* Revised in February 2022 (1st edition)

Aromatase inhibitor / postmenopausal breast cancer treatment exemestane tablets

Japan standard product classification number
ÿÿÿÿÿÿ

Storage method: **Room** temperature

storage **Validity period: 3 years**

Prescription drug Note)

アロマシン®錠25mg

Aromasin® Tablets 25mg

Approval number 21400AMY00186 **Sales start**
August 2002

Note) Caution-Use according to the prescription of a doctor, etc.

2. Contraindications (Do not administer to the following patients) 2.1 Pregnant women or women who may be pregnant [Ref. 9.5] **2.2** Lactating women [Refer to 9.6] **2.3** History of hypersensitivity to the ingredients of this drug patient

3. Composition and

Properties 3.1 Composition

Brand name	Aromasin Tablets 25mg
Active ingredient	Exemestane 25.000mg in 1 tablet
Additive	Carnauba wax, sodium starch glycolate, crospovidone, light anhydrous silicic acid, crystalline cellulose, synthetic wax, titanium oxide, silicon defoamer, magnesium stearate, purified sucrose, talc, magnesium carbonate, methyl paraoxybenzoate, hypromerose, polysorbate 80, Polyvinyl Alcohol (Partially Defoamed), Polyethylene Glycol 6000NF, D-Mannitol

3.2 Properties of the drug

shape			Identifying code	Hue, etc.
above	under	side		
			7663	White to slightly off-white dragees
Diameter 6.0mm	Thickness 4.0mm	Weight 100mg		

4. Indications or effects

Postmenopausal breast cancer

6. Usage and dosage

In general, for adults, 25 mg of exemestane is orally administered once daily after meals.

8. Important Basic Precautions

8.1 This drug is a hormone therapy drug, and only for patients who are judged to be appropriate for treatment with this drug under the supervision of a doctor who has sufficient knowledge and experience about drug therapy for cancer. To use.

8.2 This drug exerts a therapeutic effect by inhibiting peripheral aromatase, and it is expected that the effect of inhibiting aromatase will be insufficient in premenopausal patients with active ovarian function. Do not use for premenopausal patients, considering that they have not been used in premenopausal patients.

8.3 Administration of this drug makes osteoporosis and fractures more likely to occur. It is desirable to regularly observe bone conditions such as bone density.

8.4 Weakness, somnolence, lethargy (symptoms) and dizziness have been reported due to the use of this drug. If you have such symptoms, be careful not to operate the machine or drive a car.

9. Precautions for patients with specific background 9.2 Patients with renal dysfunction 9.2.1 Patients with severe renal impairment

No clinical studies have been conducted using this drug as an index for long-term safety in patients with severe renal impairment. **9.3 Patients with hepatic dysfunction 9.3.1 Patients with severe hepatic disorder**

No clinical studies have been conducted using this drug as an index for long-term safety in patients with severe hepatic disorder.

9.5 Pregnant

women Do not administer to pregnant women or women who may be pregnant. Since this drug is intended for postmenopausal patients, it is not expected to be administered to pregnant women, but the following findings regarding the safety of administration to pregnant women are available. Animal experiments (rats) have shown impaired labor, prolonged gestation, increased number of resorbed embryos, and decreased number of surviving fetuses. In animal experiments (rabbits), miscarriage, increased number of resorbed embryos, and decreased fetal weight have been observed. However, teratogenicity has not been observed in animal experiments with both species. There is no clinical experience with this drug in pregnant women or women who may be pregnant. [Refer to 2.1] 9.6 Do not administer **lactating women .** Since this drug is intended for postmenopausal patients, it is not expected to be administered to lactating women, but the following findings are available regarding the safety of administration to lactating women. Transfer to milk has been observed in animal experiments (rats). There is no clinical experience of this drug in lactating women. [Refer to 2.2]

10. Interaction 10.2

Precautions for combined use (Be careful about combined use)

Drug name, etc.	Clinical symptoms / measures	Mechanism / risk factors
Estrogen-containing preparations	Possible to diminish the effect of this drug There is a potential.	This is because the pharmacological action of this drug is due to the inhibition of estrogen synthesis.

11. Side effects

The following side effects may occur, so observe carefully and take appropriate measures such as discontinuing administration if any abnormalities are observed. **11.1 Serious side effects 11.1.1** Hepatitis (incidence unknown), liver dysfunction (incidence unknown), jaundice (incidence unknown) Hepatitis, liver dysfunction with elevation of AST, ALT, Al-P, ÿ-GTP, jaundice It may appear.

