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Pharmacological Review on Enzalutamide

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Abstract

A key therapeutic option in the treatment of prostate cancer, especially metastatic castration-resistant prostate cancer (mCRPC), is Enzalutamide, a second-generation anti androgen drug. Enzalutamide, discovered by Charles Sawyer and Michael Jung at the University of California, Los Angeles, was developed and Food and Drug Administration (FDA)-approved in 2012. Its therapeutic significance was further solidified with subsequent extensions in indications to encompass metastatic castration-sensitive prostate cancer and non-metastatic castration-resistant prostate cancer. Enzalutamide's crystalline structure and restricted water solubility are two of its physical and chemical characteristics that highlight its formulation and pharmacological implications. Enzalutamide pharmacologically inhibits the binding of dihydro testosterone to the androgen receptor in a competitive manner, hence hindering the progression of cancer. It is mostly metabolized in the liver, where it produces active metabolites that are mainly excreted in feces. Its effectiveness in improving overall survival, especially in high-risk patients, has been demonstrated in clinical trials. Although Enzalutamide has many therapeutic advantages, it also has several noticeable side effects, such as gynecomastia, exhaustion, and seizures. In addition, there are very few cases of CNS adverse effects, such as posterior reversible encephalopathy syndrome (PRES). As a result, close observation is necessary, particularly in those who already have seizure disorders. All things considered, Enzalutamide is a mainstay of the treatment of prostate cancer, providing patients with better results and a higher quality of life at different stages of the disease.

Keywords: Enzalutamide, prostate cancer, androgens, gynecomastia, metabolites

INTRODUCTION

Enzalutamide is a competitive inhibitor of dihydro testosterone, the active metabolite of testosterone, and an inhibitor of the androgen-receptor signalling pathway [1]. Clinical studies in phase III have shown that Enzalutamide improves mCRPC patients' quality of life and contributes to their overall survival [2, 3].

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It is uncertain how bio available Enzalutamide is when taken orally. Cytochrome P450 (CYP) 2C8 metabolizes Enzalutamide primarily to produce the active metabolite N-dimethyl Enzalutamide, which binds to androgen receptors with a comparable affinity and strength of inhibition as the original molecule [4]. It is a second-generation anti androgen agent that the Food and Drug Administration (FDA) approved on August 31, 2012 [5]. Enzalutamide exhibits greater efficacy attributed to its higher affinity to the androgen receptor (AR) and lack of partial agonist activity, distinguishing it from bicalutamide. Despite androgen deprivation therapy (ADT) serving as the primary treatment for prostate cancer and often achieving remission, the emergence of resistance

leads to the development of castration-resistant prostate cancer (CRPC). Until recently, docetaxel stood as the sole available treatment for metastatic CRPC. However, the advent of AR inhibitors has paved the way for more targeted therapy. Nonetheless, first-generation AR inhibitors like bicalutamide have not significantly enhanced survival rates [6].

Enzalutamide's favorable pharmacological profile led to the initiation of a phase 1 study in July 2007. Remarkably, compared to the typical timeline of 10 to 15 years for a drug to progress from pre-clinical to clinical studies, Enzalutamide underwent development relatively swiftly [7]. Enzalutamide, a non-steroidal anti androgen (NSAA) medication sold under the brand name Xtandi, is used to treat prostate cancer [8]. Castration can be used in conjunction with it to treat metastatic castration-resistant prostate cancer (mCRPC) [9].

History

Enzalutamide was discovered at the University of California, Los Angeles by Charles Sewyer and Michael Jung. Together, they synthesized and assessed around 200 thiohydantoin derivatives of RU-59063, a nilutamide analogue, for AR antagonistic activity in human prostate cancer cells. The results showed that RD-162 and Enzalutamide were the most promising compounds [10–13]. The compounds were patented in 2006 and described in 2007 [14]. Enzalutamide is a medicine used to treat prostate cancer that was created and sold [15]. In August 2012, the US Food and Drug Administration (FDA) approved it for the treatment of mCRPC in the United States, followed by its approval for the treatment of non-metastatic castration-resistant prostate cancer in July 2018 [16, 17].

Enzalutamide was given FDA approval in July 2018 to treat patients with castration-resistant prostate cancer. The indication has been expanded by the approval to cover patients with prostate cancer that is resistant to castration but is not metastatic. Patients with metastatic castration-resistant prostate cancer were previously able to get ezetimibe therapy [18].

