**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 was developed and approved by the FDA in 2012 following its discovery by Charles Sawyer and Michael Jung at the University of California, Los Angeles. Its therapeutic value has further cemented with later extensions in indications to include 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 faces. 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.

**Key words:** 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 signaling pathway1.Clinical studies in phase III have shown that Enzalutamide improves mCRPC patients' quality of life and contributes to their overall survival2,3. Currently licensed for use both pre and post chemotherapy in men with metastatic castration-resistant prostate cancer (mCRPC).

It is uncertain how bio available Enzalutamide is orally. Cytochrome P450 (CYP) 2C8 metabolizes Enzalutamide primarily to produce the active metabolite N-desmethyl Enzalutamide, which binds to androgen receptors with a comparable affinity and strength of inhibition as the original molecule4. It is a second-generation anti androgen agent that the FDA approved on August 31, 20125. It is more efficacious due to a higher affinity to AR and no partial agonist activity compared to bicalutamide. Although androgen deprivation therapy (ADT) is the first-line treatment of prostate cancer and remission can be achieved, arising resistance is inevitable, becoming castration-resistant prostate cancer. Until recently, docetaxel is the only treatment available for metastatic CRPC; however, AR inhibitors have been developed for more targeted therapy, although first-generation AR inhibitors like bicalutamide did not substantially increase the survival rate6.

Due to a favourable pharmacological profile, a phase 1 study of Enzalutamide was initiated in July 2007. Compared to the average time of 10 to 15 years for a drug to go from pre-clinical to clinical studies, Enzalutamide was developed relatively rapidly7. Prostate cancer is treated with Enzalutamide, a non steroidal anti androgen (NSAA) drug marketed under the trade name Xtandi8. When treating metastatic castration-resistant prostate cancer (mCRPC), it can be used in combination with castration9.

**History**

Enzalutamide was discovery Charles Sewyer and [Michael Jung](https://en.wikipedia.org/wiki/Michael_E._Jung) at the [University of California, Los Angeles](https://en.wikipedia.org/wiki/University_of_California%2C_Los_Angeles). They and their colleagues [synthesized](https://en.wikipedia.org/wiki/Chemical_synthesis) and evaluated nearly 200 [thiohydantoin](https://en.wiktionary.org/wiki/thiohydantoin) [derivatives](https://en.wikipedia.org/wiki/Chemical_derivative) of [RU-59063](https://en.wikipedia.org/wiki/RU-59063), an [analogue](https://en.wikipedia.org/wiki/Structural_analog) of [nilutamide](https://en.wikipedia.org/wiki/Nilutamide), for AR antagonism in human prostate cancer cells, and identified Enzalutamide and [RD-162](https://en.wikipedia.org/wiki/RD-162) as lead compounds10-13. These compounds were [patented](https://en.wikipedia.org/wiki/Patent) in 2006 and described in 200714. Enzalutamide was developed and marketed by [medication](https://en.wikipedia.org/wiki/Medivation) for the treatment of prostate cancer15. It was approved by the US [Food and Drug Administration](https://en.wikipedia.org/wiki/Food_and_Drug_Administration) (FDA) for the treatment of mCRPC in the United States in August 2012, and for the treatment of non metastatic castration-resistant prostate cancer in July 201816,17. Enzalutamide was the first new AR antagonist to be approved for the treatment of prostate cancer in over 15 years, following the introduction of the first-generation NSAA [bicalutamide](https://en.wikipedia.org/wiki/Bicalutamide) in 1995.

In July 2018, the FDA approved Enzalutamide for the treatment of people with castration-resistant prostate cancer. The approval broadens the indication to include people with both non-metastatic castration-resistant prostate cancer and metastatic castration-resistant prostate cancer. Enzalutamide was previously approved for the treatment of people with metastatic castration-resistant prostate cancer18.

In December 2019, the FDA approved Enzalutamide for the treatment of people with metastatic castration-sensitive prostate cancer (mCSPC).Enzalutamide was previously approved for the treatment of people with castration-resistant prostate cancer19.