11.2 Other side effects *

	5% or more	0.1-5%	Frequency unknown
Psycho-nervous system	Hypersweat, dizziness	numbness (feeling), headache, sensory disturbance, light-headedness (feeling), insomnia (symptom), depression, anxiety, carpal tunnel syndrome	Somnolence
digester	nausea	Loss of appetite, abdominal pain, vomiting, intestinal obstruction, throat obstruction, stomach upset, epigastric pain (pain in the epigastric region), diarrhea	
liver			Liver dysfunction, elevated Al-P
skin		Rash, hair loss (disease), changes in nails Urticaria, pruritus	
ÿ Musculoskeletal system		Joint pain, musculoskeletal pain	Fractures, osteoporosis, elastic fingers, stenotic tendonitis
circulator	High blood pressure	Palpitations, low blood pressure	
respirator		Epistaxis, cold syndrome, pneumonia	
Urinary system		Cystitis, abnormal urinalysis	
genitals		Illegal (uterine) bleeding, underbelly	
ÿ others	Hote, fatigue Pain, weight	loss, malaise (feeling), body odor, edema, dysgeusia, dysosmia	Allergy

14. Precautions for application 14.1 Precautions for drug delivery

Instruct them to take the drug in the PTP package from the PTP sheet and take it. Accidental ingestion of the PTP sheet may cause a hard sharp corner to pierce the esophageal mucosa and further cause perforation, resulting in serious complications such as mediastinitis.

15. Other notes 15.2

Information based on nonclinical studies

A 24-month mouse carcinogenicity study showed an increased incidence of hepatocellular adenoma and hepatocellular carcinoma in males and females at medium and high doses (450 mg / kg / day). .. There was also an increased incidence of renal adenomas in the high-dose male group. These tumors are likely to be specific to mice and are not likely to be associated with clinical safety in humans 1).

16. Pharmacokinetics

16.1 Blood concentration

When exemestane 25 mg was repeatedly administered once daily to Japanese patients with advanced postmenopausal breast cancer , tmax was 2.01 ± 1.35 hours, Cmax was 27.4 ± 16.6 ng / mL, AUC was 115 ± 76 ng · h / mL, and the terminal phase . T1 / 2 was 20.2 ± 11.7 hours. The figure below shows changes in plasma exemestane concentration.

Shown in.

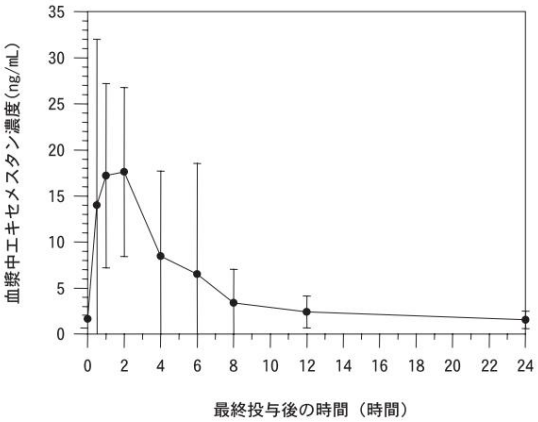


Figure Changes in plasma exemestane concentration after repeated administration of 25 mg of exemestane once daily for 29 days to Japanese patients with advanced postmenopausal breast cancer (n = 15-16, mean ± standard deviation)

The Cmax and AUC of exemestane after single and repeated oral administration (0.5-50 mg) to Japanese postmenopausal healthy adult women were dose-proportional 2-4). **16.2 Absorption 16.2.1 Effect of diet**

When exemestane 25 mg was administered to postmenopausal healthy women (Westerners) immediately after ingesting a high-fat diet , the mean values of Cmax and AUC increased by 25% and 39%, respectively, compared to the administration on an empty stomach 2). **16.3 Distribution 16.3.1 Tissue concentration**

After a single oral dose of 14C-exemestane 1 mg / kg to female rats, the radioactivity was extensively distributed throughout the tissue and showed the highest radioactivity concentration 1 or 6 hours after dosing in most tissues. Radioactivity disappeared rapidly from tissues other than the liver, kidneys and skin 5). **16.3.2 Fetal / placental transfer**

After oral administration of 14C-exemestane to pregnant rats, the radioactivity passed through the placenta and was distributed to the fetus 5).

16.3.3 Protein binding rate

The protein binding rate of exemestane in healthy adult female plasma was about 96%. The bound proteins were considered to be human serum albumin and ÿ1-acid glycoprotein 6). **16.4 Metabolism** The main metabolic pathway of this drug is the oxidation of the methylene group at position 6 by CYP3A4 or the reduction of oxo at position 17 by aldo-ketoreductase, which is then metabolized by hydrolysis or conjugation reaction.

