CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20541Orig1s023

Trade Name: **ARIMIDEX**

Generic Name: Anastrozole

Sponsor: AstraZeneca Pharmaceutical LP

Approval Date: 12/10/2008

Indications: ARIMIDEX is an aromatase inhibitor indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer
- First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer
- 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-541/SLR-020/SLR-021/SLR-023

AstraZeneca Pharmaceutical LP
Attention: E. Jane Valas, Ph.D.
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Dr. Valas:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arimidex® (anastrozole) Tablets.

SLR	Letter date	Received date	Regulatory due date	Provides for	Type
SLR-020	February 23, 2007	February 23, 2007	August 23, 2007	Adverse Events (clarifying ischemic cardiovascular events and adding carpal tunnel events)	Changed Being Effected
SLR-021	July 16, 2007	July 16, 2007	January 16, 2008	Adverse Events-Post-Marketing (hepatobiliary events)	Changed Being Effected
SLR-023	November 29, 2007	November 29, 2007	May 29, 2008	Conversion to PLR	Prior Approval

We acknowledge receipt of your November 4, 2008 submission to SLR-023.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, test for patient package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20,541/SLR-020/SLR-021/SLR-023."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alice Kacuba, Chief, project Management Staff at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Robert Justice. M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice

12/10/2008 06:18:20 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20541Orig1s023

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARIMIDEX safely and effectively. See full prescribing information for ARIMIDEX.

ARIMIDEX (anastrozole) tablet for oral use
Initial U.S. Approval: 1995

---------- RECENT MAJOR CHANGES----------

Contraindications - Premenopausal Women and Pregnancy (4.1, 8.1) 11/2008
Warnings and Precautions- Ischemic Cardiovascular Events (5.1, 6.1) 11/2008

----------INDICATIONS AND USAGE----------

ARIMIDEX is an aromatase inhibitor indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer (1.1)
- First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer (1.2)
- 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. (1.3)

---------DOSAGE AND ADMINISTRATION---------

One 1 mg tablet taken once daily (2.1)

--------DOSAGE FORMS AND STRENGTHS--------

1 mg tablets (3)

----------CONTRAINDICATIONS----------

- Women of premenopausal endocrine status, including pregnant women (4.1, 8.1)
- Patients with demonstrated hypersensitivity to ARIMIDEX or any excipient (4.2)

----------WARNINGS AND PRECAUTIONS----------

- In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events occurred with ARIMIDEX use compared to tamoxifen use. Consider risks and benefits. (5.1, 6.1)
- Decreases in bone mineral density may occur. Consider bone mineral density monitoring. (5.2)
- Increases in total cholesterol may occur. Consider cholesterol monitoring. (5.3)

----------ADVERSE REACTIONS----------

In the early breast cancer (ATAC) study, the most common (occurring with an incidence of >10%) side effects occurring in women taking ARIMIDEX included: hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, peripheral edema and lymphedema, regardless of causality. (6.1)

In the advanced breast cancer studies, the most common (occurring with an incidence of >10%) side effects occurring in women taking ARIMIDEX included: hot flashes, nausea, asthenia, pain, headache, back pain, bone pain, increased cough, dyspnea, pharyngitis and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca Pharmaceuticals LP at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Tamoxifen: Do not use in combination with ARIMIDEX. No additional benefit seen over tamoxifen monotherapy (7.1, 14.1).
- Estrogen-containing products: Combination use may diminish activity of ARIMIDEX (7.2).

----------USE IN SPECIFIC POPULATIONS----------=

- Pediatric patients: Efficacy has not been demonstrated for pubertal boys of adolescent age with gynecomastia or girls with McCune-Albright Syndrome and progressive precocious puberty. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: 11/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adjuvant Treatment

ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.

1.2 First-Line Treatment

ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer.

1.3 Second-Line Treatment

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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The dose of ARIMIDEX is one 1 mg tablet taken once a day. For patients with advanced breast cancer, ARIMIDEX should be continued until tumor progression. ARIMIDEX can be taken with or without food.

For adjuvant treatment of early breast cancer in postmenopausal women, the optimal duration of therapy is unknown. In the ATAC trial ARIMIDEX was administered for five years. *[see Clinical Studies (14.1)]*

No dosage adjustment is necessary for patients with renal impairment or for elderly patients. *[see Use in Specific Populations (8.7)]*

2.2 Patients with Hepatic Impairment

No changes in dose are recommended for patients with mild-to-moderate hepatic impairment. ARIMIDEX has not been studied in patients with severe hepatic impairment. *[see Use in Specific Populations (8.8)]*

3 DOSAGE FORMS AND STRENGTHS

The tablets are white, biconvex, film-coated containing 1 mg of anastrozole. The tablets are impressed on one side with a logo consisting of a letter “A” (upper case) with an arrowhead attached to the foot of the extended right leg of the “A” and on the reverse with the tablet strength marking “Adx 1”.

4 CONTRAINDICATIONS

4.1 Pregnancy and Premenopausal Women

ARIMIDEX may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. ARIMIDEX is contraindicated in women who are or may become pregnant. There are no adequate and well-

controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus or potential risk for loss of the pregnancy. *[see Use in Specific Populations (8.1)]*

4.2 Hypersensitivity

ARIMIDEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients. Observed reactions include anaphylaxis, angioedema, and urticaria. *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Ischemic Cardiovascular Events

In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events was observed with ARIMIDEX in the ATAC trial (17% of patients on ARIMIDEX and 10% of patients on tamoxifen). Consider risk and benefits of ARIMIDEX therapy in patients with pre-existing ischemic heart disease. *[see Adverse Reactions (6.1)]*

5.2 Bone Effects

Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving ARIMIDEX had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

5.3 Cholesterol

During the ATAC trial, more patients receiving ARIMIDEX were reported to have elevated serum cholesterol compared to patients receiving tamoxifen (9% versus 3.5%, respectively).

6. ADVERSE REACTIONS

Serious adverse reactions with ARIMIDEX occurring in less than 1 in 10,000 patients, are: 1) skin reactions such as lesions, ulcers, or blisters; 2) allergic reactions with swelling of the face, lips, tongue, and/or throat. This may cause difficulty in swallowing and/or breathing; and 3) changes in blood tests of the liver function, including inflammation of the liver with symptoms that may include a general feeling of not being well, with or without jaundice, liver pain or liver swelling [*see Adverse Reactions,(6.2)*].

Common adverse reactions (occurring with an incidence of >10%) in women taking ARIMIDEX included: hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, pain, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema.

In the ATAC trial, the most common reported adverse reaction (>0.1%) leading to discontinuation of therapy for both treatment groups was hot flashes, although there were fewer patients who discontinued therapy as a result of hot flashes in the ARIMIDEX group.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Adjuvant Therapy

Adverse reaction data for adjuvant therapy are based on the ATAC trial *[see Clinical Studies (14.1)]*. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving ARIMIDEX 1 mg and tamoxifen 20 mg, respectively.

Adverse reactions occurring with an incidence of at least 5% in either treatment group during treatment or within 14 days of the end of treatment are presented in Table 1.

Table 1 - Adverse reactions occurring with an incidence of at least 5% in either treatment group during treatment, or within 14 days of the end of treatment in the ATAC trial*

Body system and adverse reactions by COSTART preferred term	ARIMIDEX 1 mg (N = 3092)	Tamoxifen 20 mg (N= 3094)
Body as a whole		
Asthenia	575 (19)	544 (18)
Pain	533 (17)	485 (16)
Back pain	321 (10)	309 (10)
Headache	314 (10)	249 (8)
Abdominal pain	271 (9)	276 (9)
Infection	285 (9)	276 (9)
Accidental injury	311 (10)	303 (10)
Flu syndrome	175 (6)	195 (6)
Chest pain	200 (7)	150 (5)
Neoplasm	162 (5)	144 (5)
Cyst	138 (5)	162 (5)
Cardiovascular		
Vasodilatation	1104 (36)	1264 (41)
Hypertension	402 (13)	349 (11)
Digestive		
Nausea	343 (11)	335 (11)
Constipation	249 (8)	252 (8)
Diarrhea	265 (9)	216 (7)
Dyspepsia	206 (7)	169 (6)
Gastrointestinal disorder	210 (7)	158 (5)
Hemic and lymphatic		
Lymphedema	304 (10)	341 (11)
Anemia	113 (4)	159 (5)
Metabolic and nutritional		