In June 2023, the FDA approved talazoparib, in combination with Enzalutamide, for the treatment of people with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) 20.

In November 2023, the FDA approved Enzalutamide for the treatment of people with non-metastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis (high-risk BCR). Efficacy was evaluated in EMBARK (NCT02319837), a randomized, controlled clinical trial of 1068 patients with nmCSPC with high-risk BCR. All patients had prior definitive therapy with radical prostatectomy and/or radiotherapy with curative intent, had PSA doubling time ≤ 9 months, and was not candidates for salvage radiotherapy at enrollment. Patients were randomized 1:1:1 to receive blinded Enzalutamide 160 mg once daily plus leuprolide, open-label single- agent Enzalutamide 160 mg once daily, or blinded placebo once daily plus leuprolide. The application was granted [priority review](https://en.wikipedia.org/wiki/Priority_review) and [fast track](https://en.wikipedia.org/wiki/Fast_track_%28FDA%29) designations21.

**Physical properties**

These physical properties of Enzalutamide play a crucial role in its formulation, stability, and effectiveness as a therapeutic agent for prostate cancer. Understanding and optimizing these properties are essential for ensuring its safety, efficacy, and patient adherence to treatment regimens.

**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 0.08mg/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 1980C, 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 manufacturability22.

**Density:** Enzalutamide has a density of approximately 1.36 g/cm³, 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: Structure of enzalutamide**

**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.

**Cytochrome P450 metabolism:** Enzalutamide undergoes extensive hepatic metabolism primarily via the cytochrome P450 (CYP) enzyme system, particularly CYP2C8 and CYP3A4. Metabolites of Enzalutamide are pharmacologically active and contribute to its overall effects.

**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 time23.

**Chemical reactivity:** Enzalutamide is chemically reactive due to the presence of functional groups such as cyano, fluorine, and carbonyl moieties in its structure. These functional groups can participate in various chemical reactions, including metabolic transformations and interactions with other molecules.

**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. Drug interaction studies are conducted to evaluate the potential for clinically significant interactions and guide dosing recommendations24.

**Pharmacodynamics**

The androgen receptor (AR), the biological target of androgens such as testosterone and dihydrotestosterone (DHT), is selectively silently antagonistic to Enzalutamide. Enzalutamide, in contrast to bicalutamide, the first-generation NSAA, does not facilitate the translocation of AR to the cell nucleus and also inhibits the binding of AR to coactivator proteins and deoxyribonucleic acid (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 lower26.

**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 resistance27.Currently, several mechanisms have been found:

* AR mutations28,29
* AR splice variants30
* [Glucocorticoid receptor](https://en.wikipedia.org/wiki/Glucocorticoid_receptor) bypass31
* Increase in [flux](https://en.wikipedia.org/wiki/Flux) of glycolysis32
* [Autophagy](https://en.wikipedia.org/wiki/Autophagy) mediated resistance33



**Figure 2: Enzalutamide in androgen receptor**

**Pharmacokinetics**

**Absorption:** When Enzalutamide is taken orally, eating does not have a major impact on how well it is absorbed. That being said, it is advised to take it consistently 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:** The liver is the primary site of Enzalutamide metabolism. 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 faces, 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.

**Interactions with drugs:** Enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a significant inducer of 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 inhibited34.

**Prostate cancer:**

Enzalutamide 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 months35.



**Figure 3: Prostate cancer**

**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.

**Over dose**

Enzalutamide overdose may lead to seizures.

**Available Dosage Forms**

Enzalutamide is provided as a capsule or tablet36.



