

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213674Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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)

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Date of This Review:	February 10, 2020
Application Type and Number:	NDA 213674
Product Name 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. (Astellas Pharma)
Panorama #:	2019-36242780
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Xtandi, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Astellas Pharma did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Xtandi (enzalutamide) capsules, 40 mg, was approved on August 31, 2012 under NDA 203415. Astellas Pharma submitted the name, Xtandi, for the proposed new dosage form tablets for review under NDA 213674 on December 5, 2019. 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.^a

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on December 5, 2019.

Table 1. Relevant Product Information for Xtandi		
Product Name	Xtandi (NDA 203415) ^b	Xtandi (NDA 213674)
Intended Pronunciation	ex-TAN-dee	ex-TAN-dee
Initial Approval Date	August 31, 2012	Under review
Active Ingredient	enzalutamide	enzalutamide
Indication	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	

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

^b Xtandi. [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. July 2018. [cited 2019 Dec 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203415Orig1s014lbl.pdf.

Table 1. Relevant Product Information for Xtandi		
Product Name	Xtandi (NDA 203415)^b	Xtandi (NDA 213674)
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)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Xtandi.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Xtandi would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Oncology 1 (DO1) concurred with the findings of OPDP's assessment for Xtandi.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Xtandi.

2.2.1 *United States Adopted Names (USAN) Search*

There is no USAN stem present in the proposed proprietary name^c.

2.2.2 *Components of the Proposed Proprietary Name*

Astellas Pharma indicated in their submission that the proposed proprietary name, Xtandi, is an FDA approved proprietary name. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 *Comments from Other Review Disciplines at Initial Review*

In response to the OSE, December 20, 2019 e-mail, the Division of Oncology 1 (DO1) did not forward any comments or concerns relating to Xtandi at the initial phase of the review.

2.2.4 *Safety Analysis of Multiple Dosage Forms Under the Same Proprietary Name*

Xtandi 40 mg capsules were approved in 2012. Astellas Pharma now proposes tablets in 40 mg and 80 mg to be marketed under the same name, Xtandi. We considered the appropriateness of using the proprietary name, Xtandi, for the tablet formulation proposed under NDA 213674,

^c USAN stem search conducted on December 12, 2019.

which would represent an extension for this product line. We note that the Xtandi capsules and the proposed tablets share the same active ingredient, indication, strength (40 mg), recommended dosage (160 mg), and routes and frequencies of administration (see Table 1). While the Review Team's evaluation on bioequivalence of the proposed tablets to the capsules is ongoing, the proposed tablets appear to be bioequivalent to the currently approved capsules based on the Review Team's current analysis at the time of this name review. Additionally, the proposed additional 80 mg strength for the tablet formulation facilitates the 160 mg recommended dosage by reducing the number of tablets needed for the dose (from four 40 mg capsules to two 80 mg tablets).

It is common and accepted practice to have a product line with multiple dosage forms share one proprietary name and, while we note the dosage forms are different, these differences can be managed via labeling. Provided that the review team confirms that these products are bioequivalent and have no clinically significant differences, we do not anticipate this product line extension will introduce clinically significant medication errors related to switching between these dosage forms. Also, our routine postmarket safety surveillance did not identify any medication error related proprietary name confusion with Xtandi that is relevant for this review.

Therefore, we find it acceptable for the proposed tablet formulation to be marketed under the same proprietary name, Xtandi.

2.2.5 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Oncology 1 (DO1) via e-mail on February 3, 2020. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Oncology 1 (DO1) on February 10, 2020, they stated no additional concerns with the proposed proprietary name, Xtandi.

3 CONCLUSION

The proposed proprietary name, Xtandi, is acceptable.

If you have any questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

3.1 COMMENTS TO ASTELLAS PHARMA US, INC.

We have completed our review of the proposed proprietary name, Xtandi, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on December 5, 2019, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. *USAN Stems* (<https://www.ama-assn.org/about/united-states-adopted-names-approved-stems>)

USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.^d

^d National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:
- Highly similar pair: combined match percentage score $\geq 70\%$.
 - Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.

- Low similarity: combined match percentage score $\leq 54\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
 - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names^c. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
 - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign

^c Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq 70\%$).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 55\%$ to $\leq 69\%$).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) - Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. - Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. - Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names? - Is there different number or placement of cross-stroke or dotted letters present in the names? - Do the infixes of the name appear dissimilar when scripted? - Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) - Do the names have different number of syllables? - Do the names have different syllabic stresses? - Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? - Across a range of dialects, are the names consistently pronounced differently?
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Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 54\%$).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

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/s/

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