Body system and adverse reactions by COSTART preferred term	ARIMIDEX 1 mg (N = 3092)	Tamoxifen 20 mg (N= 3094)
Peripheral edema	311 (10)	343 (11)
Weight gain	285 (9)	274 (9)
Hypercholesterolemia	278 (9)	108 (3.5)
Musculoskeletal		
Arthritis	512 (17)	445 (14)
Arthralgia	467 (15)	344 (11)
Osteoporosis	325 (11)	226 (7)
Fracture	315 (10)	209 (7)
Bone pain	201 (7)	185 (6)
Arthrosis	207 (7)	156 (5)
Joint Disorder	184 (6)	160 (5)
Myalgia	179 (6)	160 (5)
Nervous system		
Depression	413 (13)	382 (12)
Insomnia	309 (10)	281 (9)
Dizziness	236 (8)	234 (8)
Anxiety	195 (6)	180 (6)
Paresthesia	215 (7)	145 (5)
Respiratory		
Pharyngitis	443 (14)	422 (14)
Cough increased	261 (8)	287 (9)
Dyspnea	234 (8)	237 (8)
Sinusitis	184 (6)	159 (5)
Bronchitis	167 (5)	153 (5)
Skin and appendages		
Rash	333 (11)	387 (13)
Sweating	145 (5)	177 (6)
Special Senses		
Cataract Specified	182 (6)	213 (7)
Urogenital		
Leukorrhea	86 (3)	286 (9)
Urinary tract infection	244 (8)	313 (10)
Breast pain	251 (8)	169 (6)
Breast Neoplasm	164 (5)	139 (5)
Vulvovaginitis	194 (6)	150 (5)

Body system and adverse reactions by COSTART preferred term	ARIMIDEX 1 mg (N = 3092)	Tamoxifen 20 mg (N= 3094)
Vaginal Hemorrhage[¶]	122 (4)	180 (6)
Vaginitis	125 (4)	158 (5)

[*] The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up.
[†] COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.
[‡] A patient may have had more than 1 adverse reaction, including more than 1 adverse reaction in the same body system.
[§] N=Number of patients receiving the treatment.
[¶] Vaginal Hemorrhage without further diagnosis.

Certain adverse reactions and combinations of adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs (see Table 2).

Table 2 — Number of Patients with Pre-specified Adverse Reactions in ATAC Trial*

	ARIMIDEX N=3092 (%)	Tamoxifen N=3094 (%)	Odds-ratio	95% CI
Hot Flashes	1104 (36)	1264 (41)	0.80	0.73 − 0.89
Musculoskeletal Events[†]	1100 (36)	911 (29)	1.32	1.19 − 1.47
Fatigue/Asthenia	575 (19)	544 (18)	1.07	0.94 − 1.22
Mood Disturbances	597 (19)	554 (18)	1.10	0.97 − 1.25
Nausea and Vomiting	393 (13)	384 (12)	1.03	0.88 − 1.19
All Fractures	315 (10)	209 (7)	1.57	1.30 − 1.88
Fractures of Spine, Hip, or Wrist	133 (4)	91 (3)	1.48	1.13 − 1.95
Wrist/Colles' fractures	67 (2)	50 (2)		
Spine fractures	43 (1)	22 (1)		
Hip fractures	28 (1)	26 (1)		
Cataracts	182 (6)	213 (7)	0.85	0.69 − 1.04
Vaginal Bleeding	167 (5)	317 (10)	0.50	0.41 − 0.61
Ischemic Cardiovascular Disease	127 (4)	104 (3)	1.23	0.95 − 1.60
Vaginal Discharge	109 (4)	408 (13)	0.24	0.19 − 0.30
Venous Thromboembolic events	87 (3)	140 (5)	0.61	0.47 − 0.80
Deep Venous Thromboembolic Events	48 (2)	74 (2)	0.64	0.45 − 0.93
Ischemic Cerebrovascular Event	62 (2)	88 (3)	0.70	0.50 − 0.97
Endometrial Cancer[§]	4 (0.2)	13 (0.6)	0.31	0.10 − 0.94

[*] Patients with multiple events in the same category are counted only once in that category.
[†] Refers to joint symptoms, including joint disorder, arthritis, arthrosis and arthralgia.
[§] Percentages calculated based upon the numbers of patients with an intact uterus at baseline

Ischemic Cardiovascular Events

Between treatment arms in the overall population of 6186 patients, there was no statistical difference in ischemic cardiovascular events (4% ARIMIDEX vs. 3% tamoxifen).

In the overall population, angina pectoris was reported in 71/3092 (2.3%) patients in the ARIMIDEX arm and 51/3094 (1.6%) patients in the tamoxifen arm; myocardial infarction was reported in 37/3092 (1.2%) patients in the ARIMIDEX arm and 34/3094 (1.1%) patients in the tamoxifen arm.

In women with pre-existing ischemic heart disease 465/6186 (7.5%), the incidence of ischemic cardiovascular events was 17% in patients on ARIMIDEX and 10% in patients on tamoxifen. In this patient population, angina pectoris was reported in 25/216 (11.6%) patients receiving ARIMIDEX and 13/249 (5.2%) patients receiving tamoxifen; myocardial infarction was reported in 2/216 (0.9%) patients receiving ARIMIDEX and 8/249 (3.2%) patients receiving tamoxifen.

Bone Mineral Density Findings

Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving ARIMIDEX had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

Cholesterol

Patients receiving ARIMIDEX had an increase in hypercholesterolemia (278 [9%]) compared to patients receiving tamoxifen (108 [3.5%]).

Other Adverse Reactions

Patients receiving ARIMIDEX had an increase in joint disorders (including arthritis, arthrosis and arthralgia) compared with patients receiving tamoxifen. Patients receiving ARIMIDEX had an increase in the incidence of all fractures (specifically fractures of spine, hip and wrist) [315 (10%)] compared with patients receiving tamoxifen [209 (7%)].

Patients receiving ARIMIDEX had a higher incidence of carpal tunnel syndrome [78 (2.5%)] compared with patients receiving tamoxifen [22 (0.7%)].

Vaginal bleeding occurred more frequently in the tamoxifen-treated patients versus the ARIMIDEX-treated patients 317 (10%) versus 167 (5%), respectively.

Patients receiving ARIMIDEX had a lower incidence of hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events and ischemic cerebrovascular events compared with patients receiving tamoxifen.

First-Line Therapy

Adverse reactions occurring with an incidence of at least 5% in either treatment group of trials 0030 and 0027 during or within 2 weeks of the end of treatment are shown in Table 3.

Table 3 – Adverse Reactions Occurring with an Incidence of at Least 5% in Trials 0030 and 0027

Body system **Adverse Reaction**	**Number (%) of subjects**	
	ARIMIDEX (n=506)	**Tamoxifen (n=511)**
Whole body		

Body system Adverse Reaction	Number (%) of subjects	
	ARIMIDEX (n=506)	**Tamoxifen (n=511)**
Asthenia	83 (16)	81 (16)
Pain	70 (14)	73 (14)
Back pain	60 (12)	68 (13)
Headache	47 (9)	40 (8)
Abdominal pain	40 (8)	38 (7)
Chest pain	37 (7)	37 (7)
Flu syndrome	35 (7)	30 (6)
Pelvic pain	23 (5)	30 (6)
Cardiovascular		
Vasodilation	128 (25)	106 (21)
Hypertension	25 (5)	36 (7)
Digestive		
Nausea	94 (19)	106 (21)
Constipation	47 (9)	66 (13)
Diarrhea	40 (8)	33 (6)
Vomiting	38 (8)	36 (7)
Anorexia	26 (5)	46 (9)
Metabolic and Nutritional		
Peripheral edema	51 (10)	41 (8)
Muscoloskeletal		
Bone pain	54 (11)	52 (10)
Nervous		
Dizziness	30 (6)	22 (4)
Insomnia	30 (6)	38 (7)
Depression	23 (5)	32 (6)
Hypertonia	16 (3)	26 (5)
Respiratory		
Cough increased	55 (11)	52 (10)
Dyspnea	51 (10)	47 (9)
Pharyngitis	49 (10)	68 (13)
Skin and appendages		
Rash	38 (8)	34 (8)
Urogenital		
Leukorrhea	9 (2)	31 (6)

* A patient may have had more than 1 adverse event.

Less frequent adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0030 or Trial 0027 were similar to those reported for second-line therapy.

Based on results from second-line therapy and the established safety profile of tamoxifen, the incidences of 9 pre-specified adverse event categories potentially causally related to one or both of the therapies because of their pharmacology were statistically analyzed. No significant differences were seen between treatment groups.

Table 4 – Number of Patients with Pre-specified Adverse Reactions in Trials 0030 and 0027

	Number (n) and Percentage of Patients	
Adverse Reaction	**ARIMIDEX 1 mg (n=506) n (%)**	**NOLVADEX 20 mg (n=511) n (%)**
Depression	23 (5)	32 (6)
Tumor Flare	15 (3)	18 (4)
Thromboembolic Disease†	18 (4)	33 (6)
Venous†	5	15
Coronary and Cerebral‡	13	19
Gastrointestinal Disturbance	170 (34)	196 (38)
Hot Flushes	134 (26)	118 (23)
Vaginal Dryness	9 (2)	3 (1)
Lethargy	6 (1)	15 (3)
Vaginal Bleeding	5 (1)	11 (2)
Weight Gain	11 (2)	8 (2)

* A patient may have had more than 1 adverse event.
† Includes pulmonary embolus, thrombophlebitis, retinal vein thrombosis.
‡ Includes myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia and cerebral infarct.

