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May 21, 2021

Dr Benedikt Huttner,
The Secretary of the Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
CH-1211 Geneva 27

Sent via email: emlsecretariat@who.int

Re: Comments on the proposal for the inclusion of enzalutamide in the WHO model list of essential medicines entitled "Proposal for the Inclusion of Enzalutamide in the WHO Model List of Essential Medicines for the Treatment of Metastatic Castration Resistant Prostate Cancer."

Dear Dr Huttner:

Astellas Pharma, Inc. ("Astellas") is dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. As a manufacturer and distributor of enzalutamide, Astellas appreciates the opportunity to submit comments to the review document recommending the inclusion of enzalutamide to the WHO Model List of Essential Medicines for the treatment of metastatic castration-resistant prostate cancer.

As noted in previously submitted comments, Astellas believes that the WHO Essential Medicines List should continue to be used for the purpose it was originally created for: to serve as a guide for countries in making their own decisions about the medicines in their own formularies and appropriate procurement of those medicines. Our comments today focus on clarifying some of the statements and correcting some errors/omissions in the application.

Availability

The application initially notes the availability of two manufacturers of enzalutamide, including Astellas and Glenmark Pharmaceuticals, headquartered in Mumbai, India. The application then references an additional four companies manufacturing enzalutamide but does not indicate which of these versions are available when denoting regulatory approval locations. Because the approval statuses, timelines and safety information are not provided in a specific manner, it is not possible to accurately assess the comparative current or future availability of generic enzalutamide in individual countries and health systems.

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Pill Burden/Dose

The application incompletely describes the topic of both dosing and pill burden between abiraterone acetate and enzalutamide. The application states that abiraterone acetate is available in a 250mg dose, which requires four pills to achieve a 1000mg dose. In fact, abiraterone acetate is also available as a 500mg formulation, requiring two pills to achieve a 1000mg dose. In addition, although metastatic castration-resistant prostate cancer patients take abiraterone acetate with prednisone 5mg orally twice daily, patients with metastatic castration-sensitive prostate cancer take abiraterone acetate with prednisone 5mg orally only once per day[2].

The application additionally notes that enzalutamide is available in 40mg capsules. Enzalutamide is now also available in 40mg and 80mg tablet formulations[1].

Incomplete Listing of Comparable Treatments

As noted in our previous comment submission, in 2017, the WHO Expert Committee recommended that a comprehensive review for prostate cancer should include all relevant medicines. Despite this recommendation, although abiraterone was added to the 2019 report, apalutamide was omitted. Apalutamide is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration resistant prostate cancer or metastatic castration-sensitive prostate cancer.[3] Apalutamide is clearly a relevant medicine, and particularly important to consider, as the treatment is referenced in the cost benefit references of the application.

In addition, since the 2019 report, darolutamide has come to market as an additional orally administered treatment option for prostate cancer that should be considered a relevant medicine. Darolutamide is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration resistant prostate cancer.[4]

Health Technology Assessment (HTA)/Cost Effectiveness

In the application, the discussion of cost effectiveness of enzalutamide appears similar to the 2019 application, and again infers that the limited assessments referenced are representative across all countries, however this is not the case. HTA analyses vary widely and cannot be compared because the evaluation processes are highly influenced by country-specific criteria, such as HTA agency processes, price negotiation rules, differences in societal values and the role of competition, differences in the approved medicines being compared, and differences in willingness to fund drug procurement with a given quality of evidence.

The application omits several HTA assessments from the submission as noted in the previous application, which may not provide a robust view of the value of enzalutamide to payers. The following applications from NICE include post-chemo mCRPC [TA316] and chemo-naïve mCRPC [TA377] for enzalutamide.

Astellas Pharma Inc.
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, Japan
Tel: +81-3-3244-3000

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Additionally, the application references examples of the cost of manufacture for enzalutamide, both in active ingredient and complete product, but does not include sourcing for the indicated costs as referenced. Further, the application compares costs of goods for manufacture, without accounting for the immense investment in research and development required to bring an innovative product to the point of manufacturing and distribution, and subsequent investment costs in entirety.

Further, Table 4 may not be representative of final and accurate prices without additional context included.

Additional Clarifications

There are several additional clarifications that should be considered:

1. The PROSPER and ENZAMET trials are missing from Table 1 in this application.
2. Table 3 addresses full dose studies; there is mention of the 2017 PROSELICA trial. PROSELICA is a Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m ^{2}) and the Currently Approved Dose (25 mg/m ^{2}) in Postdocetaxel Patients with Metastatic Castration-Resistant Prostate Cancer.
3. Enzalutamide is not approved in combinations with agents other than Androgen Deprivation Therapy (ADT).

Astellas hopes these comments will be useful to the WHO EML Expert Committee on the Selection and Use of Essential Medicines as it evaluates the application for inclusion of enzalutamide on the WHO Model List of Essential Medicines. We would welcome the opportunity to discuss these comments with the Expert Committee should that be required.

Sincerely,

Kazuhiro Sako, Ph.D.
Senior Vice President, Corporate Advocacy
Astellas Pharma, Inc.

Astellas Pharma Inc.
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, Japan
Tel: +81-3-3244-3000

References

1. Xtandi (enzalutamide) [package insert]. Northbrook, IL. Astellas Pharma US, Inc; 2020.
2. Zytiga (abiraterone acetate) [package insert]. Horsham, PA. Janssen Pharmaceutical Companies; Revised: 2020.
3. Erleada (apalutamide) [package insert]. Horsham, PA. Jansen Pharmaceutical Companies; Revised: 2020.
4. Nubeqa (darolutamide) [package insert]. Whippany, NJ. Bayer Healthcare Pharmaceuticals, Inc. Revised: 2021.

Astellas Pharma Inc.
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, Japan
Tel +81-3-3244-3000