

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**20541Orig1s027**

*Trade Name:*      **ARIMIDEX**

*Generic Name:*    Anastrozole

*Sponsor:*            AstraZeneca Pharmaceutical LP

*Approval Date:*    05/01/2013

*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:*  
**20541Orig1s027**

## CONTENTS

### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Other Review(s)</b>	<b>X</b>
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20541Orig1s027**

**APPROVAL LETTER**



NDA 020541/S-027

**SUPPLEMENT APPROVAL**

AstraZeneca Pharmaceuticals LP  
Attention: E. Jane Valas, Ph.D.  
Associate Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Dr. Valas:

Please refer to your Supplemental New Drug Application (sNDA) dated November 1, 2012, received November 2, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Arimidex® (anastrozole) Tablets, 1 mg.

We acknowledge receipt of your amendments dated April 17 and 19, 2013.

This Changes Being Effected supplemental new drug application provides for:

1. Revision to Section 6.2 Post-Marketing Experience to modify the text for trigger finger to include hypercalcemia (with or without an increase in parathyroid hormone).
2. Added myalgia to Section 6.2 Post-Marketing Experience.
3. In addition to reviewing the patient package insert, the FDA revised the text throughout the entire patient package insert.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert and patient package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **REPORTING REQUIREMENTS**

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 Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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

/s/  
-----

ROBERT L JUSTICE  
05/01/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20541Orig1s027**

**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**

### -----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, 6.1)
- Increases in total cholesterol may occur. Consider cholesterol monitoring. (5.3, 6.1)

### -----ADVERSE REACTIONS-----

In the early breast cancer (ATAC) study, the most common (occurring with an incidence of  $\geq 10\%$ ) 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](http://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: 05/2013**

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Adjuvant Treatment
- 1.2 First-Line Treatment
- 1.3 Second-Line Treatment

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose
- 2.2 Patients with Hepatic Impairment

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

- 4.1 Pregnancy and Premenopausal Women
- 4.2 Hypersensitivity

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Ischemic Cardiovascular Events
- 5.2 Bone Effects
- 5.3 Cholesterol

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Tamoxifen
- 7.2 Estrogen
- 7.3 Warfarin
- 7.4 Cytochrome P450

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

### 14 CLINICAL STUDIES

- 14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women
- 14.2 First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer
- 14.3 Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Storage

### 17 PATIENT COUNSELING INFORMATION

- 17.1 Pregnancy
- 17.2 Allergic (Hypersensitivity) Reactions
- 17.3 Ischemic Cardiovascular Events
- 17.4 Bone Effects
- 17.5 Cholesterol
- 17.6 Tamoxifen
- 17.7 Missed Doses

\* 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 (8.6)*].

#### 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 (8.7)*].

### 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. Consider bone mineral density monitoring in patients treated with ARIMIDEX [*see Adverse Reactions (6.1)*].

#### **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) [*see Adverse Reactions (6.1)*].

### **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  $\geq 10\%$ ) 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\***

<b>Body system and adverse reactions by COSTART<sup>†</sup> preferred term<sup>‡</sup></b>	<b>ARIMIDEX 1 mg (N<sup>§</sup> = 3092)</b>	<b>Tamoxifen 20 mg (N<sup>§</sup> = 3094)</b>
<b>Body as a whole</b>		
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)
<b>Cardiovascular</b>		
Vasodilatation	1104 (36)	1264 (41)
Hypertension	402 (13)	349 (11)
<b>Digestive</b>		
Nausea	343 (11)	335 (11)
Constipation	249 (8)	252 (8)
Diarrhea	265 (9)	216 (7)
Dyspepsia	206 (7)	169 (6)

<b>Body system and adverse reactions by COSTART<sup>†</sup> preferred term<sup>‡</sup></b>	<b>ARIMIDEX 1 mg (N<sup>§</sup> = 3092)</b>	<b>Tamoxifen 20 mg (N<sup>§</sup> = 3094)</b>
Gastrointestinal disorder	210 (7)	158 (5)
<b>Hemic and lymphatic</b>		
Lymphedema	304 (10)	341 (11)
Anemia	113 (4)	159 (5)
<b>Metabolic and nutritional</b>		
Peripheral edema	311 (10)	343 (11)
Weight gain	285 (9)	274 (9)
Hypercholesterolemia	278 (9)	108 (3.5)
<b>Musculoskeletal</b>		
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)
<b>Nervous system</b>		
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)
<b>Respiratory</b>		
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)
<b>Skin and appendages</b>		
Rash	333 (11)	387 (13)
Sweating	145 (5)	177 (6)
<b>Special Senses</b>		

<b>Body system and adverse reactions by COSTART<sup>†</sup> preferred term<sup>‡</sup></b>	<b>ARIMIDEX 1 mg (N<sup>§</sup> = 3092)</b>	<b>Tamoxifen 20 mg (N<sup>§</sup> = 3094)</b>
Cataract Specified	182 (6)	213 (7)
<b>Urogenital</b>		
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)
Vaginal Hemorrhage <sup>¶</sup>	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.