Second-Line Therapy

ARIMIDEX was tolerated in two 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 reaction.

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

Table 5 - Number (N) and Percentage of Patients with Adverse Reactions in Trials 0004 and 0005

Adverse Reaction	ARIMIDEX 1 mg (n=262)		ARIMIDEX 10 mg (n=246)		Megesterol Acetate 160 mg (n=253)	
	n	%	n	%	n	%
Asthenia	42	(16)	33	(13)	47	(19)
Nausea	41	(16)	48	(20)	28	(11)
Headache	34	(13)	44	(18)	24	(9)
Hot Flashes	32	(12)	29	(11)	21	(8)
Pain	28	(11)	38	(15)	29	(11)
Back Pain	28	(11)	26	(11)	19	(8)
Dyspnea	24	(9)	27	(11)	53	(21)
Vomiting	24	(9)	26	(11)	16	(6)
Cough Increased	22	(8)	18	(7)	19	(8)
Diarrhea	22	(8)	18	(7)	7	(3)
Constipation	18	(7)	18	(7)	21	(8)
Abdominal Pain	18	(7)	14	(6)	18	(7)
Anorexia	18	(7)	19	(8)	11	(4)
Bone Pain	17	(6)	26	(12)	19	(8)
Pharyngitis	16	(6)	23	(9)	15	(6)
Dizziness	16	(6)	12	(5)	15	(6)
Rash	15	(6)	15	(6)	19	(8)
Dry Mouth	15	(6)	11	(4)	13	(5)
Peripheral Edema	14	(5)	21	(9)	28	(11)
Pelvic Pain	14	(5)	17	(7)	13	(5)
Depression	14	(5)	6	(2)	5	(2)
Chest Pain	13	(5)	18	(7)	13	(5)
Paresthesia	12	(5)	15	(6)	9	(4)
Vaginal Hemorrhage	6	(2)	4	(2)	13	(5)
Weight Gain	4	(2)	9	(4)	30	(12)
Sweating	4	(2)	3	(1)	16	(6)
Increased Appetite	0	(0)	1	(0)	13	(5)

* A patient may have had more then one adverse reaction.

Other less frequent (2% to 5%) adverse reactions 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

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 reactions captured in the groups, were prospectively defined. The results are shown in the table below.

Table 6 — Number (n) and Percentage of Patients with Pre-specified Adverse Reactions in Trials 0004 and 0005

	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)	81	(33)	54	(21)
Hot Flushes	33	(13)	29	(12)	35	(14)
Edema	19	(7)	28	(11)	35	(14)
Thromboembolic Disease	9	(3)	4	(2)	12	(5)
Vaginal Dryness	5	(2)	3	(1)	2	(1)
Weight Gain	4	(2)	10	(4)	30	(12)

6.2 Post-Marketing Experience

Hepatobiliary events including increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase have been reported commonly (>1% and <10%) and gamma-GT, bilirubin and hepatitis have been reported uncommonly (> 0.1% and <1%) in patients receiving ARIMIDEX.

ARIMIDEX may also be associated with rash including cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome.

Cases of allergic reactions including angioedema, urticaria and anaphylaxis have been reported in patients receiving ARIMIDEX. *[see Contraindications (4.2)]*

7 DRUG INTERACTIONS

7.1 Tamoxifen

Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the coadministration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial. *[see Clinical Studies (14.1)]*. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole.

7.2 Estrogen

Estrogen-containing therapies should not be used with ARIMIDEX as they may diminish its pharmacological action.

7.3 Warfarin

In a study conducted in 16 male volunteers, anastrozole did not alter the exposure (as measured by C_{max} and AUC) and anticoagulant activity (as measured by prothrombin time, activated partial thromboplastin time, and thrombin time) of both R- and S-warfarin.

7.4 Cytochrome P450

Based on *in vitro* and *in vivo* results, it is unlikely that co-administration of ARIMIDEX 1 mg will affect other drugs as a result inhibition of cytochrome P450 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREGNANCY CATEGORY X *[see Contraindications (4.1)]*

ARIMIDEX may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. ARIMIDEX is contraindicated in women who are or may become pregnant. In animal studies, anastrozole caused pregnancy failure, increased pregnancy loss, and signs of delayed fetal development. There are no studies of ARIMIDEX use in pregnant women. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus and potential risk for pregnancy loss.

In animal reproduction studies, pregnant rats and rabbits received anastrozole during organogenesis at doses equal to or greater than 1 (rats) and 1/3 (rabbits) the recommended

human dose on a mg/m^2 basis. In both species, anastrozole crossed the placenta, and there was increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses). In rats, these effects were dose related, and placental weights were significantly increased. Fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), occurred in rats at anastrozole doses that produced peak plasma levels 19 times higher than serum levels in humans at the therapeutic dose ($AUC_{0\text{-}24hr}$ 9 times higher). In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 16 times the recommended human dose on a mg/m^2 basis. *[see Animal Toxicology and/or Pharmacology (13.2)]*

8.3 Nursing Mothers

It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk and because of the tumorigenicity shown for anastrozole in animal studies, or the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Clinical studies in pediatric patients included a placebo-controlled trial in pubertal boys of adolescent age with gynecomastia and a single-arm trial in girls with McCune-Albright Syndrome and progressive precocious puberty. The efficacy of ARIMIDEX in the treatment of pubertal gynecomastia in adolescent boys and in the treatment of precocious puberty in girls with McCune-Albright Syndrome has not been demonstrated.

Gynecomastia Study

A randomized, double-blind, placebo-controlled, multi-center study enrolled 80 boys with pubertal gynecomastia aged 11 to 18 years. Patients were randomized to a daily regimen of either ARIMIDEX 1 mg or placebo. After 6 months of treatment there was no statistically significant difference in the percentage of patients who experienced a ≥50% reduction in gynecomastia (primary efficacy analysis). Secondary efficacy analyses (absolute change in breast volume, the percentage of patients who had any reduction in the calculated volume of gynecomastia, breast pain resolution) were consistent with the primary efficacy analysis. Serum estradiol concentrations at Month 6 of treatment were reduced by 15.4 % in the ARIMIDEX group and 4.5% in the placebo group.

Adverse reactions that were assessed as treatment-related by the investigators occurred in 16.3% of the ARIMIDEX-treated patients and 8.1% of the placebo-treated patients with the most frequent being acne (7% ARIMIDEX and 2.7% placebo) and headache (7% ARIMIDEX and 0% placebo); all other adverse reactions showed small differences between treatment groups. One patient treated with ARIMIDEX discontinued the trial because of testicular enlargement. The mean baseline-subtracted change in testicular volume after 6 months of treatment was + 6.6 ± 7.9 cm in the ARIMIDEX-treated patients and + 5.2 ± 8.0 cm in the placebo group).

McCune- Albright Syndrome Study

A multi-center, single-arm, open-label, study was conducted in 28 girls with McCune-Albright Syndrome and progressive precocious puberty aged 2 to <10 years. All patients received a 1 mg daily dose of ARIMIDEX. The trial duration was 12 months. Patients were enrolled on the basis of a diagnosis of typical (27/28) or atypical (1/27) McCune-Albright syndrome, precocious puberty, history of vaginal bleeding, and/or advanced bone age.

Patients' baseline characteristics included the following: a mean chronological age of 5.9 ±2.0 years, a mean bone age of 8.6 ± 2.6 years, a mean growth rate of 7.9 ± 2.9 cm/year and a mean Tanner stage for breast of 2.7 ± 0.81. Compared to pre-treatment data there were no on-treatment statistically significant reductions in the frequency of vaginal bleeding days, or in the rate of increase of bone age (defined as a ratio between the change in bone age over the change of chronological age). There were no clinically significant changes in Tanner staging, mean ovarian volume, mean uterine volume and mean predicted adult height. A small but statistically significant reduction of growth rate from 7.9 ± 2.9 cm/year to 6.5 ± 2.8 cm/year was observed but the absence of a control group precludes attribution of this effect to treatment or to other confounding factors such as variations in endogenous estrogen levels commonly seen in McCune-Albright Syndrome patients.

Five patients (18%) experienced adverse reactions that were considered possibly related to ARIMIDEX. These were nausea, acne, pain in an extremity, increased alanine transaminase and aspartate transaminase, and allergic dermatitis.