Enzalutamide was given FDA approval in December 2019 to treat patients with metastatic castration-sensitive prostate cancer (mCSPC). Castration-resistant prostate cancer patients were previously prescribed Enzalutamide [19]. Talazoparib with enzalutamide was authorized by the FDA in June 2023 to treat patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) [20].

Enzalutamide was authorized by the FDA in November 2023 to treat patients with biochemically recurrent prostate cancer that is not metastatic and is at high risk of metastasizing (high-risk BCR (Biochemical Recurrence)). In EMBARK (NCT02319837), a randomized, controlled clinical study comprising 1068 patients with nmCSPC and high-risk BCR, the efficacy was assessed. At the time of recruitment, all patients were not eligible for salvage radiotherapy and had undergone radical prostatectomy and/or radiation with curative intent if their PSA (Prostate-Specific Antigen) had doubled in less than nine months. All patients were randomly assigned to receive either blinded (160 mg once daily) or open-label (160 mg once daily) Enzalutamide with leuprolide, or blinded (160 mg once daily) placebo plus leuprolide. Priority review and fast track designations were given to the application [21].

Physical Properties

These physical properties of Enzalutamide play a crucial role in its formulation, stability, and effectiveness as a therapeutic agent for prostate cancer. Its safety, effectiveness, and patient adherence to treatment regimens depend on comprehending and improving these features.

- *Appearance:* Enzalutamide is commonly observed as a white to off-white crystalline powder, facilitating its identification and handling during manufacturing processes.
- *Solubility:* Enzalutamide demonstrates limited aqueous solubility, with solubility in water of approximately 0.08 mg/mL. This characteristic can impact its dissolution rate and bioavailability, necessitating appropriate formulation strategies to enhance its solubility and absorption.

- *Melting point:* The melting point of Enzalutamide ranges from 196 to 198°C, ensuring its thermal stability during storage and manufacturing processes.
- *Hygroscopicity:* Enzalutamide exhibits minimal hygroscopicity, indicating that it does not readily absorb moisture from the atmosphere under typical storage conditions. This property contributes to its stability and ease of handling.
- *Stability:* Enzalutamide demonstrates stability under recommended storage conditions, typically at room temperature and protected from moisture and light. Stability studies are conducted to evaluate its shelf-life and storage requirements, ensuring product quality throughout its lifespan.
- *Particle size and morphology:* Particle size distribution analysis is crucial during formulation development to optimize the particle size and morphology of Enzalutamide. These characteristics influence its dissolution kinetics, bioavailability, and manufacturability [22].
- *Density:* Enzalutamide has a density of approximately 1.36 g/cm^3, providing essential information for dosage calculation and ensuring uniformity in pharmaceutical preparations.
- *Crystallinity:* Enzalutamide exists in a crystalline form, which is critical for its chemical stability and physical properties. The crystalline structure affects its dissolution behavior and solid-state characteristics.
- *pH:* While Enzalutamide itself is not characterized by a specific pH; the pH of its pharmaceutical formulations may vary depending on excipients used. pH can influence drug stability, compatibility, and absorption.

Chemical Properties

- *Chemical modifications:* Researchers may explore chemical modifications of the Enzalutamide molecule to optimize its pharmacological properties, improve metabolic stability, or enhance selectivity for the androgen receptor. Structure-activity relationship studies aid in the design of novel Enzalutamide derivatives with improved efficacy and safety profiles.
- *Chemical structure:* Enzalutamide has a complex chemical structure characterized by a core bicyclic imidazolidin-2-one ring system with various functional groups attached. IUPAC name of Enzalutamide is 4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methyl benzamide (Figure 1).
- *Androgen receptor binding:* Enzalutamide functions as a potent and selective antagonist of the androgen receptor (AR). It competitively inhibits the binding of androgens, such as testosterone and dihydrotestosterone (DHT), to the AR, thereby blocking AR-mediated signaling pathways involved in prostate cancer growth and progression.
- *Metabolism mediated by cytochrome P450:* Enzalutamide is extensively metabolized in the liver, primarily through the cytochrome P450 (CYP) enzyme system, with notable involvement of CYP2C8 and CYP3A4. Metabolites of Enzalutamide are pharmacologically active and contribute to its overall effects (Figure 2).
- *Metabolites:* The major metabolites of Enzalutamide include N-desmethyl Enzalutamide, which retains significant pharmacological activity similar to the parent compound. These metabolites are further conjugated to form glucuronide and sulfate conjugates before excretion.
- *Chemical stability:* Enzalutamide exhibits stability under recommended storage conditions, typically at room temperature and protected from light and moisture. Stability studies are conducted to assess its shelf-life and storage requirements to ensure drug quality over time [23].