**Figure 4: Enzalutamide tablets & capsules**

**Side effects**

Notable [side effects](https://en.wikipedia.org/wiki/Side_effect) of Enzalutamide seen in [clinical trials](https://en.wikipedia.org/wiki/Clinical_trial) have included [gynecomastia](https://en.wikipedia.org/wiki/Gynecomastia), [breast pain/tenderness](https://en.wikipedia.org/wiki/Mastodynia), [fatigue](https://en.wikipedia.org/wiki/Fatigue_%28medical%29), [diarrhea](https://en.wikipedia.org/wiki/Diarrhea), [hot flashes](https://en.wikipedia.org/wiki/Hot_flash), [headache](https://en.wikipedia.org/wiki/Headache), [sexual dysfunction](https://en.wikipedia.org/wiki/Sexual_dysfunction), and, less commonly, [seizures](https://en.wikipedia.org/wiki/Seizure)37.Other "common" side effects reported in clinical trials have included [neutropenia](https://en.wikipedia.org/wiki/Neutropenia), [visual hallucinations](https://en.wikipedia.org/wiki/Visual_hallucination), [anxiety](https://en.wikipedia.org/wiki/Anxiety), [cognitive disorder](https://en.wikipedia.org/wiki/Cognitive_disorder), [memory impairment](https://en.wikipedia.org/wiki/Memory_impairment), [hypertension](https://en.wikipedia.org/wiki/Hypertension), [dry skin](https://en.wikipedia.org/wiki/Dry_skin), and [pruritus](https://en.wikipedia.org/wiki/Pruritus) (itching)38. Enzalutamide monotherapy is regarded as having a moderate negative effect on sexual function and activity, significantly less than that of GnRH analogues but similar to that of other NSAAs such as bicalutamide39.

**Central adverse effects**

Seizures have occurred in approximately 1% of patients treated with Enzalutamide in clinical trials. This is thought to be due to Enzalutamide crossing the [blood–brain barrier](https://en.wikipedia.org/wiki/Blood%E2%80%93brain_barrier) and exerting off-target binding to and inhibition of the [GABAA receptor](https://en.wikipedia.org/wiki/GABAA_receptor) in the [central nervous system](https://en.wikipedia.org/wiki/Central_nervous_system) (it has been found to inhibit the GABAA receptor [*in vitro*](https://en.wikipedia.org/wiki/In_vitro) ([IC50](https://en.wikipedia.org/wiki/Half-maximal_inhibitory_concentration)Tooltip half-maximal inhibitory concentration = 3.6 μM) and induces [convulsions](https://en.wikipedia.org/wiki/Convulsion) in animals at high doses)40. In addition to seizures, other potentially GABAA receptor-related side effects observed with Enzalutamide treatment in clinical trials have included [anxiety](https://en.wikipedia.org/wiki/Anxiety), [insomnia](https://en.wikipedia.org/wiki/Insomnia), [vertigo](https://en.wikipedia.org/wiki/Vertigo), [paresthesia](https://en.wikipedia.org/wiki/Paresthesia), and headache41. Due to its ability to lower the [seizure threshold](https://en.wikipedia.org/wiki/Seizure_threshold), patients with known [seizure disorders](https://en.wikipedia.org/wiki/Seizure_disorder) or [brain injury](https://en.wikipedia.org/wiki/Brain_injury) should be closely monitored during Enzalutamide treatment42. NSAA-induced seizures are responsive to [benzodiazepine](https://en.wikipedia.org/wiki/Benzodiazepine) treatment, and it has been suggested that GABAA receptor inhibition by Enzalutamide could be treated with these drugs43. In [dose-ranging studies](https://en.wikipedia.org/wiki/Dose-ranging_study), severe [fatigue](https://en.wikipedia.org/wiki/Fatigue) was observed with Enzalutamide at doses of 240 mg/day and above.

**Rare adverse effects**

There is a single [case report](https://en.wikipedia.org/wiki/Case_report) of [posterior reversible encephalopathy syndrome](https://en.wikipedia.org/wiki/Posterior_reversible_encephalopathy_syndrome) (PRES) with Enzalutamide treatment. The [mechanism of action](https://en.wikipedia.org/wiki/Mechanism_of_action) of the side effect is unknown, but it was proposed to a consequence of inhibition of the GABAA receptor by enzalutamide44.

**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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