Pharmacokinetics in Pediatric Patients

Following 1 mg once daily multiple administration in pediatric patients, the mean time to reach the maximum anastrozole concentration was 1 hr. The mean (range) disposition parameters of anastrozole in pediatric patients were described by a CL/F of 1.54 L/h (0.77-4.53 L/h) and V/F of 98.4 L (50.7-330.0 L). The terminal elimination half life was 46.8 h, which was similar to that observed in postmenopausal women treated with anastrozole for breast cancer. Based on a population pharmacokinetic analysis, the pharmacokinetics of anastrozole was similar in boys with pubertal gynecomastia and girls with McCune- Albright Syndrome.

8.5 Geriatric Use

In studies 0030 and 0027 about 50% of patients were 65 or older. Patients ≥ 65 years of age had moderately better tumor response and time to tumor progression than patients < 65 years of age regardless of randomized treatment. In studies 0004 and 0005 50% of patients were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients.

In the ATAC study 45% of patients were 65 years of age or older. The efficacy of ARIMIDEX compared to tamoxifen in patients who were 65 years or older (N=1413 for ARIMIDEX and N=1410 for tamoxifen, the hazard ratio for disease-free survival was 0.93 (95% CI: 0.80, 1.08)) was less than efficacy observed in patients who were less than 65 years of age (N=1712 for ARIMIDEX and N=1706 for tamoxifen, the hazard ratio for disease-free survival was 0.79 (95% CI: 0.67, 0.94)).

The pharmacokinetics of anastrozole are not affected by age.

8.6 Renal Impairment

Since only about 10% of anastrozole is excreted unchanged in the urine, the renal impairment does not influence the total body clearance. Dosage adjustment in patients with renal impairment is not necessary *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

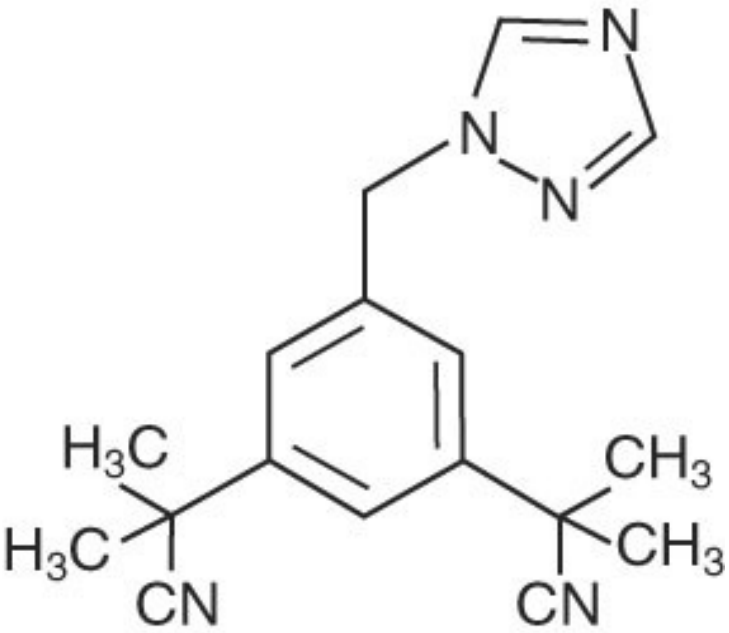
The plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials. Therefore, dosage adjustment is also not necessary in patients with stable hepatic cirrhosis. ARIMIDEX has not been studied in patients with severe hepatic impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Clinical trials have been conducted with ARIMIDEX, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were tolerated. A single dose of ARIMIDEX that results in life-threatening symptoms has not been established. There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ARIMIDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

11 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, a, a, a', a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is C17H19N5 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The growth of many cancers of the breast is stimulated or maintained by estrogens. Treatment of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen effects (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

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.

12.2 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 of 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.

The effect of ARIMIDEX in premenopausal women with early or advanced breast cancer has not been studied. Because aromatization of adrenal androgens is not a significant source of estradiol in premenopausal women , ARIMIDEX would not be expected to lower estradiol levels in premenopausal women.

Effect on Corticosteroids

In multiple daily dosing trials with 3, 5, and 10 mg, the selectivity of anastrozole was assessed by examining effects on corticosteroid synthesis. For all doses, anastrozole did not affect 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 stimulating 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.

12.3 Pharmacokinetics

Absorption

Inhibition of aromatase activity is primarily due to anastrozole, the parent drug. Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within 2 hours of dosing under fasted conditions. Studies with radiolabeled drug have demonstrated that orally administered anastrozole is well absorbed into the systemic circulation. Food reduces the rate but not the overall extent of anastrozole absorption. The mean C_{max} of anastrozole decreased by 16% and the median T_{max} was delayed from 2 to 5 hours when anastrozole was administered 30 minutes after food. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg, and do not change with repeated dosing. The pharmacokinetics of anastrozole were similar in patients and healthy volunteers.

Distribution

Steady-state plasma levels are approximately 3- to 4-fold higher than levels observed after a single dose of ARIMIDEX. Plasma concentrations approach steady-state levels at about 7 days of once daily dosing. Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Metabolism

Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of anastrozole (triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide conjugate of anastrozole itself) have been identified in human plasma and urine. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity.

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 healthy subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites.

Excretion

Eighty-five percent of radiolabeled anastrozole was recovered in feces and urine. Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Renal elimination accounts for approximately 10% of total clearance. The mean elimination half-life of anastrozole is 50 hours.

Effect of Gender and Age

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.

Effect of Race

Estradiol and estrone sulfate serum levels were similar between Japanese and Caucasian postmenopausal women who received 1 mg of anastrozole daily for 16 days. Anastrozole mean steady-state minimum plasma concentrations in Caucasian and Japanese postmenopausal women were 25.7 and 30.4 ng/mL, respectively.

Effect of Renal Impairment

Anastrozole pharmacokinetics have been investigated in subjects with renal impairment. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2) compared to controls. Total clearance was only reduced 10%. No dosage adjustment is needed for renal impairment. *[see Dosage and Administration (2.1) and Use in Specific Populations (8.7)]*

Effect of Hepatic Impairment

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, these plasma concentrations were still with the range of values observed in normal subjects. The effect of severe hepatic impairment was not studied. No dose adjustment is necessary for stable hepatic cirrhosis. *[see Dosage and Administration (2.2) and Use in Specific Populations (8.8)]*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A conventional carcinogenesis study in rats at doses of 1.0 to 25 mg/kg/day (about 10 to 243 times the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years revealed an increase in the incidence of hepatocellular adenoma and carcinoma and uterine stromal polyps in females and thyroid adenoma in males at the high dose. A dose related increase was observed in the incidence of ovarian and uterine hyperplasia in females. At 25 mg/kg/day, plasma $AUC_{0\text{-}24\ hr}$ levels in rats were 110 to 125 times higher than the level exhibited in postmenopausal volunteers at the recommended dose. A separate carcinogenicity study in mice at oral doses of 5 to 50 mg/kg/day (about 24 to 243 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years produced an increase in the incidence of benign ovarian stromal, epithelial and granulosa cell tumors at all dose levels. A dose related increase in the incidence of ovarian hyperplasia was also observed in female mice. These ovarian changes are considered to be rodent-specific effects of aromatase inhibition and are of questionable significance to humans. The incidence of lymphosarcoma was increased in males and females at the high dose. At 50 mg/kg/day, plasma AUC levels in mice were 35 to 40 times higher than the level exhibited in postmenopausal volunteers at the recommended dose.

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).

Oral administration of anastrozole to female rats (from 2 weeks before mating to pregnancy day 7) produced significant incidence of infertility and reduced numbers of viable pregnancies at 1 mg/kg/day (about 10 times the recommended human dose on a mg/m^2 basis and 9 times higher than the $AUC_{0\text{-}24\ hr}$ found in postmenopausal volunteers at the recommended dose). Pre-implantation loss of ova or fetus was increased at doses equal to or greater than 0.02 mg/kg/day (about one-fifth the recommended human dose on a mg/m^2 basis). Recovery of fertility was observed following a 5-week non-dosing period which followed 3 weeks of dosing. It is not known whether these effects observed in female rats are indicative of impaired fertility in humans.

Multiple-dose studies in rats administered anastrozole for 6 months at doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C_{ssmax} and $AUC_{0\text{-}24\ hr}$ that were 19 and 9 times higher than the respective values found in postmenopausal volunteers at the recommended dose) resulted in hypertrophy of the ovaries and the presence of follicular cysts. In addition, hyperplastic uteri were observed in 6-month studies in female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C_{ssmax} and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in postmenopausal women at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in premenopausal women.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology

Anastrozole has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about 1 and 1.9 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 1 and 1/3, respectively, the recommended human dose on a mg/m^2 basis), administered 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 $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in postmenopausal volunteers 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).

14 CLINICAL STUDIES

14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women

A multicenter, double-blind trial (ATAC) randomized 9,366 postmenopausal women with operable breast cancer to adjuvant treatment with ARIMIDEX 1 mg daily, tamoxifen 20 mg daily, or a combination of the two treatments for five years or until recurrence of the disease.

