PDR®

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# PHYSICIANS' DESK REFERENCE®

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# PHYSICIANS' DESK REFERENCE®

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## Accolate—Cont.

There is no experience to date with zafirlukast overdose in humans. It is reasonable to employ the usual supportive measures in the event of an overdose; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

### DOSAGE AND ADMINISTRATION

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years and older. Since food reduces the bioavailability of zafirlukast, ACCOLATE should be taken at least 1 hour before or 2 hours after meals.

**Elderly Patients:**
Based on cross-study comparisons, the clearance of zafirlukast is reduced in elderly patients (65 years of age and older), such that $C_{max}$ and AUC are approximately twice those of younger adults. In clinical trials, a dose of 20 mg twice daily was not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events in elderly patients.

**Patients with Hepatic Impairment:**
The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the $C_{max}$ and AUC are approximately 50–60% greater than those of normal adults. ACCOLATE has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.

**Patients with Renal Impairment:**
Dosage adjustment is not required for patients with renal impairment.

**Pediatric Patients:**
The safety and effectiveness of ACCOLATE in pediatric patients below the age of 12 years have not been established.

### HOW SUPPLIED

20 mg Tablets, (NDC 0310-0402) white, round, biconvex, coated tablets identified with "ZENECA" debossed on one side and "ACCOLATE 20" debossed on the other side are supplied in opaque HDPE bottles of 60 tablets and hospital Unit Dose blister packages of 100 tablets.
Store at controlled room temperature, (20°–25° C) (68°–77°F) [see USP]. Protect from light and moisture. Dispense in the original air-tight container.
Manufactured for:
**Zeneca Pharmaceuticals**
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
By: IPR Pharmaceuticals Inc.
Carolina, Puerto Rico
670005 G 06/98

*Shown in Product Identification Guide, page 345*

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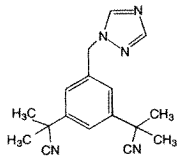
## ARIMIDEX®

℞

**anastrozole**
**TABLETS**

### DESCRIPTION

ARIMIDEX® (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is $C_{17}H_{19}N_5$ and its structural formula is:




Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.
Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

### CLINICAL PHARMACOLOGY

**Mechanism of Action**
Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogens. In post-menopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated sues, such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.
Treatment of breast cancer has included efforts to decrease estrogen levels by ovariectomy premenopausally and by use of antiestrogens and progestational agents both pre- and post-menopausally, and these interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.
Anastrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.

**Pharmacokinetics**
Inhibition of aromatase activity is primarily due to anastrozole, the parent drug. Studies with radiolabeled drug have demonstrated that orally administered anastrozole is well absorbed into the systemic circulation with 83 to 85% of the radiolabel recovered in urine and feces. Food does not affect the extent of absorption. Elimination of anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), and anastrozole has a mean terminal elimination half-life of approximately 50 hours in postmenopausal women. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the approximately 2-day terminal elimination half-life, plasma concentrations approach steady-state levels at about 7 days of once daily dosing and steady-state levels are approximately three- to four-fold higher than levels observed after a single dose of ARIMIDEX. Anastrozole is 40% bound to plasma proteins in the therapeutic range.
**Metabolism and Excretion:** Studies of postmenopausal women demonstrated that anastrozole is extensively metabolized with about 10% of the dose excreted in the urine as unchanged drug within 72 hours of dosing, and the remainder (about 60% of the dose) excreted in the urine as metabolites. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucoronidation. Three metabolites of anastrozole have been identified in human plasma and urine. The known metabolites are triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole itself. Several minor (less than 5% of the radioactive dose) metabolites have not been identified.
Because renal elimination is not a significant pathway of elimination, total body clearance of anastrozole is unchanged even in severe (creatinine clearance less than 30 mL/min/1.73m$^2$) renal impairment; dosing adjustment in patients with renal dysfunction is not necessary (see Special Populations and DOSAGE AND ADMINISTRATION sections). Dosage adjustment is also unnecessary in patients with stable hepatic cirrhosis (see Special Populations and DOSAGE AND ADMINISTRATION sections).