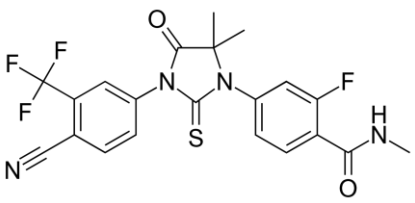

Figure 1. Structure of enzalutamide.

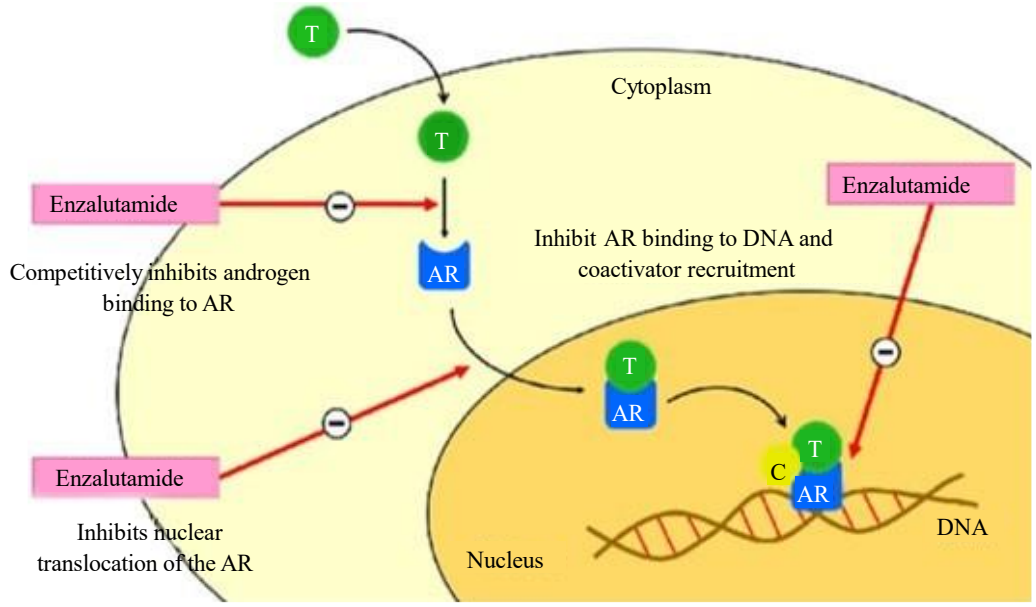

Figure 2. Enzalutamide in androgen receptor.

- *Chemical reactivity:* Enzalutamide is chemically reactive due to the presence of functional groups such as cyano, fluorine, and carbonyl moieties in its structure. Studies on drug interactions seek to assess the possibility of clinically meaningful interactions and provide direction for recommended dosages.
- *Hydrophobicity:* Enzalutamide is moderately hydrophobic, which influences its distribution and partitioning in biological fluids and tissues. Its hydrophobic nature contributes to its ability to cross cellular membranes and access intracellular targets such as the androgen receptor.
- *Chemical synthesis:* Enzalutamide is synthesized through multistep organic synthesis routes involving the coupling of various intermediates and functional group transformations. The synthesis process is carefully optimized to ensure high yield, purity, and reproducibility of the final product.
- *Chemical interactions:* Enzalutamide may interact with other drugs or chemicals that affect its metabolism, binding to plasma proteins, or elimination. The purpose of drug interaction studies is to assess the possibility of interactions that might be clinically significant and provide advice on dosage recommendations [24].