The primary endpoint of the trial was disease-free survival (i.e., time to occurrence of a distant or local recurrence, or contralateral breast cancer or death from any cause). Secondary endpoints of the trial included distant disease-free survival, the incidence of contralateral breast cancer and overall survival. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor positive subpopulation. This treatment arm was discontinued from the trial. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. *[see Drug Interactions (7.3)]*

Demographic and other baseline characteristics were similar among the three treatment groups (see Table 7).

Table 7 - Demographic and Baseline Characteristics for ATAC Trial

Demographic Characteristic	ARIMIDEX 1 mg (N=3125)	Tamoxifen 20 mg (N=3116)	ARIMIDEX 1 mg plus Tamoxifen 20 mg (N=3125)
Mean age (yrs.)	64.1	64.1	64.3
Age Range (yrs.)	38.1 - 92.8	32.8 - 94.9	37.0 - 92.2
Age Distribution (%)			
<45 yrs.	0.7	0.4	0.5
45-60 yrs.	34.6	35.0	34.5
>60 <70 yrs.	38.0	37.1	37.7
>70 yrs.	26.7	27.4	27.3
Mean Weight (kg)	70.8	71.1	71.3
Receptor Status (%)			
Positive[‡]	83.5	83.1	84.0
Negative[§]	7.4	8.0	7.0
Other[¶]	8.8	8.6	9.0
Other Treatment (%) prior to Randomization			
Mastectomy	47.8	47.3	48.1
Breast conservation[#]	52.3	52.8	51.9
Axillary surgery	95.5	95.7	95.2
Radiotherapy	63.3	62.5	61.9
Chemotherapy	22.3	20.8	20.8
Neoadjuvant Tamoxifen	1.6	1.6	1.7
Primary Tumor Size (%)			
T1 (≤2 cm)	63.9	62.9	64.1
T2 (>2 cm and ≤5 cm)	32.6	34.2	32.9
T3 (>5 cm)	2.7	2.2	2.3
Nodal Status (%)			
Node positive	34.9	33.6	33.5
1-3 (# of nodes)	24.4	24.4	24.3
4-9	7.5	6.4	6.8
>9	2.9	2.7	2.3
Tumor Grade (%)			
Well-differentiated	20.8	20.5	21.2

Demographic Characteristic	ARIMIDEX 1 mg (N=3125)	Tamoxifen 20 mg (N=3116)	ARIMIDEX 1 mg plus Tamoxifen 20 mg (N=3125)
Moderately differentiated	46.8	47.8	46.5
Poorly/undifferentiated	23.7	23.3	23.7
Not assessed/recorded	8.7	8.4	8.5

* N=Number of patients randomized to the treatment
† The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up
‡ Includes patients who were estrogen receptor (ER) positive or progesterone receptor (PgR) positive, or both positive
§ Includes patients with both ER negative and PgR negative receptor status
¶ Includes all other combinations of ER and PgR receptor status unknown
# Among the patients who had breast conservation, radiotherapy was administered to 95.0% of patients in the ARIMIDEX arm, 94.1% in the tamoxifen arm and 94.5% in the ARIMIDEX plus tamoxifen arm.

Patients in the two monotherapy arms of the ATAC trial were treated for a median of 60 months (5 years) and followed for a median of 68 months. Disease-free survival in the intent-to-treat population was statistically significantly improved [Hazard Ratio (HR) = 0.87, 95% CI: 0.78, 0.97, p=0.0127 in the ARIMIDEX arm compared to the tamoxifen arm. In the hormone receptor-positive subpopulation representing about 84% of the trial patients, disease-free survival was also statistically significantly improved (HR =0.83, 95% CI: 0.73, 0.94, p=0.0049) in the ARIMIDEX arm compared to the tamoxifen arm.

Figure 1 — Disease-Free Survival Kaplan Meier Survival Curve for all Patients Randomized to ARIMIDEX or Tamoxifen Monotherapy in the ATAC trial (Intent-to-Treat)

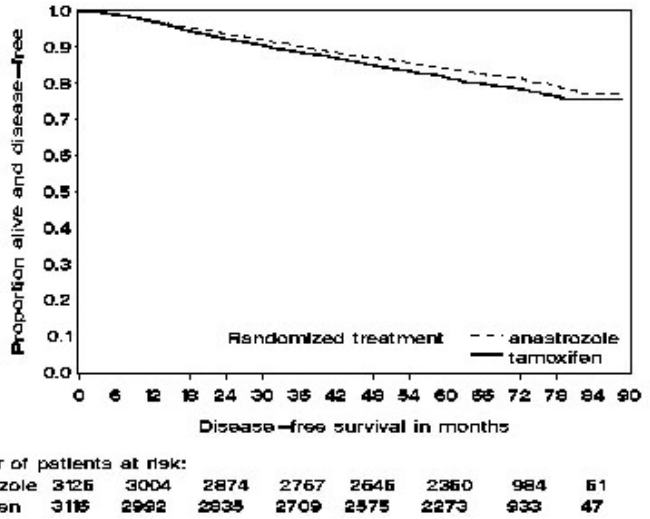
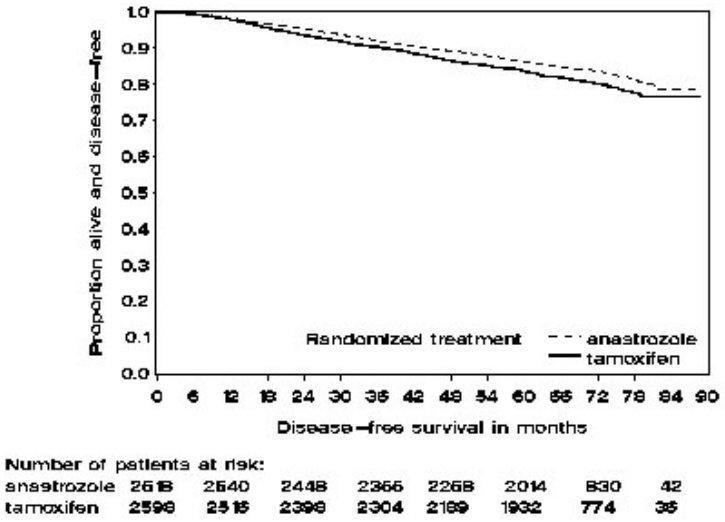


Figure 2 — Disease-free Survival for Hormone Receptor-Positive Subpopulation of Patients Randomized to ARIMIDEX or Tamoxifen Monotherapy in the ATAC Trial



The survival data with 68 months follow-up is presented in Table 9.

In the group of patients who had previous adjuvant chemotherapy (N=698 for ARIMIDEX and N=647 for tamoxifen), the hazard ratio for disease-free survival was 0.91 (95% CI: 0.73 to 1.13) in the ARIMIDEX arm compared to the tamoxifen arm.

The frequency of individual events in the intent-to-treat population and the hormone receptor-positive subpopulation are described in Table 8.

Table 8- All Recurrence and Death Events*

	Intent-To-Treat Population		**Hormone Receptor-Positive Subpopulation**	
	ARIMIDEX 1 mg (N=3125)	**Tamoxifen 20 mg (N=3116)**	**ARIMIDEX 1 mg (N=2618)**	**Tamoxifen 20 mg (N=2598**
Median Duration of Therapy (mo)	**60**	**60**	**60**	**60**
Median Efficacy Follow-up (mo)	**68**	**68**	**68**	**68**
Loco-regional recurrence	**119 (3.8)**	**149 (4.8)**	**76 (2.9)**	**101 (3.9)**
Contralateral breast cancer	**35 (1.1)**	**59 (1.9)**	**26 (1.0)**	**54 (2.1)**
Invasive	27 (0.9)	52 (1.7)	21 (0.8)	48 (1.8)
Ductal carcinoma	8 (0.3)	6 (0.2)	5 (0.2)	5 (0.2)

	Intent-To-Treat Population		Hormone Receptor-Positive Subpopulation	
	ARIMIDEX 1 mg (N=3125)	**Tamoxifen 20 mg (N=3116)**	**ARIMIDEX 1 mg (N=2618)**	**Tamoxifen 20 mg (N=2598**
in situ				
Unknown	0	1 (<0.1)	0	1 (<0.1)
Distant recurrence	**324 (10.4)**	**375 (12.0)**	**226 (8.6)**	**265 (10.2)**
Death from Any Cause	**411 (13.2)**	**420 (13.5)**	**296 (11.3)**	**301 (11.6)**
Death breast cancer	218 (7.0)	248 (8.0)	138 (5.3)	160 (6.2)
Death other reason (including unknown)	193 (6.2)	172 (5.5)	158 (6.0)	141 (5.4)

* The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up.
† N=Number of patients randomized
‡ Patients may fall into more than one category.

A summary of the study efficacy results is provided in Table 9.