<sup>†</sup> COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

<sup>‡</sup> A patient may have had more than 1 adverse reaction, including more than 1 adverse reaction in the same body system.

<sup>§</sup> N=Number of patients receiving the treatment.

<sup>¶</sup> 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\***

	<b>ARIMIDEX N=3092 (%)</b>	<b>Tamoxifen N=3094 (%)</b>	<b>Odds-ratio</b>	<b>95% CI</b>
Hot Flashes	1104 (36)	1264 (41)	0.80	0.73 – 0.89
Musculoskeletal Events <sup>†</sup>	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

	<b>ARIMIDEX N=3092 (%)</b>	<b>Tamoxifen N=3094 (%)</b>	<b>Odds-ratio</b>	<b>95% CI</b>
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.

Because ARIMIDEX lowers circulating estrogen levels it may cause a reduction in bone mineral density.

A post-marketing trial assessed the combined effects of ARIMIDEX and the bisphosphonate risedronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture.

Postmenopausal women with early breast cancer scheduled to be treated with ARIMIDEX should have their bone status managed according to treatment guidelines already available for postmenopausal women at similar risk of fragility fracture.

### *Cholesterol*

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

A post-marketing trial also evaluated any potential effects of ARIMIDEX on lipid profile. In the primary analysis population for lipids (ARIMIDEX alone), there was no clinically significant change in LDL-C from baseline to 12 months and HDL-C from baseline to 12 months.

In secondary population for lipids (ARIMIDEX+risedronate), there also was no clinically significant change in LDL-C and HDL-C from baseline to 12 months.

In both populations for lipids, there was no clinically significant difference in total cholesterol (TC) or serum triglycerides (TG) at 12 months compared with baseline.

In this trial, treatment for 12 months with ARIMIDEX alone had a neutral effect on lipid profile. Combination treatment with ARIMIDEX and risedronate also had a neutral effect on lipid profile.

The trial provides evidence that postmenopausal women with early breast cancer scheduled to be treated with ARIMIDEX should be managed using the current National Cholesterol Education Program guidelines for cardiovascular risk-based management of individual patients with LDL elevations.

### *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.

### *10-year median follow-up Safety Results from the ATAC Trial*

Results are consistent with the previous analyses.

Serious adverse reactions were similar between ARIMIDEX (50%) and tamoxifen (51%).

- Cardiovascular events were consistent with the known safety profiles of ARIMIDEX and tamoxifen.
- The cumulative incidences of all first fractures (both serious and non-serious, occurring either during or after treatment) was higher in the ARIMIDEX group (15%) compared to the tamoxifen group (11%). This increased first fracture rate during treatment did not continue in the post-treatment follow-up period.
- The cumulative incidence of new primary cancers was similar in the ARIMIDEX group (13.7%) compared to the tamoxifen group (13.9%). Consistent with the previous analyses, endometrial cancer was higher in the tamoxifen group (0.8%) compared to the ARIMIDEX group (0.2%).
- The overall number of deaths (during or off-trial treatment) was similar between the treatment groups. There were more deaths related to breast cancer in the tamoxifen than in the ARIMIDEX treatment group.

#### 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)
<b>Whole body</b>		
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)
<b>Cardiovascular</b>		
Vasodilation	128 (25)	106 (21)
Hypertension	25 (5)	36 (7)
<b>Digestive</b>		
Nausea	94 (19)	106 (21)



<b>Body system Adverse Reaction*</b>	<b>Number (%) of subjects</b>	
	<b>ARIMIDEX (N=506)</b>	<b>Tamoxifen (N=511)</b>
Constipation	47 (9)	66 (13)
Diarrhea	40 (8)	33 (6)
Vomiting	38 (8)	36 (7)
Anorexia	26 (5)	46 (9)
<b>Metabolic and Nutritional</b>		
Peripheral edema	51 (10)	41 (8)
<b>Musculoskeletal</b>		
Bone pain	54 (11)	52 (10)
<b>Nervous</b>		
Dizziness	30 (6)	22 (4)
Insomnia	30 (6)	38 (7)
Depression	23 (5)	32 (6)
Hypertonia	16 (3)	26 (5)
<b>Respiratory</b>		
Cough increased	55 (11)	52 (10)
Dyspnea	51 (10)	47 (9)
Pharyngitis	49 (10)	68 (13)
<b>Skin and appendages</b>		
Rash	38 (8)	34 (8)
<b>Urogenital</b>		
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**

Adverse Reaction*	Number (n) and Percentage of Patients	
	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 <sup>†</sup>	18 (4)	33 (6)
Venous <sup>†</sup>	5	15
Coronary and Cerebral <sup>‡</sup>	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 reaction.

<sup>†</sup> Includes pulmonary embolus, thrombophlebitis, retinal vein thrombosis.

