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Exemestane

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Contents

Abstract

▲ Exemestane is a steroidal agent which causes inactivation of the aromatase enzyme by binding irreversibly to the substrate binding site.

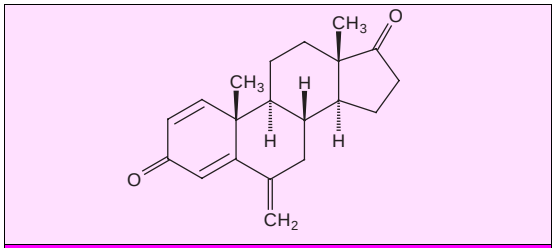
▲ Oral exemestane 25 mg/day inactivates peripheral aromatase activity (~98% inactivation) and reduces basal plasma estrone, estradiol and estrone sulphate levels by 85 to 95% in postmenopausal women with advanced breast cancer.

▲ Phase II trials indicate that oral exemestane 25 mg/day is an effective second- or third-line agent in the treatment of postmenopausal women with advanced breast cancer (achieving an objective response in up to 28 and 26% of patients, respectively).

▲ Results from a phase III trial indicate that exemestane achieves a similar objective response rate to megestrol as a second-line therapy; however, exemestane achieved a significantly longer duration of overall success, time to disease progression and survival time.

▲ Exemestane is at least as well tolerated as megestrol, but is associated with significantly fewer bodyweight changes, mainly bodyweight gain (≥10%). Other common adverse events are hot flushes, nausea and fatigue.

Features and properties of exemestane (PNU 155971, FCE 24304)	
Indications	
Advanced breast cancer in postmenopausal women	Approved in UK; pre-registration in Europe and US
Mechanism of action	
Steroidal aromatase inactivator	Irreversible inactivation of the aromatase enzyme which converts androgens to estrogens
Dosage and administration	
Usual dosage in clinical trials	25 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (25mg dose)	
Peak plasma concentration	17.7 μg/L
Area under plasma concentration-time curve	41 μg/L•h
Adverse events	
Most frequent	Hot flushes, nausea, fatigue, dizziness, increased sweating, headache, bodyweight change (mainly gain ≥10%)



Exemestane

Inhibition of estrogen biosynthesis by selective aromatase inhibitors is an important endocrine treatment option in postmenopausal women with breast cancer. After menopause the major biosynthetic pathway for estrogen production involves the conversion of androgens to estrogens in peripheral tissues. This is catalysed by the aromatase enzyme. Exemestane is an orally-active steroidal aromatase inactivator which binds irreversibly to the substrate binding site of the enzyme to inhibit its activity and, thus, reduce plasma estrogen levels. It has been studied as a second- and third-line therapy in postmenopausal women with estrogen-responsive advanced breast cancer.

1. Pharmacodynamic Profile

In Vitro and *In Vivo* Studies

- Exemestane has shown potent and specific inactivation of the aromatase enzyme in *in vitro* and *in vivo* studies.[1-4]

- Exemestane competes with the natural substrate androstenedione (in coincubation studies) with an apparent inhibitory constant (K_i) of 4.3 nmol/L compared with a K_i of 671 nmol/L for aminoglutethimide.[4]

- In preincubation studies in the absence of substrate, exemestane bound irreversibly to human aromatase enzyme [through a reduced NADPH (nicotinamide-adenine-dinucleotide phosphate cofactor)-dependent mechanism] causing inactivation of the enzyme (suicide inhibition).[4] The time required to inactivate enzyme activity by 50% ($t_{1/2}$) was 15.1 minutes and the concentration required to reduce enzyme activity by 50% [$K_{i(inact)}$] was 66.5 nmol/L.

- The specificity of exemestane for aromatase has been demonstrated *in vitro* using various enzyme or receptor preparations.[2,3] In these models, exemestane had no effect on testosterone 5α-reductase or desmolase activity, had very low affinity for the rat prostate androgen receptor (0.2% that of 5α-dihydrotestosterone) and showed no significant binding to the estrogen receptor.

- Exemestane, unlike formestane, effectively inhibited aromatase activity *in vivo* after both oral and subcutaneous administration.[1] Concentrations of exemestane and formestane required to achieve 50% enzyme inhibition (ED_{50}) following subcutaneous administration were 1.8 and 3.1 mg/kg, respectively. In contrast, with oral administration ED_{50}s for exemestane and formestane were 3.7 and >100 mg/kg, respectively.