Pharmacodynamics

Enzalutamide selectively and silently antagonizes the androgen receptor (AR), the biological target of androgens such as testosterone and dihydrotestosterone (DHT). In contrast to bicalutamide, the first-generation NSAA, Enzalutamide does not facilitate the translocation of AR to the cell nucleus. Furthermore, it inhibits the binding of AR to coactivator proteins and DNA [25]. As such, it has been called both an antagonist and an inhibitor of AR signaling. The medication is referred to as a "second-generation" NSAA due to its significantly higher anti androgen effectiveness when compared to "first-generation" NSAAs such as bicalutamide and flutamide. Compared to DHT, the natural ligand of the AR in the prostate gland, the drug's affinity for the AR is just two times lower [26].

Prostate Cancer Resistance Mechanisms

Enzalutamide is only effective for a limited amount of time; beyond that, this anti androgen does not stop the cancer from growing. Extensive research is being done on the processes underlying Enzalutamide resistance [27]. Currently, several mechanisms have been found:

- AR mutations [28, 29]
- AR splice variants [30]
- Glucocorticoid receptor bypass [31]

- Increase in flux of glycolysis [32]
- Autophagy mediated resistance [33]

Pharmacokinetics

- *Absorption:* When Enzalutamide is taken orally, eating does not have a major impact on how well it is absorbed. It is recommended to take it consistently, whether with or without meals. About 84% of Enzalutamide is available in the body in its absolute form.
- *Distribution:* Enzalutamide is mostly (more than 97%) attached to albumin, a highly protein-bound substance. Given its strong protein binding, Enzalutamide's tissue distribution may be restricted. The wide tissue distribution of Enzalutamide is shown by its enormous volume of distribution.
- *Metabolism:* Enzalutamide undergoes primary metabolism in the liver. Here, the hepatic cytochrome P450 (CYP) enzymes, namely CYP2C8 and CYP3A4, oxidize the drug. N-desmethyl Enzalutamide is the principal metabolite that is produced and possesses pharmacological action. Some CYP enzymes also metabolize ezetimibe to a lower degree.
- *Excretion:* Roughly 71% of Enzalutamide and its metabolites are excreted in feces, while roughly 14% are excreted in urine. Enzalutamide is removed from the body slowly, as seen by its elimination half-life of around 5.8 days.
- *Drug interactions:* Enzalutamide induces CYP2C9 and CYP2C19 moderately, while it significantly induces CYP3A4. Consequently, it may enhance the metabolism of substances that act as substrates for these enzymes, which may result in a decrease in the effectiveness of concurrently delivered pharmaceuticals. On the other hand, Enzalutamide and its active metabolites may be exposed to higher levels when these enzymes are inhibited [34].
- *Prostate cancer:* nzalutamide has been shown to be a useful treatment for raising overall survival in patients with high-risk, non-metastatic castration-resistant prostate cancer, especially in those whose PSA doubling time is less than six months [35] (Figure 3).

Medicinal Uses

Patients with castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, and non-metastatic castration-sensitive prostate cancer with a biochemical recurrence and a high risk of metastasis should be treated with Enzalutamide (Figure 4).

Overdose

Enzalutamide overdose may lead to seizures.

Available Dosage Forms

Enzalutamide is provided as a capsule or tablet [36].

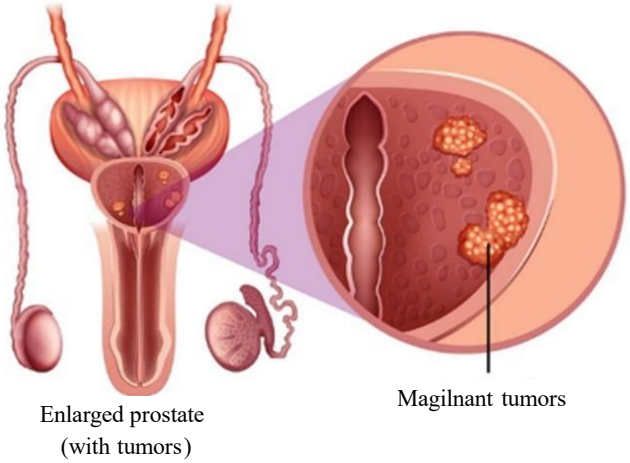

Figure 3. Prostate cancer.

