

# Exemestane in Breast Cancer Treatment: Literature Review

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**Abstract.** Breast cancer (BC) is a pervasive global health concern, impacting millions each year. This literature review explores the role of exemestane in BC treatment. Exemestane inhibits the development of hormone receptor-positive (HR+) BC by drastically lowering oestrogen levels. Its efficacy is evident in early and advanced BC stages, with potential cost-effectiveness. While predominantly used in postmenopausal women, it shows promise in premenopausal patients when combined with ovarian suppression. Caution is needed in elderly populations when combined with other drugs, as adverse effects are more pronounced. Exemestane emerges as a crucial therapeutic tool, necessitating personalized treatment decisions for optimal patient outcomes.

**Keywords:** Exemestane, breast cancer (BC), hormone receptor-positive (HR+), oestrogen receptor-positive (ER+), premenopausal, postmenopausal, adjunctive therapy; early-stage BC, advanced BC.

## 1. Introduction

Over 2.1 million people are diagnosed with BC every year [1]. This disease has a global impact. In addition to this, it is expected to be the leading cause of roughly 685,000 deaths worldwide attributable to cancer in the year 2020 [1]. BC ranks as the second most prevalent underlying factor that leads to malignant neoplasms and cancer-associated mortality, making it a significant contributor to the global burden of illness [1]. Research conducted in the field of epidemiology has produced empirical data that lends credence to the concept that BC mutations are related to oestrogen levels [1]. The pharmaceutical exemestane has shown effectiveness on female patients aged 55 and older with late-stage BC. Following 24-36 months of tamoxifen treatment, exemestane is commonly administered as an adjuvant therapy for individuals diagnosed with oestrogen receptor-positive (ER+) cancer. Research has demonstrated the benefits of adjuvant therapy in postmenopausal women with early-stage BC [2]. The target population for this medication is women who have gone through menopause. Exemestane was demonstrated to have potential as a pharmacological intervention for the late-stage BC in women who had continuous menopause following treatment with tamoxifen in clinical studies examining the efficacy of exemestane therapy [2]. These women might have gone through menopause naturally or have had it induced after artificial methods. In a similar vein, it may be claimed that exemestane contains characteristics that render it a feasible and secure treatment mechanism for extra treatment for both premenopausal and postmenopausal ladies, as well as a prophylactic strategy against chemotherapy and a late-stage therapy for BC [2]. In addition, exemestane has the potential to be utilised either as a therapy on its own or in conjunction with other targeted therapeutic agents [2].

The aim of this article is to supply readers with a comprehensive assessment of a selection of exemestane-related scientific publications. The elucidation of the drug's targets, the investigation of the responses of these targets to medication, the investigation of the drug's therapeutic applications for BC, particularly in older female, also the analysis of the differences in treatment effects between premenopausal and postmenopausal women will be the primary focuses of this study. We will analyse the properties of the drug, as well as its limits, and make ideas for further study.

## 2. Discussion

### 2.1. Biology mechanism

#### 2.1.1. Classification

BC affects more women than any other type of cancer [3]. On the basis of molecular and histological evidence, BC is divided into HR (expressing progesterone receptor or ER), human epidermal receptor 2, and triple-negative subtypes. Decisions regarding BC treatment should be grounded in the tumour's molecular attributes [4].

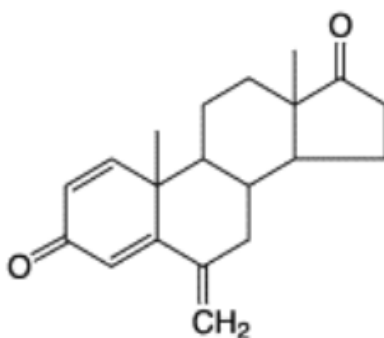
#### 2.1.2. Drug target

Aromatase serves as a significant focal point within the framework of BC, as it performs a function in the aberrant proliferation and expansion of cells. Methylane, an agent acting as an aromatase inhibitor, has been substantiated as an efficacious pharmaceutical intervention [5]. Exemestane is often employed for use in treatment and management strategies for BC, whereas a comparable protein is employed in the treatment of colon cancer [6]. The amino acid sequences of sixty proteins out of one hundred and sixteen were discovered in PDB, and the pharmacological interactions of thirty-nine proteins were worked out using the structural information that was readily accessible [6].