<sup>‡</sup> 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		ARIMIDEX		Megestrol Acetate	
	1 mg (N=262) n	%	10 mg (N=246) n	%	160 mg (N=253) n	%

Adverse Reaction*	ARIMIDEX		ARIMIDEX		Megestrol Acetate	
	1 mg		10 mg		160 mg	
	(N=262)		(N=246)		(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 than 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 (alopecia); pruritus

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

The incidences of the following adverse reaction 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**

Adverse Reaction Group	ARIMIDEX		ARIMIDEX		Megestrol Acetate	
	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

These adverse reactions are reported voluntarily from a population of uncertain size. Therefore, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The following have been reported in post-approval use of Arimidex:

- Hepatobiliary events including increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-GT, and bilirubin; hepatitis
- Rash including cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome
- Cases of allergic reactions including angioedema, urticaria and anaphylaxis [*see Contraindications (4.2)*]
- Myalgia, trigger finger and hypercalcemia (with or without an increase in parathyroid hormone)

## 7 DRUG INTERACTIONS

### 7.1 Tamoxifen

Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration 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 of 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<sup>2</sup> 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<sub>0-24hr</sub> 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<sup>2</sup> 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  $\geq 50\%$  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  $+ 6.6 \pm 7.9$  cm<sup>3</sup> in the ARIMIDEX-treated patients and  $+ 5.2 \pm 8.0$  cm<sup>3</sup> 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  $5.9 \pm 2.0$  years, a mean bone age of  $8.6 \pm 2.6$  years, a mean growth rate of  $7.9 \pm 2.9$  cm/year and a mean Tanner stage for breast of  $2.7 \pm 0.81$ . 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  $7.9 \pm 2.9$  cm/year to  $6.5 \pm 2.8$  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  $\geq 65$  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)*].

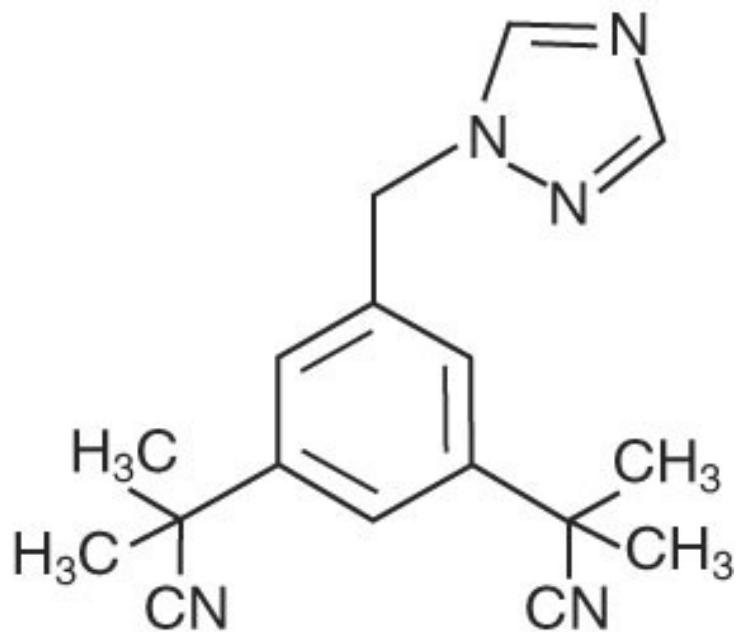
## 10 OVERDOSAGE

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 overdose 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  $C_{17}H_{19}N_5$  and its structural formula is:





Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The growth of many cancers of the breast is stimulated or maintained by estrogens.

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 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  $K_i$  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<sup>2</sup>) 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 (8.6)*].

#### *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 within 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 (8.7)*].

## **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<sup>2</sup> 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<sub>0-24 hr</sub> 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<sup>2</sup> 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<sup>2</sup> basis and 9 times higher than the AUC<sub>0-24 hr</sub> 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<sup>2</sup> 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<sub>ssmax</sub> and AUC<sub>0-24 hr</sub> 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<sub>ssmax</sub> and AUC<sub>0-24 hr</sub> 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<sup>2</sup> 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<sup>2</sup> 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  $AUC_{0-24\text{ hr}}$  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  $\text{mg}/\text{m}^2$  basis); there was no evidence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a  $\text{mg}/\text{m}^2$  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 (7.1)*].