**Special Populations**
**Geriatric:** Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. No age related effects were seen over the range <50 to >80 years.
**Race:** Anastrozole pharmacokinetic differences due to race have not been studied.
**Renal Insufficiency:** Anastrozole pharmacokinetics have been investigated in subjects with renal insufficiency. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance less than 30 mL/min/1.73m$^2$) compared to controls. Since only about 10% of anastrozole is excreted unchanged in the urine, the reduction in renal clearance did not influence the total body clearance (see DOSAGE AND ADMINISTRATION).
**Hepatic Insufficiency:** Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials (see DOSAGE AND ADMINISTRATION), so that no dosage adjustment is needed.
**Drug-Drug Interactions:** Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 times higher than the mean steady-state $C_{max}$ values observed following a 1-mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 *in vitro*. Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to subjects had no effect on the clearolites. Based on these *in vitro* and *in vivo* results, it is unlikely that co-administration of ARIMIDEX 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450 mediated metabolism.

**Pharmacodynamics**
**Effect on Estradiol:** Mean serum concentrations of estradiol were evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10 mg if ARIMIDEX in postmenopausal women with advanced breast cancer. Clinically significant suppression of serum estradiol was seen with all doses. Doses of 1 mg and higher resulted in suppression of mean serum concentrations of estradiol to the lower limit of detection (3.7 pmol/L). The recommended daily dose, ARIMIDEX 1 mg, reduced estradiol by approximately 70% within 24 hours and by approximately 80% after 14 days of daily dosing. Suppression of serum estradiol was maintained for up to 6 days after cessation of daily dosing with ARIMIDEX 1 mg.
**Effect on Corticosteroids:** In multiple daily dosing trials with 3, 5, and 10 mg, the selectivity of anastrozole was assessed by examining the effects on corticosteroid synthesis. For all doses, anastrozole did not effect cortisol or aldosterone secretion at baseline or in response to ACTH. No glucocorticoid or mineralocorticoid replacement therapy is necessary with anastrozole.
**Other Endocrine Effects:** In multiple daily dosing trials with 5 and 10 mg, thyroid stimulation hormone (TSH) was measured; there was no increase in TSH during the administration of ARIMIDEX. ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

**Clinical Studies**
Anastrozole was studied in two well-controlled clinical trials (0004, a North American study; 0005, a predominately European study) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. Some of the patients had also received previous cytotoxic treatment. Most patients were ER-positive; a smaller fraction were ER-unknown or ER-negative (the ER-negative patients were eligible only if they had had a positive response to tamoxifen). Eligible patients with measurable and non-measurable disease were randomized to receive either a single daily dose of 1 mg or 10 mg of ARIMIDEX or megestrol acetate 40 mg four times a day. The studies were double-blinded with respect to ARIMIDEX. Time to progression and objective response (only patients with measurable disease could be considered partial responders) rates were the primary efficacy variables. Objective response rates were calculated based on the Union Internationale Contre le Cancer (UICC) criteria. The rate of prolonged (more than 24 weeks) stable disease, the rate of progression, and survival were also calculated.
Both trials included over 375 patients; demographics and other baseline characteristics were similar for the three treatment groups in each trial. Patients in the 0005 trial had responded better to prior tamoxifen treatment. Of the patients entered who had prior tamoxifen therapy for advanced disease (58% in Trial 0004; 57% in Trial 0005), 18% of these patients in Trial 0004 and 42% in Trial 0005 were reported by the primary investigator to have responded. In Trial 0004, 81% of patients were ER-positive, 13% were ER-unknown, and 6% were ER-negative. In Trial 0005, 58% of patients were ER-positive, 37% were ER-unknown, and 5% were ER-negative. In Trial 0004, 62% of patients had measurable disease compared to 79% in Trial 0005. The sites of metastatic disease were similar among treatment groups for each trial. On average, 40% of the patients had soft tissue metastases, 60% had bone metastases, and 40% had visceral (15% liver) metastases.
As shown in the table below, similar results were observed among treatment groups and between the two trials. None of the within-trial differences were statistically significant.