- The antitumour effects of oral exemestane have been shown in ovariectomised rats bearing dimethylbenzanthracene-induced mammary tumours (a rodent model of postmenopausal endocrine-responsive breast cancer).[5] Tumour growth was induced by testosterone propionate administration. Oral exemestane 10, 50 or 100 mg/kg/day reduced the incidence of new tumours per animal from 0.6 in controls to 0.2, 0.3 and 0.1, respectively (statistical significance not specified). In addition, exemestane caused regression of 76 to 88% of existing tumours compared with regression of 52% of existing tumours in control animals.

Human Studies

- Maximum suppression of plasma estrogen production was achieved with a single dose of exemestane 25mg in postmenopausal women (all had previously had either malignant or benign breast tumours but had no evidence of recurrent disease).[6] In this dose-finding study (0.5 to 800mg), a single oral 25mg dose of exemestane reduced plasma estrone, estradiol and estrone sulphate levels to 35, 28 and 39% of basal levels, respectively. Maximum suppression occurred 3 days after treat-

ment and persisted for 5 days. Both 5 and 12.5mg doses reduced plasma estrone, estradiol and estrone sulphate levels, however a 0.5mg dose was ineffective.[6]

• Multiple doses of exemestane 25 mg/day inactivated peripheral aromatase by approximately 98% (measured by injection of [^{3}H]-labelled androstenedione and [^{14}C]-labelled estrone) in 10 postmenopausal women with advanced breast cancer whose disease progressed during previous tamoxifen therapy.[7]

• Exemestane 25 mg/day reduced basal plasma levels of estrone, estradiol and estrone sulphate by 85 to 95% in postmenopausal women with advanced breast cancer (fig. 1).[7-9] Plasma levels of estrogens, assayed every 2 weeks, were suppressed throughout the 12-week trial period (data not shown).[9] Plasma levels of estrogens were measured by radioimmunoassay (RIA) after high performance liquid chromatography purification of the sample to remove exemestane metabolites which demonstrate nonspecific cross-reactivity with RIA assays.[8]

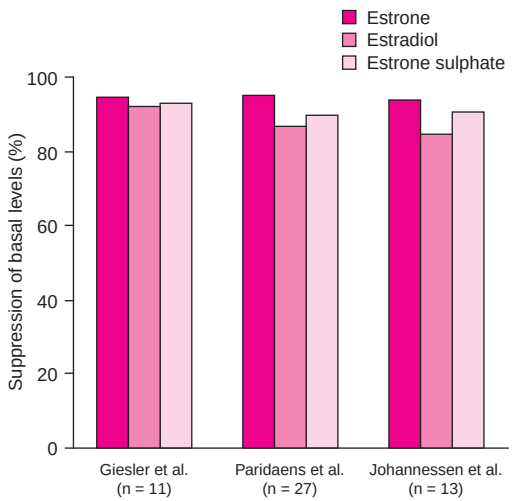


Fig. 1. Mean maximal suppression of estrone, estradiol and estrone sulphate plasma levels in postmenopausal women with advanced breast cancer during treatment with oral exemestane 25 mg/day in 2 phase I studies (Paridaens et al;[9] Johannessen et al[8]) and a multicentre phase II study (Geisler et al).[7]

• There were no significant effects on most other endocrine variables in postmenopausal patients receiving exemestane.[6,8] For example, in a 12-week dose-escalating (5 to 200 mg/day) study, no significant changes in plasma levels of cortisol, aldosterone, luteinizing hormone, follicle stimulating hormone, androstenedione and testosterone were seen, but plasma levels of 17-hyroxyprogesterone and dehydroepiandrosterone sulphate (DHEAS) increased with exemestane 200mg.[8] Sex hormone binding globulin (SHBG) plasma levels decreased significantly in a dose-dependent manner at exemestane doses of ≥25 mg/day; with exemestane 200mg, SHBG declined from 48.6 to 22.5 nmol/L.

2. Pharmacokinetic Profile

Pharmacokinetic properties of exemestane have been investigated in healthy postmenopausal women (some of whom had previous breast cancer).[6,10-13] Sugar-coated tablets and hard-gelatin capsules (used in clinical trials) had a similar rate and extent of absorption and were shown to be bioequivalent.[11]

• Exemestane is absorbed rapidly, with the time to reach maximum plasma concentrations (t_{max}) being between 1 and 2 hours.[6,12,13]

• The mean maximum plasma concentration (C_{max}) with a single oral dose of exemestane 25mg (after a meal) was 17.7 μg/L.[13] With multiple doses of 1, 2.5, 5 and 10 mg/day, C_{max} values were 0.83, 2.18, 7.29 and 11.04 μg/L, respectively, and demonstrated dose-proportional pharmacokinetics.[12] C_{max} values with exemestane 50, 200, 400 and 800mg single doses were 27, 221, 343 and 414 μg/L, respectively.[6]

