of Oncology 1 (DO 1)

William Pierce, PharmD, Associate Director for Labeling, DO 1

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xtandi (enzalutamide) tablets, for oral use

NDA: 213674

In response to DO 1's consult request dated December 9, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Xtandi (enzalutamide) tablets, for oral use.

PI and PPI: OPDP has reviewed the draft PI received by electronic mail from DO 1 on April 29, 2020 (attached for reference), and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on April 29, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer, PharmD at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 6, 2020

To: Alice Lee, PharmD
Division of Oncology I (DO1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted: Patient Package Insert (PPI)

Drug Name (established name): XTANDI (enzalutamide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213674

Applicant: Astellas Pharma US, Inc.

1 INTRODUCTION

On October 30, 2019, Astellas Pharma US, Inc. submitted for the Agency's review an original New Drug Application (NDA) 213674 for XTANDI (enzalutamide) tablets. This NDA proposes an alternative immediate-release dosage form as a 40 mg and 80 mg film-coated tablet. There is a currently approved product, NDA 203415, for XTANDI (enzalutamide) immediate-release 40 mg soft gelatin capsule.

On December 9, 2020, the Division of Oncology I (DOI) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for XTANDI (enzalutamide) tablets.

2 MATERIAL REVIEWED

- Draft XTANDI (enzalutamide) tablets PPI received on October 30, 2019, and received by DMPP and OPDP on April 29, 2020.
- Draft XTANDI (enzalutamide) tablets PPI Prescribing Information (PI) received on October 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 29, 2020.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 19, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 213674
Product Name, Dosage Form, and Strength:	Xtandi (Enzalutamide) tablets, 40 mg and 80 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
FDA Received Date:	December 20, 2019
OSE RCM #:	2019-2337
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the review process for Xtandi (Enzalutamide) tablets, the Division of Oncology 1 (DO1) requested that we review the proposed Xtandi prescribing information (PI), Patient Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Xtandi was approved in 2012 and is currently marketed as 40 mg capsules. Astellas proposed the tablet formulation in strengths of 40 mg and 80 mg to help address the needs of patients who have difficulty swallowing and to reduce pill burden.^a Furthermore, Astellas Pharma stated

(b) (4)

and that Xtandi is primarily dispensed in the special pharmacy in their December 5, 2019 request for proprietary name review submission.^b

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a Xtandi® (enzalutamide, MDV3100). 2.2 Introduction. Northbrook (IL): Astellas Pharma US, Inc. 2019 Oct 30. Available from: [\\cdsesub1\evsprod\nda213674\0001\m2\22-intro\2-2-introduction-tablet-2.pdf](#).

^b Request for Proprietary Name Review. Enzalutamide Tablets. NDA 213674. 2019 Dec 5. Northbrook (IL): Astellas Pharma US, Inc. Available from: [\\cdsesub1\evsprod\nda213674\0003\m1\us\proprietary-name-request-05dec19-final.pdf](#)

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed Xtandi tablets have the same 40 mg strength as the currently marketed 40 mg capsules, and one additional strength of 80 mg. The proposed Xtandi tablets also have the same indication and recommended dosage as the currently marketed Xtandi capsules. Furthermore, the Review Team confirmed that the proposed Xtandi tablets are substitutable with Xtandi capsules on a milligram-to-milligram basis. Therefore, we do not anticipate the proposed Xtandi tablets to introduce any new risk of medication errors.

3.1 PRESCRIBING INFORMATION (PI) AND PATIENT INFORMATION (PPI)

We reviewed Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information, and find the proposed changes acceptable from a medication error perspective.

3.2 CONTAINER LABELS AND CARTON LABELING

The proposed container label and carton labeling may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed Xtandi PI and Patient Information are acceptable from a medication error perspective. The proposed Xtandi container labels and carton labeling may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)

1. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of similar numbers for the middle digits is not an effective differentiating feature (e.g., -0625- for the 40 mg, and -0725- for the 80 mg). Revise the product code in the NDC numbers to ensure that the middle 4 digits are not similar between the strengths. If for some reason that middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.

B. Container Labels

1. Revise the statement: (b) (4) to read “Recommended Dosage: See prescribing information” to be consistent with the terminology used in the Prescribing Information.

2. Add the storage information in Celsius to ensure consistency with the storage information presented on the carton labeling and the Prescribing Information.
3. As currently presented, the format for the expiration date is “MM YYYY”. However, it is unclear whether the month (MM) will be displayed using numerical (for example, 06) or alphabetical (for example, JU) characters. Therefore, we were not able to assess the appropriateness of the proposed expiration date format from a medication safety perspective. Please clarify whether you propose to use only numerical characters for the expiration date, or whether you propose to use alphabetical characters for the month. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. See Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers>.

C. Carton Labeling

1. Revise the statement (b) (4) to “Recommended Dosage: See prescribing information” to be consistent with the terminology used in the Prescribing Information.
2. As currently presented, there is no product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The draft guidance is available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xtandi received on December 20, 2019 from Astellas Pharma US, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Xtandi and the Listed Drug		
Product Name	Xtandi capsules^c NDA 203415	Xtandi tablets NDA 213674
Initial Approval Date	August 31, 2012	N/A
Active Ingredient	Enzalutamide	Enzalutamide
Indication	treatment of patients with castration-resistant prostate cancer	treatment of patients with castration-resistant prostate cancer
Route of Administration	Oral	Oral
Dosage Form	Capsules	tablets
Strength	40 mg	40 mg and 80 mg
Dose and Frequency	Recommended dose: 160 mg once daily If a patient experiences a $\geq$ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to $\leq$ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted	
How Supplied	Bottle of 120 capsules	40 mg: Bottle of 120 tablets 80 mg: Bottle of 60 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F)	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	packaged and supplied in 300-cc, white opaque high density polyethylene (HDPE) bottles with 53-mm (b) (4) closures lined with induction seals.	packaged in 75-cc high density polyethylene (HDPE) bottles with child resistant closures.

^c Xtandi [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 July 13. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203415Orig1s014lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 15, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Xtandi. Our search identified 3 previous reviews^{d,e,f}, and we considered our previous recommendations to see if they are applicable for this current review.

^d DeFronzo, K. Label and Labeling Review for Xtandi (NDA 203415). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JULY 11. RCM No.: 2012-1216.

^e Brave, M and S. Christopher Jones. FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis for Xtandi (NDA 203415). Silver Spring (MD): FDA, CDER (US); 2016 May 24. Panorama No.: 2015-2220.

^f Gao, T. Label and Labeling Review for Xtandi (NDA 203415/S-014). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Mar 20. RCM No.: 2018-326.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^g along with postmarket medication error data, we reviewed the following Xtandi labels and labeling submitted by Astellas Pharma US, Inc.

- Container labels received on December 20, 2019
- Carton labeling received on December 20, 2019
- Patient Information (Image not shown) received on December 20, 2019, available from <\\cdsesub1\evsprod\nda213674\0005\m1\us\234833-xta-usa-annotated-tablets-17dec2019.doc>
- Prescribing Information (Image not shown) received on December 20, 2019, available from <\\cdsesub1\evsprod\nda213674\0005\m1\us\234833-xta-usa-annotated-tablets-17dec2019.doc>

^g Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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