| | ARIMIDEX 1 mg | ARIMIDEX 10 mg | Megestrol Acetate 160 mg |
|---|---|---|---|
| Trial 0004 (N. America) | (n=128) | (n=130) | (n=128) |
| Median Follow-up (months)* | 31.3 | 30.9 | 32.9 |
| Median Time to Death (months) | 29.6 | 25.7 | 26.7 |
| 2 Year Survival Probability (%) | 62.0 | 58.0 | 53.1 |
| Median Time to Progression (months) | 5.7 | 5.3 | 5.1 |
| Objective Response (all patients) (%) | 12.5 | 10.0 | 10.2 |
| Stable Disease for >24 weeks (%) | 35.2 | 29.2 | 32.8 |
| Progression (%) | 86.7 | 85.4 | 90.6 |

| Trial 0005 (Europe, Australia, S.Africa) | (n=135) | (n=118) | (n=125) |
|---|---|---|---|
| Median Follow-up (months)* | 31.0 | 30.9 | 31.5 |
| Median Time to Death (months) | 24.3 | 24.8 | 19.8 |
| 2 Year Survival Probability (%) | 50.5 | 50.9 | 39.1 |
| Median Time to Progression (months) | 4.4 | 5.3 | 3.9 |
| Objective Response (all patients) (%) | 12.6 | 15.3 | 14.4 |
| Stable Disease for >24 weeks (%) | 24.4 | 25.4 | 23.2 |
| Progression (%) | 91.9 | 89.8 | 92.0 |

* Surviving Patients

More than 1/3 of the patients in each treatment group in both studies had either an objective response or stabilization of their disease for greater than 24 weeks. Among the 263 patients who received ARIMIDEX 1 mg, there were 11 complete responders and 22 partial responders. In patients who had an objective response, more than 80% were still responding at 6 months from randomization and more than 45% were still responding at 12 months from randomization.

When data from the two controlled trials are pooled, the objective response rates and median times to progression and death were similar for patients randomized to ARIMIDEX 1 mg and megestrol acetate. There is, in this data, no indication that ARIMIDEX 10 mg is superior to ARIMIDEX 1 mg.

| | ARIMIDEX 1 mg | ARIMIDEX 10 mg | Megestrol Acetate 160 mg |
|---|---|---|---|
| Trials 0004 & 0005 (Pooled Data) | (n=263) | (n=248) | (n=253) |
| Median Time to Death (months) | 26.7 | 25.5 | 22.5 |
| 2 Year Survival Probability (%) | 56.1 | 54.6 | 46.3 |
| Median Time to Progression (months) | 4.8 | 5.3 | 4.6 |
| Objective Respose (all patients) (%) | 12.5 | 12.5 | 12.3 |

Objective response rates and median times to progression and death for ARIMIDEX 1 mg were similar to megestrol acetate for women over or under 65. There were too few nonwhite patients studied to draw conclusions about racial differences in response.

## INDICATIONS AND USAGE

ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

## CONTRAINDICATIONS

None known.

## WARNINGS

ARIMIDEX can cause fetal harm when administered to a pregnant woman. Anastrozole has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about $^3/_4$ and 1.5 times the recommended human dose, respectively, on a mg/m$^2$ basis. Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about $^3/_4$ and $^1/_3$, respectively, the recommended human dose on a mg/m$^2$ basis), administration during the period of organogenesis showed that anastrozole increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose-related in rats. Placental weights were significantly increased in rats at doses of 0.1 mg/kg/day or more.

Evidence of fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), was observed in rats administered doses of 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0-24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). There was no evidence of teratogenicity in rats administered doses up to 1.0 mg/kg/day. In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m$^2$ basis); there was no evidence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a mg/m$^2$ basis).

There are no adequate and well-controlled studies in pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

## PRECAUTIONS

**General:** Before starting treatment with ARIMIDEX, pregnancy must be excluded (see WARNINGS).

ARIMIDEX should be administered under the supervision of a qualified physician experienced in the use of anticancer agents.

**Laboratory Tests:** Three-fold elevations of mean serum gamma glutamyl transferase (GT) levels have been observed among patients with liver metastases receiving ARIMIDEX or megestrol acetate. These changes were likely related to the progression of liver metastases in these patients, although other contributing factors could not be ruled out.