The concept of repositioning simulation refers to the process of strategically relocating or repositioning objects or entities inside a simulated environment. The pharmaceutical company geneXpharma has successfully developed a total of 651 medicines that are known to interact with 39 specific target proteins. The drugs were then screened based on the approval granted by the FDA, which has extensively explored the relationship between colorectal cancer (CRC) and its correlation with various factors. Additionally, significant attention has been given to investigating the three-dimensional structure of CRC on PubChem [6]. Finally, 8 drugs for 4 proteins were identified (PML, GSK3B, CDKN2A, HDAC2) (Abacavir, Volcano, Exemestane, Chelamethylene Acid Sodium, Tocampane, Methylmethane Acid Clomid, Ribosine and Tealate) [6].

#### 2.1.3. Drug molecule

The chemical molecule that is often known as isymethane shown in Fig.1 may also be referred to by its full name, which is 1,4-diylene-3,17-ketone-6-methylethane. Its chemical formula is  $C_{20}H_{24}O_2$ , and its total mass is 296.41 atomic mass units. Its mass may be expressed as atomic mass units.



**Figure 1.** Chemical structure of exemestane [7]

#### 2.1.4. Mechanism of action

Tumours of the breast, wombs, and kidneys, and the cancer from a prostatic hyperplasia are some of the pathological disorders that are related with oestrogens [7]. The issue of contention is the categorisation of aromatase inhibitors, which are classified based on their reversibility or irreversible factors with a particular focus on their mechanism of action [7]. The compounds that are being considered need to have a structural similarity to androstenedione, and they need to be created in such a way that they are able to undergo enzymatic transformation by the enzyme that is being targeted, which will then result in the synthesis of reactive species [7]. Following this, the creation of covalent

bonds appears at the enzyme's nucleophilic site, which ultimately results in blocking an enzyme's ability to catalyse a reaction, rendering it useless [8].

Because of the irreversibility of the blockage, it is necessary to produce a new enzyme called aromatase in order to restart the process of producing oestrogen [9]. Because of the inhibitor's potential to continue having an effect on the body long after it has been destroyed, the use of the inhibitor as a pharmaceutical agent would lead to a reduction in the number of adverse responses that patients experience [7]. As a consequence of this, the presence of the drug is not necessary in order to keep the inhibition in place [7].

## **2.2. Drug application**

### **2.2.1. Target BC type**

Exemestane primarily serves as a treatment for HR+ BC, specifically targeting cases where the cancer cells express ER+ properties. HR+ BC is characterised by cancer cells bearing receptors for specific hormones, such as oestrogen and progesterone [10, 11]. These receptors, found on the surface of cancer cells, can bind to hormones and receive signals that fuel cancer growth. HR+ BC, in particular, relies on hormones like oestrogen for their proliferation. ER+ BC signifies that the cancer cells specifically possess receptors for oestrogen [11]. In this subtype, oestrogen sensitivity is pronounced, and the presence of oestrogen fuels the expansion of these cancer cells. Exemestane, functioning as an aromatase inhibitor, operates by diminishing oestrogen levels within the body [12]. This action aims to deprive ER+ BC cells of the oestrogen required for their growth and division. Consequently, this can decelerate or even arrest the advancement of this specific subtype of BC.

### **2.2.2. Exemestane utilised in premenopausal patients**

Exemestane is commonly prescribed for postmenopausal women due to their naturally lower levels of aromatase substrates like oestrogen, which differ from the higher levels found in premenopausal women [13]. In premenopausal women, ovarian function remains active, leading to elevated oestrogen levels, and as a result, alternative treatments such as ovarian suppression are often considered [13, 14]. In a cohort of premenopausal females experiencing testosterone receptor-positive BC, the implementation of adjunctive endocrine treatment combining exemestane with ovarian suppression has resulted in notable enhancements in disease-free survival, extended periods without BC recurrence, in addition to prolonged intervals free from distant recurrence when compared to the use of tamoxifen in conjunction with ovarian suppression [14]. Findings from randomised trials that recruit postmenopausal women comparing the effectiveness of adjunctive aromatase inhibitors to tamoxifen are encouraging. The relative risk (RR) of BC recurrence, second invasive cancer, or mortality decreased by 28%, and the RR of BC recurrence in premenopausal women decreased by 34% [14].