• With a single oral dose of exemestane 25mg (after a meal), the mean area under the plasma concentration-time curve (AUC) was 41 μg/L · h.[13] With multiple doses of 1, 2.5, 5 and 10 mg/day, the mean $AUC_{(0-24)}$ values were 2.3, 6.02, 15.24 and 29.98 μg/L · h, respectively, suggesting linear pharmacokinetics at therapeutic doses.[12] However, nonlinear pharmacokinetics were observed with single supratherapeutic doses of exemestane

(200, 400 and 800mg); AUC values were 566, 907 and 1081 μg/L · h, respectively.[6]

• Food enhanced absorption of exemestane; the plasma AUC was approximately 40% higher in the fed state compared with the fasted state (41.3 *vs* 29.7 μg/L · h, respectively).[13] However, this difference in absorption had no effect on the inhibition of estrone sulphate (75.6 and 69.5% inhibition).[13]

• Exemestane is extensively metabolised.[14] The biotransformation involved oxidation of the methylene group at position 6, and/or reduction of the 17-keto group. Unidentified metabolites derived from hydrolysis and conjugation reactions were also observed.

• After administration of radiolabelled-exemestane, radioactivity was excreted in the urine and faeces in similar quantities (42%) over a 168-hour period.[10]

• Plasma concentrations of exemestane declined polyexponentially, with a terminal elimination half-life ($t_{½\lambda}$) of approximately 24 hours.[13]

3. Therapeutic Trials

The clinical efficacy of exemestane in postmenopausal women with advanced breast cancer has been investigated in several phase II trials[15-20] and in a large phase III trial which compared exemestane with megestrol.[21,22] In these trials, exemestane was used to treat either patients who had progressed or relapsed while receiving antiestrogens (mainly tamoxifen)[19-22] or who had failed multiple hormonal therapies and were now refractory to them.[15-18] Patients in the phase II trials had a performance status of 0 to ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale; in the phase III trial, both treatment groups had similar performance status (ECOG median value was 1; data on file, Pharmacia & Upjohn). In all studies, tumour responses were evaluated according to modified WHO criteria (data on file, Pharmacia & Upjohn).

• In phase II studies in patients who had progressed or relapsed while on tamoxifen, exemestane induced objective responses (complete and partial) in 23 to 28% of patients.[19,20] A further 19 to 24% of these patients achieved disease stabilisation for ≥24 weeks. The median time to response was 16 weeks. The median time to progression was 24 to 25 weeks.

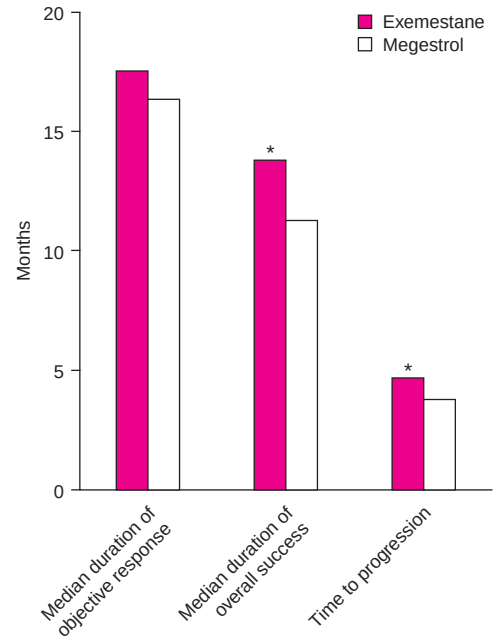


Fig. 2. Clinical efficacy of oral exemestane 25 mg/day (n = 366) versus megestrol 160 mg/day (n = 403) in postmenopausal women with advanced breast cancer who had relapsed following initial hormone therapy with tamoxifen.[21] **Objective response** = complete response + partial response; **Overall success** = complete response + partial response + stable disease over a period of ≥24 weeks; * $p < 0.05$ vs megestrol.

• In phase II studies in patients who had failed multiple hormonal therapies, exemestane 25 mg/day induced objective responses in 7 to 26% of patients and disease stabilisation (≥24 weeks) in a further 11 to 19% of patients.[15-18] The median time to response was 8 to 16 weeks. Median time to progression was 9 to 21 weeks.