**Drug Interactions:** (See CLINICAL PHARMACOLOGY)

Anastrozole inhibited *in vitro* metabolic reactions catalyzed by cytochromes P450 1A2, 2C8/9, and 3A4 but only at relatively high concentrations. Anastrozole did not inhibit P450 2A6 or the polymorphic P450 2D6 in human liver microsomes. Anastrozole did not alter the pharmacokinetics of antipyrine. Although there have been no formal interaction studies other than with antipyrine, based on these *in vivo* and *in vitro* studies, it is unlikely that co-administration of a 1-mg dose of ARIMIDEX with other drugs will result in clinically significant drug inhibition of cytochrome P450-mediated metabolism of the other drugs.

**Drug/Laboratory Test Interactions:** No clinically significant changes in the results of clinical laboratory tests have been observed.

**Carcinogenesis:** No long-term animal studies have been conducted to assess the carcinogenic potential of ARIMIDEX.

**Mutagenesis:** ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. coli bacterial tests, CHO-K1 gene mutation assay) or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).

**Impairment of Fertility:** Studies to investigate the effect of ARIMIDEX on fertility have not been conducted; however, chronic studies indicated hypertrophy of the ovaries and the presence of follicular cysts in rats administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0-24\ hr}$ that were 19 and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). In addition, hyperplastic uteri were observed in chronic studies of female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0-24\ hr}$ that were 22 times and 16 times higher than the respective values found in post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

**Pregnancy: Pregnancy Category D:** (See WARNINGS).

**Nursing Mothers:** It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman (see WARNINGS and PRECAUTIONS).

**Pediatric Use:** The safety and efficacy of ARIMIDEX in pediatric patients have not been established.

**Geriatric Use:** Fifty percent of patients in studies 0004 and 0005 were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients.

## ADVERSE REACTIONS

ARIMIDEX was generally well tolerated in two well-controlled clinical trials (i.e., Trials 0004 and 0005), with less than 3.3% of the ARIMIDEX-treated patients and 4.0% of the megestrol acetate-treated patients withdrawing due to an adverse event.

The principal adverse event more common with ARIMIDEX than megestrol acetate was diarrhea. Adverse events reported in greater than 5% of the patients in any of the treatment groups in these two well-controlled clinical trials, regardless of causality, are presented below:

**Number (n) and Percentage of Patients with Adverse Event †**

| | ARIMIDEX 1 mg (n=262) | | ARIMIDEX 10 mg (n=246) | | Megestrol Acetate 160 mg (n=253) | |
|---|---|---|---|---|---|---|
| Adverse Event | n | % | n | % | n | % |
| Asthenia | 42 | (16.0) | 33 | (13.4) | 47 | (18.6) |
| Nausea | 41 | (15.6) | 48 | (19.5) | 28 | (11.1) |
| Headache | 34 | (13.0) | 44 | (17.9) | 24 | (9.5) |
| Hot Flushes | 32 | (12.2) | 29 | (10.6) | 21 | (8.3) |
| Pain | 28 | (10.7) | 38 | (15.4) | 29 | (11.5) |
| Back Pain | 28 | (10.7) | 26 | (10.6) | 19 | (7.5) |
| Vomiting | 24 | (9.2) | 26 | (10.6) | 16 | (6.3) |
| Cough Increased | 22 | (8.4) | 18 | (7.3) | 19 | (7.5) |
| Diarrhea | 22 | (8.4) | 18 | (7.3) | 7 | (2.8) |
| Constipation | 18 | (6.9) | 18 | (7.3) | 21 | (8.3) |
| Abdominal Pain | 18 | (6.9) | 14 | (5.7) | 18 | (7.1) |
| Anorexia | 18 | (6.9) | 19 | (7.7) | 11 | (4.3) |
| Bone Pain | 17 | (6.5) | 26 | (11.8) | 19 | (7.5) |
| Pharyngitis | 16 | (6.1) | 23 | (9.3) | 15 | (5.9) |
| Dizziness | 16 | (6.1) | 12 | (4.9) | 15 | (5.9) |
| Rash | 15 | (5.7) | 15 | (6.1) | 19 | (7.5) |
| Dry Mouth | 15 | (5.7) | 11 | (4.5) | 13 | (5.1) |
| Peripheral Edema | 14 | (5.3) | 21 | (8.5) | 28 | (11.1) |
| Pelvic Pain | 14 | (5.3) | 17 | (6.9) | 13 | (5.1) |
| Depression | 14 | (5.3) | 6 | (2.4) | 5 | (2.0) |
| Chest Pain | 13 | (5.0) | 18 | (7.3) | 13 | (5.1) |
| Paresthesia | 12 | (4.6) | 15 | (6.1) | 9 | (3.6) |
| Vaginal Hemorrhage | 6 | (2.3) | 4 | (1.6) | 13 | (5.1) |
| Weight Gain | 4 | (1.5) | 9 | (3.7) | 30 | (11.9) |
| Sweating | 4 | (1.5) | 3 | (1.2) | 16 | (6.3) |
| Increased Appetite | 0 | (0) | 1 | (0.4) | 13 | (5.1) |