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	Tamoxifen	ARIMIDEX 1 mg
	1 mg (N*=3125)	20 mg (N*=3116)	plus Tamoxifen <sup>†</sup> 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
<b>Age Distribution (%)</b>			
<45 yrs.	0.7	0.4	0.5

<b>Demographic Characteristic</b>	<b>ARIMIDEX 1 mg (N*=3125)</b>	<b>Tamoxifen 20 mg (N*=3116)</b>	<b>ARIMIDEX 1 mg plus Tamoxifen<sup>†</sup> 20 mg (N*=3125)</b>
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
<b>Receptor Status (%)</b>			
Positive <sup>‡</sup>	83.5	83.1	84.0
Negative <sup>§</sup>	7.4	8.0	7.0
Other <sup>¶</sup>	8.8	8.6	9.0
<b>Other Treatment (%) prior to Randomization</b>			
Mastectomy	47.8	47.3	48.1
Breast conservation <sup>#</sup>	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
<b>Primary Tumor Size (%)</b>			
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
<b>Nodal Status (%)</b>			
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
<b>Tumor Grade (%)</b>			
Well-differentiated	20.8	20.5	21.2
Moderately differentiated	46.8	47.8	46.5
Poorly/undifferentiated	23.7	23.3	23.7

Demographic Characteristic	ARIMIDEX 1 mg (N*=3125)	Tamoxifen 20 mg (N*=3116)	ARIMIDEX 1 mg plus Tamoxifen <sup>†</sup> 20 mg (N*=3125)
Not assessed/recorded	8.7	8.4	8.5

\* N=Number of patients randomized to the treatment

<sup>†</sup> The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up

<sup>‡</sup> Includes patients who were estrogen receptor (ER) positive or progesterone receptor (PgR) positive, or both positive

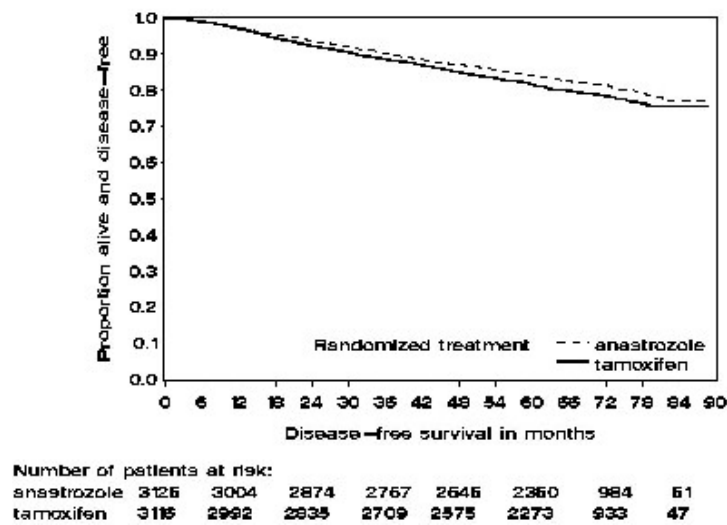
<sup>§</sup> Includes patients with both ER negative and PgR negative receptor status

<sup>¶</sup> Includes all other combinations of ER and PgR receptor status unknown

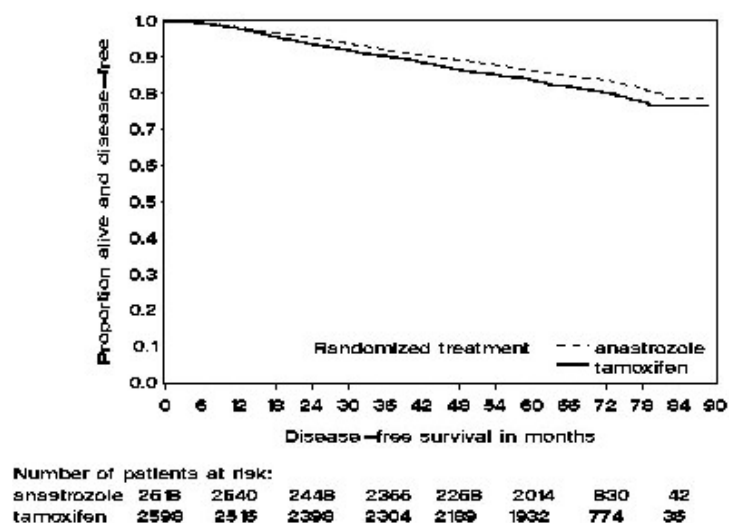
<sup>#</sup> Among the patients who had breast conservation, radiotherapy was administered to 95.0% of patients in the ARIMIDEX arm, 94.1% in the tamoxifen arm and 94.5% in the ARIMIDEX plus tamoxifen arm.

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 <sup>†</sup>		Hormone Receptor-Positive Subpopulation <sup>‡</sup>	
	ARIMIDEX 1 mg (N <sup>†</sup> =3125)	Tamoxifen 20 mg (N <sup>†</sup> =3116)	ARIMIDEX 1 mg (N <sup>‡</sup> =2618)	Tamoxifen 20 mg (N <sup>‡</sup> =2598)
Median Duration of Therapy (mo)	60	60	60	60
Median Efficacy Follow-up (mo)	68	68	68	68
Loco-regional	119 (3.8)	149 (4.8)	76 (2.9)	101 (3.9)



	Intent-To-Treat Population <sup>‡</sup>		Hormone Receptor-Positive Subpopulation <sup>‡</sup>	
	ARIMIDEX 1 mg (N <sup>†</sup> =3125)	Tamoxifen 20 mg (N <sup>†</sup> =3116)	ARIMIDEX 1 mg (N <sup>†</sup> =2618)	Tamoxifen 20 mg (N <sup>†</sup> =2598)
recurrence				
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 in situ	8 (0.3)	6 (0.2)	5 (0.2)	5 (0.2)
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.