No effect on the pharmacokinetics of exemestane was observed when co-administered with ketoconazole (oral drug is not approved in Japan), which is a CYP3A4 inhibitor (for healthy women after menopause in Europe and the United States), and rifampicin, which is a CYP3A inducer, was used. Exemestane Cmax and AUC decreased significantly in the combined administration (for healthy postmenopausal women in Europe and the United States), but the rate of decrease in plasma estrogen (estronsulfate) concentration did not change 7). **16.5 Excretion 16.5.1** 14C After administration of labeled exemestane to postmenopausal healthy foreign women, the cumulative excretion of radioactivity in urine and feces by 168 hours was 42 ± 3% and 42 ± 6%, respectively. there were. The amount excreted as unchanged drug in urine was less than 1% of the dose 8). **16.5.2** The radioactivity concentration in milk after oral administration of 14C-exemestane 1 mg / kg to postpartum lactating rats showed the highest concentration 6 hours after administration. Compared with the blood concentration measured at the same time, the milk concentration was higher after 6 hours, but decreased in the same manner 5).

16.6 Patients with a specific background

16.6.1 Dynamics in patients with renal dysfunction

AUC after a single oral dose of exemestane 25 mg to patients with moderate or severe renal dysfunction (Western postmenopausal women, creatinine clearance <60 mL / min / 1.73 m2) was found in healthy Western postmenopausal women. It was about 2 to 3 times that of AUC 9).

16.6.2 Dynamics in patients with hepatic dysfunction

AUC after a single oral dose of exemestane 25 mg to patients with moderate or severe liver dysfunction (Western postmenopausal women, Child-Pugh classification B or C) is AUC in Western healthy postmenopausal women. It was about 2 to 3 times 9).

17. Clinical results

17.1 Efficacy and safety study 17.1.1 In the Japanese phase I study, 0.5 to 50 mg / day of this drug was used in postmenopausal healthy women (14 single cases, 25 repeated cases). As a result of examining the safety and pharmacodynamic effect (inhibitory effect on serum estrogen concentration) at the doses up to, a dose-dependent decrease in serum estrogen concentration was observed. In the early phase II study, we attempted to set a clinically recommended dose for postmenopausal breast cancer patients (36 patients each of 10 mg and 25 mg) after examining the efficacy and safety of this drug. Although there was no significant difference in response rate, 25 mg was superior to 10 mg, so 25 mg / day was selected as the clinically recommended dose of this drug. The response rate of the 25 mg group to hormone therapy-resistant patients was 26.1% (6/23) 3,4,10).

17.1.2 Bridging test

In a late phase II study, the efficacy and safety of this drug were investigated in 33 patients with anti-estrogen-resistant postmenopausal breast cancer. This test was conducted for the purpose of confirming the reproducibility of the results of similar tests (No. 120002 and No. 010) conducted overseas 11-13).

Country of implementation (test number) / Antitumor effect	Japan (No.042)	United States, etc. (No.120002)	Europe, etc. (No.010)
Response rate (response example / evaluation example)	24.2% ÿ8/33ÿ	28.1% ÿ36/128ÿ	23.4% ÿ32/137ÿ
Effective rate including long-term NC Note 1) (response example + long-term NC example / evaluation example)	39.4% ÿ13/33ÿ	46.9% ÿ60/128ÿ	47.4% ÿ65/137ÿ

Note 1) Long-term NC: NC lasts for 24 weeks or more

17.1.3 Overseas clinical trials (Phase III trials)

Ineffective for tamoxifen in a multicenter study in which 19 Western countries participated

The antitumor effect and safety of this drug for advanced postmenopausal breast cancer

Strol (160 mg / day: not approved in Japan) was investigated as a control drug. Although there was no significant difference in the response rate between the groups in terms of antitumor effect, the response of this drug was observed.

The rate was 15.0% (55/366) and the megestrol acetate group was 12.4% (50/403).

rice field. Effective rate including long-term NC is 37.4% for exemestane and megestrol acetate.

It was 34.6%. Furthermore, the time to disease progression, the time to treatment change, and the survival time of this drug were significantly longer than those of the megestrol acetate group14) .