† A patient may have more than one adverse event.

Other less frequent (2% to 5%) adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0004 or Trial 0005 are listed below. These adverse experiences are listed by body system and are in order of decreasing frequency within each body system regardless of assessed causality.

**Body as a Whole:** Flu syndrome; fever; neck pain; malaise; accidental injury; infection

**Cardiovascular:** Hypertension; thrombophlebitis

**Hepatic:** Gamma GT increased; SGOT increased; SGPT increased

**Hematologic:** Anemia; leukopenia

**Metabolic and Nutritional:** Alkaline phosphatase increased; weight loss

Mean serum total cholesterol levels increased by 0.5 mmol/L among patients receiving ARIMIDEX. Increases in LDL cholesterol have been shown to contribute to these changes.

**Musculoskeletal:** Myalgia; arthralgia; pathological fracture

**Nervous:** Somnolence; confusion; insomnia; anxiety; nervousness

**Respiratory:** Sinusitis; bronchitis; rhinitis

**Skin and Appendages:** Hair thinning; pruritus

**Urogenital:** Urinary tract infection; breast pain

Vaginal bleeding has been reported infrequently, mainly in patients during the first few weeks after changing from existing hormonal therapy to treatment with ARIMIDEX. If bleeding persists, further evaluation should be considered.

The incidences of the following adverse event groups, potentially causally related to one or both of the therapies because of their pharmacology, were statistically analyzed: weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness. These six groups, and the adverse events captured in the groups, were prospectively defined. The results are shown in the table below.

**Number (n) and Percentage of Patients**

| | ARIMIDEX 1 mg (n=262) | | ARIMIDEX 10 mg (n=246) | | Megestrol Acetate 160 mg (n=253) | |
|---|---|---|---|---|---|---|
| Adverse Event Group | n | % | n | % | n | % |
| Gastrointestinal Disturbance | 77 | (29.4) | 81 | (32.9) | 54 | (21.3) |
| Hot Flushes | 33 | (12.6) | 29 | (11.8) | 35 | (13.8) |
| Edema | 19 | (7.3) | 28 | (11.4) | 35 | (13.8) |
| Thromboembolic Disease | 9 | (3.4) | 4 | (1.6) | 12 | (4.7) |
| Vaginal Dryness | 5 | (1.9) | 3 | (1.2) | 2 | (0.8) |
| Weight Gain | 4 | (1.5) | 10 | (4.1) | 30 | (11.9) |

More patients treated with megestrol acetate reported weight gain as an adverse event compared to patients treated with ARIMIDEX 1 mg ($p<0.0001$). Other differences were not statistically significant.

An examination of the magnitude of change in weight in all patients was also conducted. Thirty-four percent (87/253) of the patients treated with megestrol acetate experienced weight gain of 5% or more and 11% (27/253) of the patients treated with megestrol acetate experienced weight gain of 10% or more. Among patients treated with ARIMIDEX 1

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