<sup>†</sup> N=Number of patients randomized.

<sup>‡</sup> 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	
<b>Disease-free Survival</b>	575	651	424	497
Hazard ratio	0.87		0.83	

	<b>Intent-To-Treat Population</b>		<b>Hormone Receptor-Positive Subpopulation</b>	
	<b>ARIMIDEX</b>	<b>Tamoxifen</b>	<b>ARIMIDEX</b>	<b>Tamoxifen</b>
	<b>1 mg</b>	<b>20 mg</b>	<b>1 mg</b>	<b>20 mg</b>
	<b>(N=3125)</b>	<b>(N=3116)</b>	<b>(N=2618)</b>	<b>(N=2598)</b>
	<b>Number of Events</b>		<b>Number of Events</b>	
2-sided 95% CI	0.78 to 0.97		0.73 to 0.94	
p-value	0.0127		0.0049	
<b>Distant Disease-free Survival</b>	500	530	370	394
Hazard ratio	0.94		0.93	
2-sided 95% CI	0.83 to 1.06		0.80 to 1.07	
<b>Overall Survival</b>	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.

#### *10-year median follow-up Efficacy Results from the ATAC Trial*

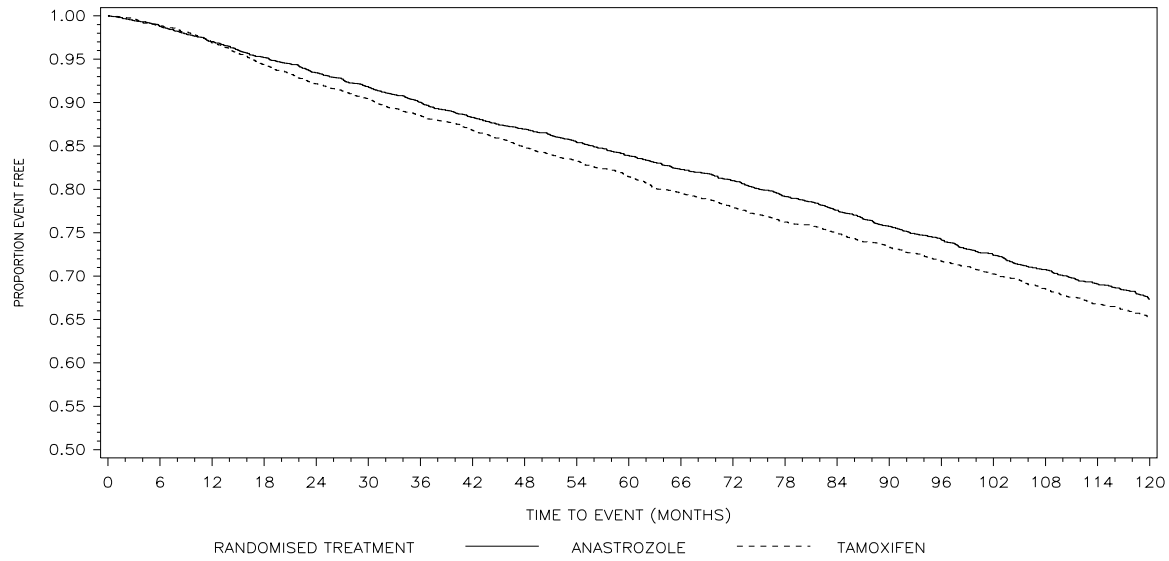
In a subsequent analysis of the ATAC trial, patients in the two monotherapy arms were followed for a median of 120 months (10 years). Patients received study treatment for a median of 60 months (5 years) (see Table 10).

**Table 10 - Efficacy Summary**

	<b>Intent-To-Treat Population</b>		<b>Hormone Receptor-Positive Subpopulation</b>	
--	-----------------------------------	--	--	--

	<b>ARIMIDEX</b>	<b>Tamoxifen</b>	<b>ARIMIDEX</b>	<b>Tamoxifen</b>
	<b>1 mg</b>	<b>20 mg</b>	<b>1 mg</b>	<b>20 mg</b>
	<b>(N=3125)</b>	<b>(N=3116)</b>	<b>(N=2618)</b>	<b>(N=2598)</b>
	<b>Number of Events</b>		<b>Number of Events</b>	
<b>Disease-free Survival</b>	953	1022	735	924
Hazard ratio	0.91		0.86	
2-sided 95% CI	0.83 to 0.99		0.78 to 0.95	
p-value	0.0365		0.0027	
<b>Overall Survival</b>	734	747	563	586
Hazard ratio	0.97		0.95	
2-sided 95% CI	0.88 to 1.08		0.84 to 1.06	