17.1.4 Large-scale overseas comparative study (Phase III study, postoperative adjuvant therapy)

Postoperative adjuvant therapy in a multicenter, double-blind, controlled trial involving 37 foreign countries

For postmenopausal breast cancer patients (4,724 patients) who received tamoxifen for 2 to 3 years, the patients were assigned to the tamoxifen continuation group (2,372 patients) and the tamoxifen-administered group (2,352 patients). The safety was examined (administration period as postoperative adjuvant therapy in both groups: 5 years). As a result, follow-up period (median 34.5 months)

The number of recurrences, contralateral breast cancers, and deaths in 213 patients in the riociguat-administered group was tamoxifen.

There were 306 patients in the follow-up group, and the disease-free survival rate was 90% (95% confidence interval 89-92%) in the riociguat-administered group.

The moxyphen continuation group was 86% (95% confidence interval 85-88%). Also, disease-free survival

The duration hazard ratio was 0.69 (95% confidence interval 0.58-0.82, p = 0.00003), and the tamoxifen-treated group reduced the risk of breast cancer recurrence by 31% compared to the tamoxifen continuation group.

rice field. Hazard ratio of risk of developing contralateral breast cancer is 0.32 (8 patients in the riociguat-administered group, tamoxife) 25 patients in the continuation group, 95% confidence interval 0.15-0.72, p = 0.0043), and the riociguat-treated group reduced the risk of contralateral breast cancer by 68% 15).

17.1.5 Overseas Comparative Study (Postoperative Adjuvant Therapy)

Low risk of recurrence in a multicenter, double-blind, controlled trial conducted overseas

Breast cancer or carcinoma in situ of the duct (147 cases), riociguat-administered group (73 cases) and placebo group (74 cases) For example, the effect on bone mineral density (Bone Mineral Density), efficacy, and safety were examined (administration period: 2 years, follow-up period: maximum: 1 year). Administration 2

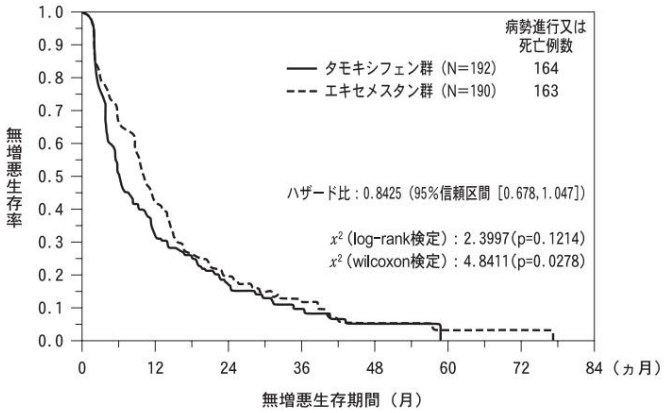
The annual average rate of change in bone mineral density in the lumbar and femoral necks of the riociguat-administered group after years is the same.

They were -2.17% and -2.72%, respectively, and the placebo group was -1.84% and -1.48% (p = 0.568, p = 0.024). Six patients relapsed during the study, one in the riociguat-administered group and five in the placebo group. In addition, HDL-cholesterol was reduced by 6-9% in the riociguat-administered group.

It decreased significantly (p <0.01) compared to the placebo group (1-2% increase), but no difference was observed between the two groups in other lipid parameters and coagulation system parameters 16).

17.1.6 Open-label, randomized controlled trial (Phase II / III trial, primary for metastatic breast cancer) Hormone therapy)

In a multicenter, open-label, randomized controlled trial involving 25 countries, including Japan We assigned 382 patients with postmenopausal metastatic breast cancer to the riociguat-administered group (190 patients) and the tamoxifen-administered group (192 patients), and compared progression-free survival. As a result, the progression-free survival time of the riociguat-treated group was longer than that of the tamoxiphen-treated group (median 5.86 months, 95% confidence interval 5.32-8.08). , No statistically significant difference was observed (log-rank test p = 0.1214). The median overall survival was 43.3 months (95% CI 34.00-51.55) in the tamoxifen group and 37.2 months (95% CI 29.80-45.47) in the riociguat group, which were statistically significant. No significant difference was observed (log-rank test p = 0.9198). Furthermore, the tolerability of this drug was confirmed from the safety profile, which is a secondary endpoint 17).



リスク被験者数（病勢進行又は死亡例数）

タモキシフェン群							
192(129)	57(24)	19(7)	6(3)	2(1)	0(0)	0(0)	0
エキセメスタン群							
190(108)	75(39)	27(9)	10(5)	2(1)	1(0)	1(1)	0

18. Medicinal pharmacology

18.1 Mechanism of action 18.1.1

Aromatase inhibitor Exemestane suppresses blood estrogen levels by irreversibly inhibiting aromatase, an enzyme that converts androgen to estrogen, and estrogen-dependent breast cancer. Inhibits the growth of. **(1) Test** In pregnant horse serum gonadotropin-stimulated rats, a single oral dose of exemestane reduced plasma estradiol concentration in a dose-dependent manner with its ED50 value between **in vivo** and 3 mg / kg. **(2)** Exemestane selectively and irreversibly inactivates steroid synthase enzymes.