Table 9 - ATAC Efficacy Summary*

	Intent-To-Treat Population		**Hormone Receptor-Positive Subpopulation**	
	ARIMIDEX 1 mg (N=3125)	**Tamoxifen 20 mg (N=3116)**	**ARIMIDEX 1 mg (N=2618)**	**Tamoxifen 20 mg (N=2598)**
	Number of Events		**Number of Events**	
Disease-free Survival	575	651	424	497
Hazard ratio	0.87		0.83	
2-sided 95% CI	0.78 to 0.97		0.73 to 0.94	
p-value	0.0127		0.0049	
Distant Disease-free Survival	500	530	370	394
Hazard ratio	0.94		0.93	
2-sided 95% CI	0.83 to 1.06		0.80 to 1.07	
Overall Survival	411	420	296	301
Hazard ratio	0.97		0.97	
2-sided 95% CI	0.85 to 1.12		0.83 to 1.14	

* The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up.

14.2 First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer

Two double-blind, controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of ARIMIDEX compared with tamoxifen as first-line therapy for hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1021 patients between the ages of 30 and 92 years old were randomized to receive trial treatment. Patients were randomized to receive 1 mg of ARIMIDEX once daily

or 20 mg of tamoxifen once daily. The primary end points for both trials were time to tumor progression, objective tumor response rate, and safety.

Demographics and other baseline characteristics, including patients who had measurable and no measurable disease, patients who were given previous adjuvant therapy, the site of metastatic disease and ethnic origin were similar for the two treatment groups for both trials. The following table summarizes the hormone receptor status at entry for all randomized patients in trials 0030 and 0027.

Table 10 – Demographic and Other Baseline Characteristics

	Number (%) of subjects			
	Trial 0030		**Trial 0027**	
Receptor status	**ARIMIDEX 1 mg (n=171)**	**Tamoxifen 20 mg (n=182)**	**ARIMIDEX 1 mg (n=340)**	**Tamoxifen 20 mg (n=328)**
ER* and/or PgR†	151 (88.3)	162 (89.0)	154 (45.3)	144 (43.9)
ER* unknown, PgR†	19 (11.1)	20 (11.0)	185 (54.4)	183 (55.8)
Unknown				

* ER=Estrogen receptor
† PgR=Progesterone receptor

For the primary endpoints, trial 0030 showed that ARIMIDEX had a statistically significant advantage over tamoxifen (p=0.006) for time to tumor progression; objective tumor response rates were similar for ARIMIDEX and tamoxifen. Trial 0027 showed that ARIMIDEX and tamoxifen had similar objective tumor response rates and time to tumor progression (see Table 11 and Figure 3 and 4)

Table 11 below summarizes the results of trial 0030 and trial 0027 for the primary efficacy endpoints.

Table 11 – Efficacy Results of First-line Treatment

Endpoint	**Trial 0030**		**Trial 0027**	
	ARIMIDEX 1 mg (n=171)	**Tamoxifen 20 mg (n=182)**	**ARIMIDEX 1 mg (n=340)**	**Tamoxifen 20 mg (n=328)**
Time to progression (TTP)				
Median TTP (months)	11.1	5.6	8.2	8.3
Number (%) of subjects Who progressed	114 (67%)	138 (76%)	249 (73%)	247 (75%)

Endpoint	Trial 0030		Trial 0027	
	ARIMIDEX 1 mg (n=171)	**Tamoxifen 20 mg (n=182)**	**ARIMIDEX 1 mg (n=340)**	**Tamoxifen 20 mg (n=328)**
Hazard ratio (LCL[*])[†]	1.42 (1.15)		1.01 (0.87)	
2-sided 95% CI[‡]	(1.11, 1.82)		(0.85, 1.20)	
p-value[§]	0.006		0.920	
Best objective response rate				
Number (%) of subjects With CR[¶] + PR[#]	36 (21.1%)	31 (17.0%)	112 (32.9%)	107 (32.6%)
Odds Ratio (LCL[*])[♠]	1.30 (0.83)		1.01 (0.77)	

[*] LCL=Lower Confidence Limit
[†] Tamoxifen:ARIMIDEX
[‡] CI=Confidence Interval
[§] Two-sided Log Rank
[¶] CR=Complete Response
[#] PR=Partial Response
[♠] ARIMIDEX:Tamoxifen

Figure 3 - Kaplan-Meier probability of time to disease progression for all randomized patients (intent-to-treat) in Trial 0030

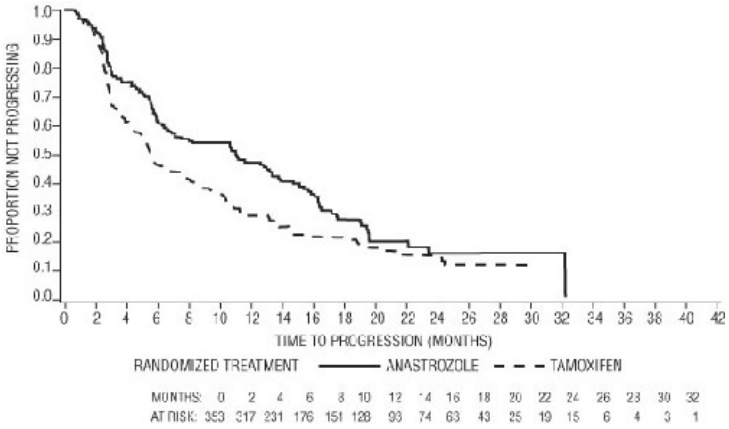
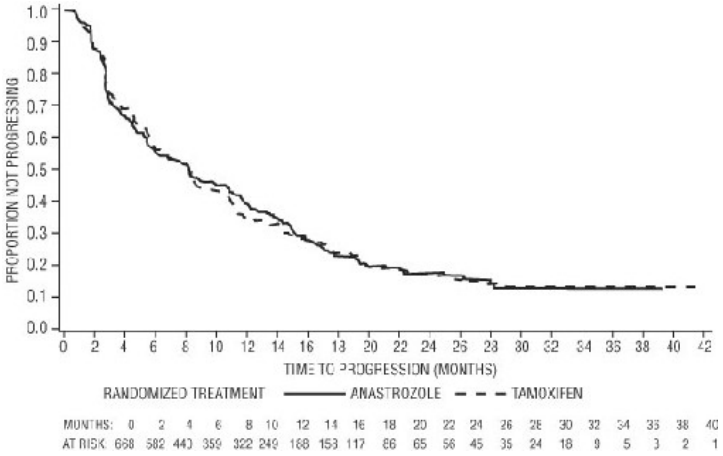


Figure 4 - Kaplan-Meier probability of time to progression for all randomized patients (intent-to-treat) in Trial 0027



Results from the secondary endpoints were supportive of the results of the primary efficacy endpoints. There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

14.3 Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy

Anastrozole was studied in two 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.

Efficacy results from the two studies were similar as presented in Table 12. In both studies there were no significant differences between treatment arms with respect to any of the efficacy parameters listed in the table below.

Table 12– Efficacy Results of Second-line Treatment

	ARIMIDEX 1 mg	**ARIMIDEX 10 mg**	**Megestrol Acetate 160 mg**
Trial 0004			
(N. America)	(n=128)	(n=130)	(n=128)
Median Fol1ow-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

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.

Table 13 – Pooled Efficacy Results of Second-line Treatment

Trials 0004 & 0005 (Pooled Data)	ARIMIDEX 1 mg N=263	ARIMIDEX 10 mg N=248	Megestrol Acetate 160 mg 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	4.8	5.3	4.6
Objective Response (all patients) (%)	12.5	12.5	12.3

16 HOW SUPPLIED/STORAGE AND HANDLING

These tablets are supplied in bottles of 30 tablets (NDC 0310-0201-30).

Storage:

Store at controlled room temperature, 20-25°C (68-77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

17.1 Pregnancy

Patients should be advised that ARIMIDEX may cause fetal harm. They should also be advised that ARIMIDEX is not for use in premenopausal women; therefore, if they become pregnant they should stop taking ARIMIDEX and immediately contact their doctor.

17.2 Allergic (Hypersensitivity) Reactions

Patients should be informed of the possibility of serious allergic reactions with swelling of the face, lips, tongue and/or throat (angioedema) which may cause difficulty in swallowing and/or breathing and to immediately report this to their doctor.

17.3 Ischemic Cardiovascular Events

Patients with pre-existing ischemic heart disease should be informed that an increased incidence of cardiovascular events has been observed with ARIMIDEX use compared to tamoxifen use.

17.4 Bone Effects

Patients should be informed that ARIMIDEX lowers the level of estrogen. This may lead to a loss of the mineral content of bones, which might decrease bone strength. A possible consequence of decreased mineral content of bones is an increase in the risk of fractures.

17.5 Cholesterol

Patients should be informed that an increased level of cholesterol might be seen while receiving ARIMIDEX.