**Figure 3 - Disease-Free Survival Kaplan Meier Survival Curve for all Patients Randomized to ARIMIDEX or Tamoxifen Monotherapy in the ATAC Trial (Intent-to-Treat)<sup>(a)</sup>**



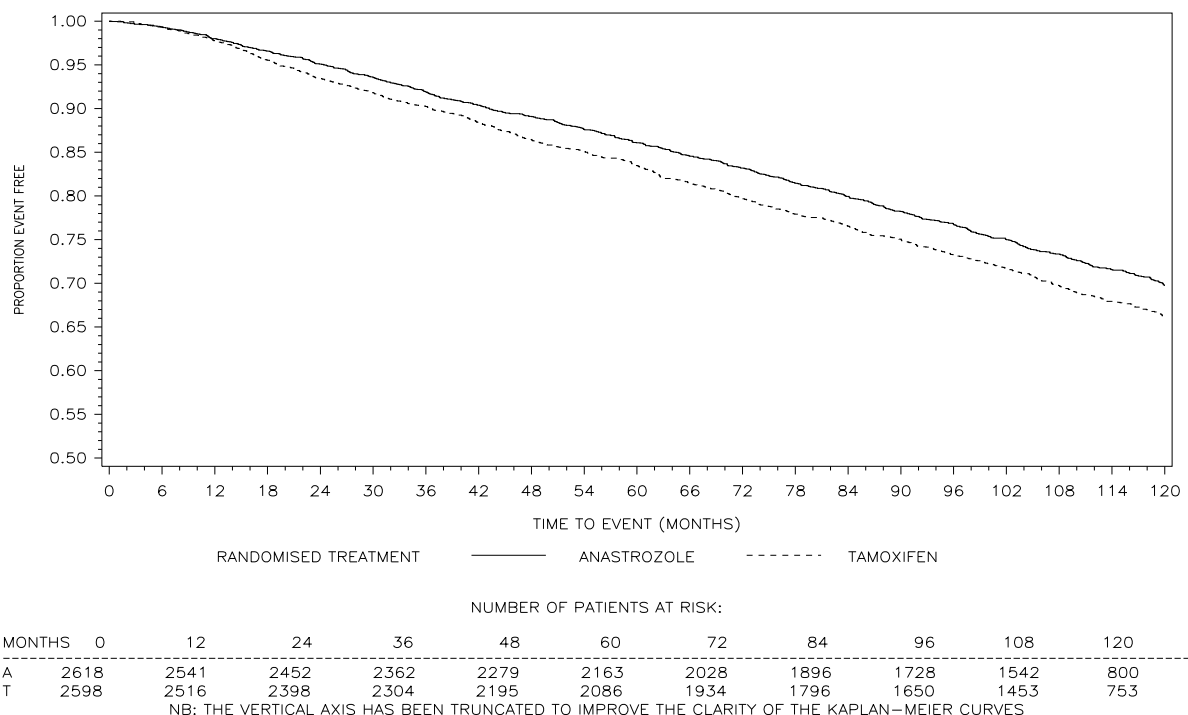
NUMBER OF PATIENTS AT RISK:

MONTHS	0	12	24	36	48	60	72	84	96	108	120
A	3125	3005	2878	2765	2658	2519	2356	2194	1991	1773	934
T	3116	2992	2836	2711	2584	2439	2261	2107	1940	1709	898

NB: THE VERTICAL AXIS HAS BEEN TRUNCATED TO IMPROVE THE CLARITY OF THE KAPLAN-MEIER CURVES

<sup>a</sup> The proportion of patients with 120 months' follow-up was 29.4%.

**Figure 4 - Disease-Free Survival for Hormone Receptor-Positive Subpopulation of Patients Randomized to ARIMIDEX or Tamoxifen Monotherapy in the ATAC Trial<sup>(b)</sup>**



<sup>b</sup> The proportion of patients with 120 months' follow-up was 29.8%.

### 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 endpoints 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 11 – Demographic and Other Baseline Characteristics**

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

\* 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 12 and Figures 5 and 6).

Table 12 below summarizes the results of trial 0030 and trial 0027 for the primary efficacy endpoints.