### **2.2.3. Exemestane utilised in postmenopausal patients**

Exemestane is a productive therapy option for women after menopause with early-stage or advanced breast malignancy, offering potential benefits in terms of disease-free survival and cost-effectiveness [15].

#### **1) Effectiveness in BC treatment**

In the early stage of BC, transitioning to exemestane after 24-36 months of adjunctive tamoxifen treatment promotes survival without disease significantly in ER+ cases [15]. As a primary adjuvant treatment, preliminary data indicates that exemestane rivals tamoxifen's effectiveness and may even extend the time until distant repetition. In advanced BC, exemestane matches the efficacy of alternative treatments like megestrol or fulvestrant, particularly in patients who have previously shown resistance to anti-oestrogen therapies [15].

#### **2) Pharmacological features**

Exemestane functions by irreversibly inhibiting the aromatase enzyme, resulting in a powerful suppression of oestrogen synthesis while having minimal impact on other steroid hormones [15]. This medication is swiftly absorbed when taken orally, with a short half-life of approximately 24 hours. It

is worth noting that exemestane may potentially influence lipid levels and bone density, necessitating additional research to fully understand these effects [15].

### 3) Tolerability profile

Exemestane is well-tolerated in patients experiencing BC, with mostly gentle to moderate side-effects [15]. These commonly include hot flashes, arthralgia, and joint stiffness. In comparison to tamoxifen, exemestane exhibits a more favourable profile concerning gynaecological events and endometrial thickening. However, it is associated with a higher incidence of musculoskeletal symptoms. Fracture incidence did not differ substantially between those taking exemestane and those taking tamoxifen, although it varied depending on post-treatment analysis [15].

### 4) Economic considerations

According to cost-utility assessments, it has been shown that moving from tamoxifen therapy to exemestane after 24-36 months might potentially be a cost-effective approach. This transition has been found to result in a more advantageous cost per quality-adjusted life-year when compared to keeping on taking tamoxifen [15]. Notably, this switch from tamoxifen to exemestane is projected to result in cost savings when compared to other long-term hormonal therapies in certain countries.

## 2.2.4. Exemestane utilised in conjunction with other targeted therapeutic agents

In addition to exemestane's use in conjunction with ovarian suppression and its use along with tamoxifen, exemestane can be employed in conjunction with everolimus for treating BC that is sensitive to endocrine therapy and has exhibited metastatic characteristics [10, 16]. A subanalysis of the BOLERO-2 experiment found that the practice of using everolimus and exemestane together was investigated for its potential therapeutic effects, which exhibited a considerable impact on improving progression-free survival in a setting of elderly individuals diagnosed with endocrine-responsive advanced BC [10]. However, older patients on everolimus experienced more side-effects, including reduced appetite, dyspnea, anaemia, and weakness. There has been an elevation in the levels of creatinine and urinary tract infections. Significantly, it is worth noting that the group receiving combination therapy had a clinically significant reduction in weight (4.8 kg) in comparison to the group administered exemestane alone (1.7 kg). The incidence of treatment termination owing to the adverse events was found to be greater in the elderly patient population (17.4%) as compared to the younger patient population (6.3%). Similarly, older patients also indicated a greater frequency of self-initiated withdrawal (19.0%) than younger patients (6.3%). The study revealed a tenfold increase in the occurrence of severe adverse events in the combination group, and a notable observation was made about the vulnerability of senior individuals aged 70 years and over who received a combination of everolimus and exemestane, as they exhibited an increased propensity for experiencing severe adverse events that led to fatality. The findings of this study indicate that caution should be used when considering the administration of everolimus and exemestane together to older individuals with endocrine sensitive metastatic BC [16].

## 3. Summary

Exemestane, as an aromatase inhibitor, holds substantial promise in the multifaceted landscape of BC treatment. Exhibiting targeted efficacy against HR+ BC in the early and mature phases, highlights its clinical importance. Furthermore, its potential application in patients who are premenopausal and have ovarian suppression expands its utility. However, it is imperative to acknowledge the presence of manageable side-effects and the nuanced consideration of cost-effectiveness. Additionally, when administered alongside other drugs, particularly in elderly populations, vigilance is essential due to an elevated risk of adverse events.

In closing, exemestane emerges as a versatile and potent therapeutic option in BC management. Personalised treatment decisions should remain at the forefront of clinical practice to maximise its benefits while minimising risks. Ongoing research promises further insights into its efficacy and safety, contributing to improved BC care worldwide.

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## Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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