17.6 Tamoxifen

Patients should be advised not to take ARIMIDEX with Tamoxifen.

17.7 FDA-Approved Patient Labeling

PATIENT INFORMATION

ARIMIDEX®
(anastrozole) (an as' troe zole)
Tablets

Read the information that comes with ARIMIDEX before you start taking it and each time you get a refill. The information may have changed. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. Talk with your doctor about ARIMIDEX when you start taking it and at regular checkups.

What is ARIMIDEX?

ARIMIDEX is a prescription medicine used in women who have finished menopause ("the change of life") for:

- treatment of early breast cancer
  - after surgery, with or without radiation
  - in women whose breast cancer is hormone receptor-positive

- first treatment of locally advanced or metastatic breast cancer, in women whose breast cancer is hormone receptor-positive or the hormone receptors are not known.

- treatment of advanced breast cancer, if the cancer has grown, or the disease has spread after tamoxifen therapy.

ARIMIDEX does not work in women with breast cancer who have not finished menopause (premenopausal women).

Who should not take ARIMIDEX?

Do not take ARIMIDEX if you:

- are pregnant, think you may be pregnant, or plan to get pregnant. ARIMIDEX may harm your unborn child. If you become pregnant while taking ARIMIDEX, tell your doctor right away.
- have not finished menopause (are premenopausal)
- are allergic to any of the ingredients in ARIMIDEX. See the end of this leaflet for a list of the ingredients in ARIMIDEX.
- are a man or child

What is the most important information I should know about ARIMIDEX?

ARIMIDEX may cause serious side effects including:

- **Heart disease.** Women with early breast cancer, who have a history of blockages in heart arteries (ischemic heart disease) and who take ARIMIDEX may have a slight increase in this type of heart disease compared to similar patients who take tamoxifen.
  - Stop taking ARIMIDEX and call your doctor right away if you have chest pain or shortness of breath. These can be symptoms of heart disease.

- **Osteoporosis (bone softening and weakening).** ARIMIDEX lowers estrogen in your body, which may cause your bones to become softer and weaker. This can increase your chance of fractures, specifically of the spine, hip and wrist. Your doctor may order a test for you called a bone mineral density study before you start taking ARIMIDEX and during treatment with ARIMIDEX as needed.

What should I tell my doctor before taking ARIMIDEX?

ARIMIDEX may not be right for you. Before taking ARIMIDEX, tell your doctor about all your medical conditions, including if you:

- have not finished menopause. Talk to your doctor if you are not sure. See "Who should not take ARIMIDEX?"
- have had a previous heart problem
- have a condition called osteoporosis
- have high cholesterol
- are pregnant, planning to become pregnant, or breast feeding. See "Who should not take ARIMIDEX?"
- are nursing a baby. It is not known if ARIMIDEX passes into breast milk. You and your doctor should decide if you will take ARIMIDEX or breast feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **Tamoxifen.** You should not take **ARIMIDEX** with tamoxifen. Taking tamoxifen with ARIMIDEX may lower the amount of ARIMIDEX in your blood and may cause ARIMIDEX not to work as well.

- **Medicines containing estrogen.** ARIMIDEX may not work if taken with one of these medicines:
  - hormone replacement therapy
  - birth control pills
  - estrogen creams
  - vaginal rings
  - vaginal suppositories

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take ARIMIDEX?

- Take ARIMIDEX exactly as prescribed by your doctor. Keep taking ARIMIDEX for as along as your doctor prescribes it for you.
- Take one ARIMIDEX tablet each day.
- ARIMIDEX can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Take your next regularly scheduled dose. Do not take two doses at the same time.
- If you have taken more ARIMIDEX than your doctor has prescribed, contact your doctor right away. Do not take any additional ARIMIDEX until instructed to do so by your doctor.

Talk with your doctor about any health changes you have while taking ARIMIDEX.

What are possible side effects of ARIMIDEX?

ARIMIDEX can cause serious side effects including:

- See **"What is the most important information I should know about ARIMIDEX?"**
- **increased blood cholesterol (fat in the blood).** You doctor may check your cholesterol while you take ARIMIDEX therapy.
- **skin reactions**. Stop taking ARIMIDEX and call your doctor right away if you get any skin lesions, ulcers, or blisters.
- **severe allergic reactions**. Get medical help right away if you have:
    - swelling of the face, lips, tongue, or throat.
    - trouble swallowing
    - trouble breathing
- **liver problems**. ARIMIDEX can cause inflammation of the liver and changes in blood tests of the liver function. Your doctor may monitor you for this. Stop taking ARIMIDEX and call your doctor right away if you have any of these signs or symptoms of a liver problem:
    - a general feeling of not being well
    - yellowing of the skin or whites of the eyes
    - pain on the right side of your abdomen

Common side effects in women taking ARIMIDEX include:

- hot flashes
- weakness
- joint pain
- pain
- sore throat
- mood changes
- high blood pressure
- depression
- nausea and vomiting
- rash

- back pain
- sleep problems
- bone pain
- headache
- swelling
- increased cough
- shortness of breath
- lymphedema (build up of lymph fluid in the tissues of your affected arm)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

HOW SHOULD I STORE ARIMIDEX?

- Store ARIMIDEX at 68°F to 77°F (20°C to 25°C).
- Keep ARIMIDEX and all medicines out of the reach of children.

General information about ARIMIDEX.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take ARIMIDEX for a condition for which it was not prescribed. Do not give ARIMIDEX to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about ARIMIDEX. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ARIMIDEX that is written for health professionals.For more information call 1-866-992-9276 or go to www.ARIMIDEX.com.

What are the ingredients in ARIMIDEX?

Active ingredient: anastrozole

Inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose,
polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

November 2008

Rev 11-04-08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20541Orig1s023

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 19, 2008
To:	Robert Justice, M.D., Director **Division of Drug Oncology Products (DDOP)**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling #2 (Patient Package Insert)
Drug Name(s):	Arimidex (anastrazole) tablet for oral use
Application Type/Number:	NDA 20-541
Submission Number:	023
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2008-568

1 INTRODUCTION

AstraZeneca submitted a Prior Approval Labeling Supplement, with a request for expedited review, to their New Drug Application (NDA) for Arimidex, sNDA20-541/S-023 on November 29, 2007. The purpose of the supplement is to convert the existing labeling to PLR format. The sponsor has submitted patient labeling in the form of a Patient Package Insert (PPI) as part of section 17 in the proposed draft PI. The sponsor currently has a Type 6 New Drug Application, NDA 22-214 with the Division of Metabolism and Endocrinology Drug Products which is pending the review of this supplement by the Division of Drug Oncology Products.

The Patient Labeling and Education Team previously reviewed the sponsor's proposed PPI and review division revisions to the PI and Professional Information (PI) for the this supplement, on May 2, 2008. Following this review, the review division requested additional comments from OSE in response to changes to the PPI submitted by the sponsor on September 10, 2008. Comments were provided to the review division by email on September 19th. The review division provided their most updated labeling (PI and PPI) to the patient information reviewer at a labeling meeting on September 24, 2008. Upon further review, it was noted that with conversion of the PI to PLR format, certain information from the ATAC study was moved to the Warnings and Precautions section of the PI, and possibly new information was added to the PI.

2 MATERIAL REVIEWED

- DRAFT Arimidex Professional Information (PI) as revised by the review division September 24, 2008
- DRAFT Arimidex Professional Information (PI) as revised by the review division April 22, 2008
- DRAFT Arimidex Professional Information (PI) as revised by the review division April 8, 2008
- Arimidex Patient Package Insert (PPI) submitted April 22, 2008
- Arimidex Patient Package Insert (PPI) submitted by the sponsor on September 10, 2008
- Arimidex Patient Package Insert (PPI) revised by the review division on September 14, 2008.
- Dr. Bhupinder Mann's completed document "Review of Ischemic Cardiovascular Events, dated September 25, 2008.

3 DISCUSSION

In reviewing the September 24, 2008 PI as revised by the review division, the Patient Information Reviewer noted that general information was added to the Warnings and Precautions section of the PI and more detailed information was added to the Adverse Reactions section of the PI addressing increase in ischemic cardiovascular events in the patient population with pre-existing heart disease in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial. It is unclear whether the added information represents new information or re-analysis of existing data. Dr. Bhupinder Mann's "Review of Ischemic Cardiovascular Events" highlighted significant concerns on the part of the reviewer. The recommendation for regulatory action states:

- "The reviewer finds the finding of increase in the ischemic cardiovascular events in patient population with pre-existing ischemic heart disease concerning. It is recommended that this information be included in the Arimidex label under the Warnings and Precautions."