**Table 12 – 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%)
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				

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)
Number (%) of subjects With CR <sup>¶</sup> + PR <sup>#</sup>	36 (21.1%)	31 (17.0%)	112 (32.9%)	107 (32.6%)
Odds Ratio (LCL <sup>*</sup> ) <sup>▲</sup>	1.30 (0.83)		1.01 (0.77)	

\* LCL=Lower Confidence Limit

† Tamoxifen:ARIMIDEX

‡ CI=Confidence Interval

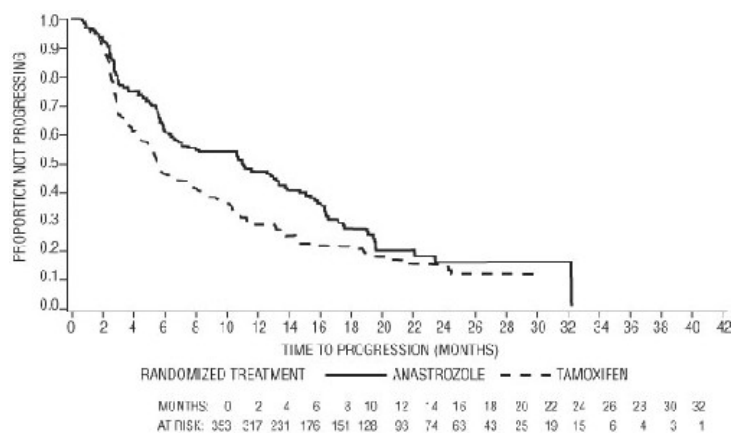
§ Two-sided Log Rank

¶ CR=Complete Response

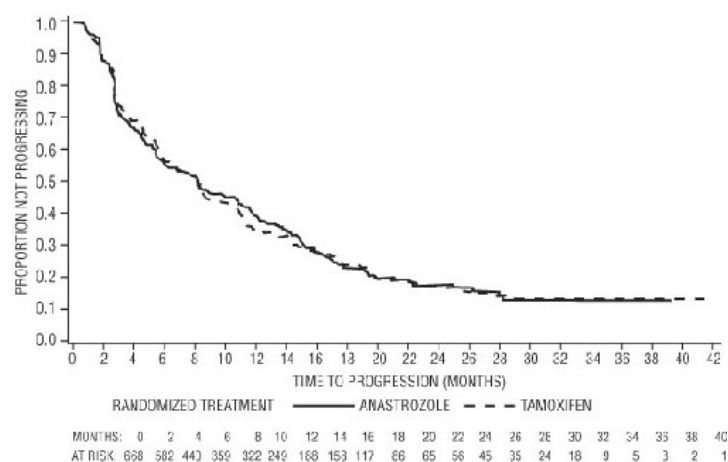
# PR=Partial Response

▲ ARIMIDEX:Tamoxifen

**Figure 5 - Kaplan-Meier probability of time to disease progression for all randomized patients (intent-to-treat) in Trial 0030**



**Figure 6 - 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 13. 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 13 – Efficacy Results of Second-line Treatment**

	<b>ARIMIDEX 1 mg</b>	<b>ARIMIDEX 10 mg</b>	<b>Megestrol Acetate 160 mg</b>
<b>Trial 0004</b>			
<b>(N. America)</b>	<b>(N=128)</b>	<b>(N=130)</b>	<b>(N=128)</b>
Median Follow-up (months)*	31.3	30.9	32.9
Median Time to Death (months)	29.6	25.7	26.7
2 Year Survival Probability (%)	62.0	58.0	53.1
Median Time to Progression (months)	5.7	5.3	5.1
Objective Response (all patients) (%)	12.5	10.0	10.2
Stable Disease for >24 weeks (%)	35.2	29.2	32.8
Progression (%)	86.7	85.4	90.6
<b>Trial 0005</b>			
<b>(Europe, Australia, S. Africa)</b>	<b>(N=135)</b>	<b>(N=118)</b>	<b>(N=125)</b>
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 14 – Pooled Efficacy Results of Second-line Treatment**

<b>Trials 0004 &amp; 0005 (Pooled Data)</b>	<b>ARIMIDEX 1 mg N=263</b>	<b>ARIMIDEX 10 mg N=248</b>	<b>Megestrol Acetate 160 mg N=253</b>
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**

See FDA approved patient labeling (Patient 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 seek medical attention immediately.

**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. If patients have new or worsening chest pain or shortness of breath they should seek medical attention immediately.

#### **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 Missed Doses**

Inform patients that if they miss a dose, take it as soon as they remember. If it is almost time for their next dose, skip the missed dose and take the next regularly scheduled dose. Patients should not take two doses at the same time.

**Patient Information**  
**ARIMIDEX®**  
**A-rim-eh-dex**  
**(anastrozole)**  
**tablets**

**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 blockage in their heart arteries (ischemic heart disease) and who take ARIMIDEX, may have an increase in symptoms of decreased blood flow to their heart compared to similar women who take tamoxifen.

**Get medical help right away if you have new or worsening chest pain or shortness of breath during treatment with ARIMIDEX.**

**What is ARIMIDEX?**

ARIMIDEX is a prescription medicine used in women after menopause (“the change of life”) for:

- treatment of early breast cancer
  - after surgery
  - in women whose breast cancer is hormone receptor-positive
- the first treatment of breast cancer that has spread to nearby tissue or lymph nodes (locally advanced) or has spread to other parts of the body (metastatic), 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 gone through menopause (premenopausal women).