• Exemestane was superior to megestrol when both drugs were given as second-line therapy to postmenopausal patients with advanced breast cancer who had progressed or relapsed on tamoxifen.[21,22]

In this double-blind, multicentre, randomised trial in 769 patients, objective responses were slightly more frequent with exemestane 25mg once daily (n = 366) compared with megestrol 40mg 4 times daily (n = 403) [15 and 12%, respectively]. A further 17% of patients achieved long term disease stabilisation with exemestane compared with 18% of patients receiving megestrol, resulting in a higher overall success rate with exemestane-treated patients that lasted for a longer period of time (13.8 *vs* 11.3 months; p = 0.025; fig. 2).

- Importantly, exemestane was associated with a significantly longer time to disease progression compared with megestrol (4.7 *vs* 3.8 months, respectively; p = 0.037; fig. 2).[21,22] In addition, patients receiving exemestane showed a prolonged survival time (median not yet reached) compared with those receiving megestrol (median 28.4 months; p = 0.039).

- A subgroup of these patients (n = 207) who had predominant visceral disease (having failed on other antiestrogen therapies) achieved overall response rates with exemestane of 13.5% compared with 10.5% in those receiving megestrol.[23] In addition, the response rates in lung lesions (25%) and liver lesions (19%) were higher with exemestane than with megestrol (17 and 11%, respectively). Importantly, with exemestane, the survival of breast cancer patients (with predominant visceral disease) was similar to that achieved in patients with less extensive disease; it was also longer than that achieved with megestrol (no values reported).[23]

4. Tolerability

- Evidence from noncomparative phase II studies showed that exemestane 25 mg/day was well tolerated in postmenopausal women with advanced breast cancer.[15-20] Common adverse events (≥5% of patients) in these trials were usually mild to moderate in severity and included nausea, hot flushes, dizziness, increased sweating and headache (data on file, Pharmacia & Upjohn). Other less common adverse events (incidence ≥2%) were insomnia, pain, skin rash, abdominal pain, anorexia, vomiting, depression, alopecia, peripheral or leg oedema, constipation and dyspepsia (data on file, Pharmacia & Upjohn).

- Grade 3 to 4 adverse events were rare with exemestane 25 mg/day, usually each event was reported in 1 patient in each trial (incidence less than 1%).[15-20]

- In a large phase III trial, exemestane was better tolerated than megestrol.[21,22] The frequency of grade 3 to 4 events was lower with exemestane than with megestrol (4.7 *vs* 7.5%, respectively; statistical significance not specified). In addition, exemestane was associated with significantly fewer bodyweight changes ≥10%, mainly bodyweight gains (7.6 *vs* 17.1%; p = 0.001; fig. 3). The most common adverse events (usually grade 1 to 2) with exemestane were hot flushes, nausea and fatigue (fig. 3), whereas with megestrol they were hot flushes, nausea, fatigue, increased sweating and increased appetite. Drug-related treatment withdrawals were also more common with megestrol

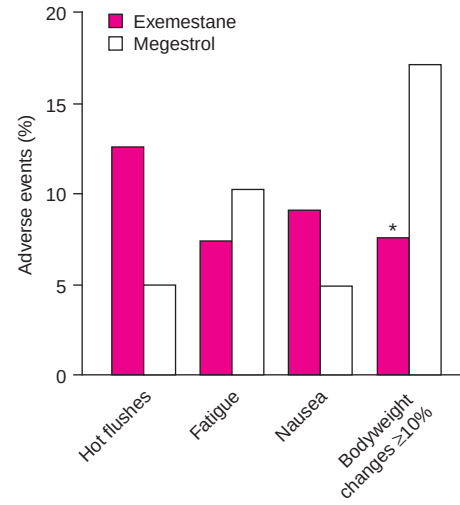


Fig. 3. Comparison of the most common adverse events in postmenopausal women with tamoxifen-refractory advanced breast cancer receiving oral exemestane 25 mg/day (n = 366) or megestrol 160 mg/day (n = 403).[21] * p = 0.001 *vs* megestrol.

than with exemestane (5.0 *vs* 1.7%, respectively; p = 0.011).[24]

5. Exemestane: Current Status

Exemestane is an irreversible aromatase inhibitor that is currently approved in the UK and is in preregistration in Europe and the US for the treatment of postmenopausal women with advanced breast cancer. Clinical trial data indicate that exemestane achieves a similar objective response rate to megestrol in patients with tamoxifen refractory advanced breast cancer, but has shown a longer median time to disease progression and median survival time and is better tolerated. Further clinical trials in postmenopausal women with early breast cancer are ongoing.

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