Dr. Mann's conclusions and recommendations state the following:

- "Data from ATAC and other anastrozole trials strongly suggest that anastrazole increases the risk of ischemic cardiovascular events in a patient population with increased baseline cardiovascular risk."
- "Data from two letrazole studies heightens this concern and is supportive of a class effect, although, there may be differences between steroidal and non-steroidal aromatase inhibitors."

In light of Dr. Mann'sconcerns, the suggested labeling changes, and information from the ATAC trial, OSE considered the need for a Medication Guide (MG) to convey the concerns about the increased risk of ischemic cardiovascular events associated with ARIMIDEX in the identified subset of patients. OSE feels that a MG is warranted for Arimidex to inform patients with pre-existing ischemic cardiovascular disease of the increased risk of ischemic cardiovascular events. The review division has conveyed in discussion and email that they do not feel that there is sufficient evidence to support the need for a MG at this time for Arimidex.

The Medication Guide Regulations as specified in 21 CFR208.1 (a) states that a Medication Guide may be required for products that FDA "…determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information." OSE feels that under 21 CFR208.1 (c), Arimidex may meet the requirements for a Medication Guide based on criteria 2:

"The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning risk(s) could affect patients' decision to use, or to continue to use, the product."

On October 17, 2008, OSE staff met with members of DDOP to discussour concerns and reasons why we believe that a MG is warranted for Arimidex..

At that time, the review division clarified that the information now proposed for inclusion in the PI is based on an exploratory subset analysis. Cardiovascular events were a pre-specified endpoint in the ATAC trial; however, this is a re-analysis of existing data. The review division stated that the new information in the PI represents a new signal; however, OSE and DDOP agree that there is significant disparity in the data making it difficult to reach a firm conclusion. It is not possible to compare data with Femara. The Femara trial ended early due to the findings of efficacy. Additionally, since the ATAC trial showed that disease-free survival was statistically significantly better in women taking Arimidex compared with Tamoxifen alone or in combination in postmenopausal women whose early-stage tumors were hormone receptor positive, the review division expressed concern about unduly worrying and burdening patients until the risk can be further clarified.

4 CONCLUSIONS AND RECOMMENDATIONS

1. OSE does not agree with DDOP's proposal to wait for the review division to complete a review of a recently submitted PSUR and OSE review of AERS cases before determining

if a MG is needed. OSE believes that data from randomized clinical trials is needed to adequately look at this issue. Spontaneous reports from AERS and PSUR data are not adequate to address this issue. OSE suggests consultation by DCRP to look at the available data for input on the cardiovascular signal.

2. OSE concurs with the DDOP suggestion that DDOP develop a proposal for AstraZeneca to provide a new analysis of all trials involving Arimidex, including those with placebo and other products to look at the issue of cardiovascular events in the subset of interest specifically. This will be included as a Post-Marketing Request to the sponsor.

   In the interim, the proposed language will be included in the Warnings and Precautions and Adverse Reactions sections of the PI.

3. OSE concurs that a PPI will suffice until further analyses are conducted. However, because there is no distribution requirement for PPIs, OSE remains concerned that patients will not likely receive the important information. Arimidex tablets are supplied in bottles of 30 tablets. Except where drug products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. Requiring a MG would require the manufacturer to comply with the Medication Guide Regulations and ensure distribution of the MG to each patient who receives a prescription for Arimidex. Since DDOP determined that a MG will not be implemented at this time, more responsibility will be placed on healthcare providers to appropriately educate patients about the risks and benefits associated with Arimidex. The sponsor should ensure that healthcare providers receive adequate education about this issue.

4. Significant revisions were made to the PPI. This was because of the new information in the PI, and because many of our revisions from our May 2, 2008 review were not incorporated by DDOP. Language in some areas such as "What is Arimidex?" was not consistent with the language in the PI. We reiterate that we do not agree with patterning the Arimidex PPI after the Evista PPI.

5. We have again bulleted the section "What are the possible side effects of Arimidex?" for improved readability.

6. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

   In our review of the PPI, we have:
   - simplified wording where possible,
   - made it consistent with the Professional Information,
   - rearranged information due to conversion of the PI to PLR format,
   - removed unnecessary or redundant information
   - Although not required for Patient Information, we have put this PPI in the question–and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
   - ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

7. See the attached document for our marked up and clean revisions to the PPI. Comments to the review division are ***bolded, underlined, and italicized.*** We will provide the review division with a marked-up and clean copy of the revised PPI in Word.

   All future relevant changes to the PI should also be reflected in the PPI. OSE will reconsider the need to convert the PPI to a Medication Guide as new information becomes available.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Mills
10/20/2008 09:25:37 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
10/20/2008 10:30:41 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 2, 2008
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Education and Labeling Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Arimidex (anastrazole) tablets
Application Type/Number:	NDA 20-541
Submission Number:	023
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2008-568

1 INTRODUCTION

AstraZeneca submitted a Prior Approval Labeling Supplement, with a request for expedited review, to their New Drug Application (NDA) for Arimidex, sNDA20-541/S-023 on November 29, 2007. The purpose of the supplement is to convert the existing labeling to PLR format. The sponsor has submitted patient labeling in the form of a PPI as part of section 17 in the proposed draft PI. The sponsor currently has a Type 6 New Drug Application, NDA 22-214 with the Division of Metabolism and Endocrinology Drug Products which is pending the review of this supplement by the Division of Drug Oncology Products

2 MATERIAL REVIEWED

- Arimidex Patient Package Insert (PPI) submitted April 22, 2008
- Arimidex Prescribing Information (PI) revised by the review division on April 8, 2008
- Arimidex Prescribing Information (PI) revised and submitted by the sponsor on April 22, 2008

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 6.5, and a Flesch Reading Ease score of 64.8. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question–and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

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See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The Review Division should consult the Safety Requirements Team as soon as possible to determine if this new PPI will trigger a Risk Mitigation and Evaluation Strategy (REMS).

2. Arimidex tablets are supplied in bottles of 30 tablets. A PPI for TRADENAME is voluntary. Except where drug products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The Sponsor should state their mechanism for intended distribution of the PPI to patients.

3. In the section "What are the possible side effects of Arimidex?"
   - General feeling of not being well, jaundice, liver pain and liver swelling are the symptoms that the sponsor lists in the PI and tells patients to report about possible liver problems. Clarify if other liver signs and symptoms have been seen, such as fatigue, itching, nausea, dark urine, etc. If so, add to the PI and PPI. The PI and the PPI must be consistent. Patients will not be able to distinguish liver pain from other abdominal pain, as well as liver swelling. We have revised this to say "pain on the right side of your abdomen". As stated, these are clinical diagnoses and have been deleted.
   - (b) (4) We deleted this information from the fracture bullet.
   - We recommend listing side effects in two lists: serious and common. The serious side effects should always be listed first. The PPI as proposed by the sponsor and revised by the RD and sponsor, has two lists of common side effects: those occurring in greater than 10% and those occurring in less than 10% of patients. Both lists are lengthy. The highlights section of the PI lists the most common (greater than 10%) by early breast cancer and advanced breast cancer. We suggest listing only those adverse events occurring in >10% of patients, (b) (4) . State "the most common side effects of ARIMIDEX include:" Use a column format to list the common side effects since the list is lengthy.
   - Clarify if the bullet for "joint symptoms (b) (4) ,, describes the adverse event called "bone pain" in the highlights section of the PI.
   - The bullet for (b) (4) has been deleted. It is not listed in the highlights section of the PI or in the second paragraph in section 6. (b) (4)

4. We have added the statement, "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008).

Although not required for voluntary PPIs like Arimidex, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

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/s/

Sharon Mills
5/2/2008 01:34:47 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
5/2/2008 02:47:23 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20541Orig1s023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Kacuba, Alice

From: Kacuba, Alice
Sent: Wednesday, October 29, 2008 2:12 PM
To: Valas, E Jane
Cc: Johnson, Jennifer
Subject: Arimidex FDA revised labeling

Importance: High

Attachments: 10-29-08-Combined-w-OSE-FDA-revised-labeling.doc

Hi,

The purpose of this email is to provide you the latest "FDA revised" labeling which includes OSE revisions to the PPI. Please reply with your concurrence by Tuesday, 11-4-08 by 2 PM so that I can provide Metabolic and Endocrine the "agreed upon" lableing.

Thank you.

Alice
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Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
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(f)301-796-9845
alice.kacuba@fda.hhs.gov

10-29-08-Combined
-w-OSE-FDA-re...

Tracking:

Recipient	Read
Valas, E Jane	
Johnson, Jennifer	Read: 10/29/2008 2:42 PM
Cortazar, Patricia	Read: 10/29/2008 2:58 PM
Fedenko, Katherine	Read: 10/29/2008 3:29 PM

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/s/

Alice Kacuba
10/30/2008 06:46:07 PM
Archiving FDA revised labeling that was sent to the Sponsor on 10-29-08.

Kacuba, Alice

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/s/

Alice Kacuba

10/29/2008 02:19:15 PM