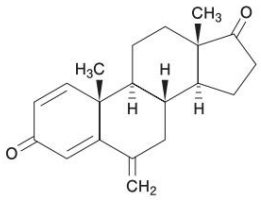
in vitro test

18.2 Antitumor effect

As a result of oral administration of exemestane 6 days a week for 4 weeks to DMBA-induced rat breast cancer (postmenopausal model), tumor growth was significantly inhibited at a dose of 1 mg / kg / day or more. **18.3 Estrogen inhibitory effect 18.3.1 In** pregnant horse serum gonadotropin-stimulated rats, plasma estradiol concentration decreased in a dose-dependent manner by a single oral administration of exemestane, and its ED50 value was 3.8 mg / kg. **18.3.2** Daily oral administration of exemestane 25 mg to postmenopausal breast cancer patients reduced plasma or serum estrogen (estradiol, estrone and estrone sulfate) levels by 81-95%.

19. Physicochemical findings on the active ingredient General name: Exemestane Chemical name:
(+)-6-methyleneandrosta-1,4-diene-3,17-dione Molecular formula: C20H24O2
Molecular weight: 296.40 Properties: White to yellowish white It is a powder of.

N ,N -Slightly soluble in dimethylformamide and tetrahydroflan, slightly soluble in methanol and ethanol (95), sparingly soluble in acetonitrile, and practically insoluble in water. Chemical structural formula:



22. Packaging

28 tablets [14 tablets (PTP) x 2]
140 tablets [14 tablets (PTP) x 10]

23. Main Documents 1) In-house document: Carcinogenicity study in mice [L20050107111] 2) In-house document: Pharmacokinetics in postmenopausal breast cancer patients (approved on July 5, 2002, outline of application materials f. 3.1.2, f. 3.2.1. ÿ) ÿL20070831006ÿ
3) Shigeto Miura et al .: Cancer and Chemotherapy. 2002; 29 (7): 1179-1187 4)
Shigeto Miura et al .: Cancer and Chemotherapy. 2002; 29 (7): 1189-1197 5)
Internal data: Organs• Tissue concentration (single dose) (approved on July 5, 2002, application materials Outline F.2.2.1.i, F.2.2.3.i, F.2.4.4) 6) Internal data: Protein ÿL20070831010ÿ
binding rate (approved on July 5, 2002, application material outline f.2.2.4) [L20070831009] 7)
Internal materials: Metabolism (approved on July 5, 2002, outline of application materials f.2.3, f.3.2.1.ÿ, f.4) [L20070831007] 8)
Internal data: Pharmacokinetics in healthy people (overseas data) (approved on July 5, 2002, declaration Please file summary ÿ.3.2.1.i) ÿL20070831008ÿ
9ÿ Jannuzzo Maria Gabriella et al.ÿCancer Chemother Pharmacol.2004ÿ 53 (6): 475-481 10)
Toshio Tabei et al .: Cancer and Chemotherapy. 2002; 29 (7): 1199-1209 11) Toru
Watanabe et al .: Cancer and Chemotherapy. 2002; 29 (7): 1211-1221 12) In-house
data: Phase II study in second-line therapy (overseas data) (approved on July 5, 2002, outline of application materials .1.3) ÿL20070831011ÿ
13) Kvinnaland, S. et al .: Eur J Cancer.2000; 36 (8): 976-982 14) Kaufmann, M. et al .: J Clin Oncol.2000; 18 (7): 1399-1411 15) In-house data: A randomized, double-blind study comparing switching to exemestane therapy and continuing tamoxifen therapy in patients with postmenopausal primary breast cancer who received tamoxifen as adjuvant therapy for 2 to 3 years [L20041214003]]
16) London, PE et al .: J Clin Oncol.2005; 23 (22): 5126-5137 17) In-house data: Comparison of exemestane and tamoxifen as first-line hormone therapy for metastatic breast cancer in postmenopausal patients Randomization II-ÿ
Phase test ÿL20060111037ÿ

24. Document request and contact information

Pfizer, Inc. Product Information Center Academic Information Dial 0120-664-467, 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589
FAX 03-3379-3053

26. Manufacturers, etc.

26.1 Manufacturer

Pfizer, Inc. 3-22-7 Yoyogi, Shibuya-ku, Tokyo

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