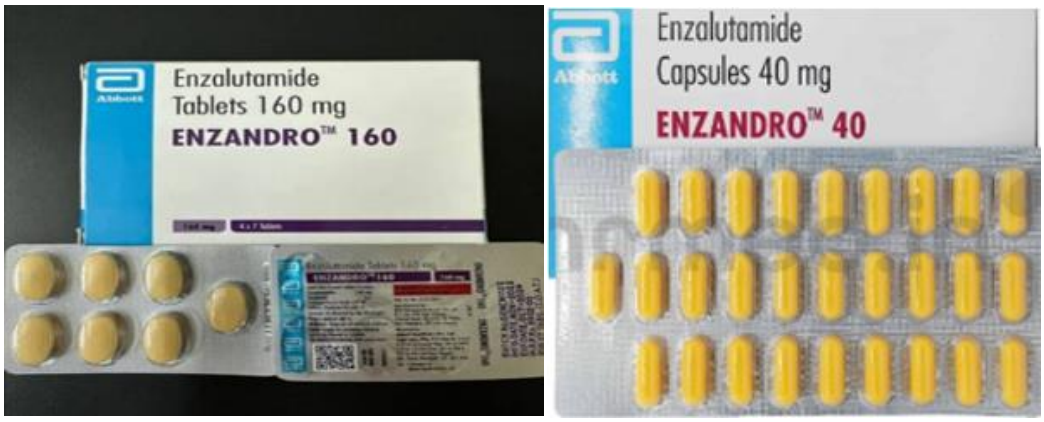

Figure 4. Enzalutamide tablets and capsules.

Adverse Reactions

Gynecomastia, breast pain/tenderness, fatigue, diarrhea, hot flashes, headache, sexual dysfunction, and seizures are notable side effects observed in clinical trials of Enzalutamide [37]. Additionally, common side effects reported in these trials include neutropenia, visual hallucinations, anxiety, cognitive disorder, memory impairment, hypertension, dry skin, and pruritus (itching) [38]. Enzalutamide monotherapy's impact on sexual function and activity is noted to be moderate, significantly less than GnRH analogues but similar to other NSAAs like bicalutamide [39].

Adverse Effects on the Central Nervous System

In clinical trials, seizures have been reported in about 1% of patients treated with Enzalutamide. This occurrence is believed to result from Enzalutamide's ability to penetrate the blood-brain barrier and interact with the GABAA receptor in the central nervous system, as evidenced by its inhibition of the GABAA receptor *in vitro* (with an IC_{50} of 3.6 μM) and its induction of convulsions in animals at high doses [40]. Alongside seizures, Enzalutamide treatment in clinical trials has revealed other potential GABAA receptor-related side effects such as anxiety, insomnia, vertigo, paraesthesia, and headache [41]. Given its propensity to reduce the seizure threshold, individuals with known seizure disorders or brain injuries require careful monitoring during Enzalutamide therapy [42]. NSAA-induced seizures are responsive to benzodiazepine treatment, and it has been suggested that $GABA_A$ receptor inhibition by Enzalutamide could be treated with these drugs [43]. In dose-ranging studies, severe fatigue was observed with Enzalutamide at doses of 240 mg/day and above.

Adverse Effects that Occur Infrequently

A solitary case report exists concerning posterior reversible encephalopathy syndrome (PRES) associated with Enzalutamide treatment. The mechanism behind this side effect remains unidentified; however, it has been suggested that it could result from the inhibition of the $GABA_A$ receptor by Enzalutamide [44].

CONCLUSION

One essential treatment option for prostate cancer, especially metastatic castration-resistant prostate cancer (mCRPC), is Enzalutamide. With its discovery, medical science made tremendous progress in treating patients and improving their quality of life and length of survival. Even with its remarkable effectiveness, Enzalutamide’s pharmacological properties and formulation call for careful thought in order to achieve the best possible dose and administration. Although Enzalutamide has great therapeutic advantages, it also has a number of tolerable adverse effects, such as gynecomastia, lethargy, and, very seldom, seizures. Significantly, its link to central side effects like seizures emphasizes how crucial it is to closely monitor patients, particularly those who already have seizure disorders. Furthermore, more research into the underlying processes of the uncommon incidence of adverse effects such posterior reversible encephalopathy syndrome (PRES) is necessary. Enzalutamide's contribution to the treatment

of prostate cancer represents a noteworthy advancement overall, providing patients with better results and optimism at different phases of the illness.

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