**Who should not take ARIMIDEX?**

**Do not take ARIMIDEX if you:**

- are pregnant or able to become pregnant. ARIMIDEX may harm your unborn baby. If you become pregnant while taking ARIMIDEX, tell your doctor right away.
- have not gone through menopause (are premenopausal)
- have had a severe allergic reaction to anastrozole or any of the ingredients in ARIMIDEX. See the end of this leaflet for a complete list of ingredients in ARIMIDEX. Symptoms of a severe allergic reaction to ARIMIDEX include: swelling of the face, lips, tongue or throat, trouble breathing or swallowing, hives and itching.

## What should I tell my doctor before taking ARIMIDEX?

### Before you take ARIMIDEX, tell your doctor if you:

- have not gone through menopause. Talk to your doctor if you are not sure.
- have or had a heart problem
- have been told you have bone thinning or weakness (osteoporosis)
- have high cholesterol
- have any other medical conditions
- are pregnant or plan to become pregnant. ARIMIDEX may harm your unborn baby. See “Who should not take ARIMIDEX?”
- are breastfeeding or plan to breastfeed. It is not known if ARIMIDEX passes into breast milk. You and your doctor should decide if you will take ARIMIDEX or breastfeed. You should not do both.

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

- **tamoxifen.** You should not take **ARIMIDEX** if you take tamoxifen. Taking ARIMIDEX with tamoxifen may lower the amount of ARIMIDEX in your blood and may cause ARIMIDEX not to work as well.
- **Medicines that contain estrogen.** ARIMIDEX may not work if taken with any 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 to show your doctor and pharmacist when you get a new medicine.

## How should I take ARIMIDEX?

- Take ARIMIDEX exactly as your doctor tells you to take it.
- Continue taking ARIMIDEX until your doctor tells you to stop.
- 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 take too much ARIMIDEX, call your doctor or go to the nearest hospital emergency room right away.

## What are the possible side effects of ARIMIDEX?

### ARIMIDEX may cause serious side effects including:

- See “**What is the most important information I should know about ARIMIDEX?**”

- **bone thinning or weakness (osteoporosis).** ARIMIDEX lowers estrogen in your body, which may cause your bones to become thinner and weaker. This may increase your risk of fractures, especially of your spine, hip and wrist. Your doctor may order a bone mineral density test before you start and during treatment with ARIMIDEX to check you for bone changes.
- **increased blood cholesterol (fat in the blood).** Your doctor may do blood tests to check your cholesterol while you are taking ARIMIDEX.
- **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 get:
  - swelling of your face, lips, tongue, or throat
  - trouble swallowing or breathing
- **liver problems.** ARIMIDEX can cause inflammation of your liver and changes in liver function blood tests. Your doctor may check 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 your skin or whites of your eyes
- pain on the right side of your stomach-area (abdomen)

Common side effects in women taking ARIMIDEX include:

- hot flashes
- weakness
- joint aches
- joint pain, stiffness or swelling (arthritis)
- pain
- sore throat
- high blood pressure
- depression
- nausea and vomiting
- rash
- back pain
- sleep problems
- bone pain
- headache
- swelling of your legs, ankles, or feet
- increased cough
- shortness of breath
- build up of lymph fluid in the tissues of your affected arm (lymphedema )

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ARIMIDEX. For more information, ask your doctor or pharmacist.

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 room temperature between 68°F to 77°F (20°C to 25°C).

**Keep ARIMIDEX and all medicines out of the reach of children.**

### **General information about the safe and effective use of ARIMIDEX.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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 that you have. It may harm them.

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](http://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.

This Patient Information has been approved by the U.S. Food and Drug Administration.

May/2013

Distributed by:  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

ARIMIDEX is a registered trademark of the AstraZeneca group of companies.  
©2009 AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850. All rights reserved.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20541Orig1s027**

**MEDICAL REVIEW(S)**



## Medical Officer Review of Labeling Supplement Division of Oncology Products 1

**NDA #:** 20,541

**SLR #:** 027

**eCTD sequence #:** 45

**Drug:** Arimidex (anastrozole) Tablets

**Sponsor:** AstraZeneca

**Submission Date:** Nov. 1, 2012

**Submission Type:** Labeling supplement

**Primary Reviewer:** Nancy S. Scher, M.D.

**Secondary Reviewer/Team Leader:** Patricia Cortazar, M.D.

**Regulatory Project Manager:** Amy Tilley

**Date Review Completed:** April 18, 2013

**Indication:** 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.

**Original FDA Approval Date:** 1995

**Background:** AstraZeneca proposes an update to Section 6.2 (Post-Marketing Experience) of the Package Insert (PI) and to the Patient PI/Patient Information (What are possible side effects?).

The sponsor's Core Data Sheet was revised to include "myalgia" and "hypercalcemia" during the Periodic Safety Update Report (PSUR) time period covering 12 August 2011 through 11 August 2012. The sponsor proposes to add these adverse events to Section 6.2 of the PI and to the PPI.

### Myalgia

AstraZeneca (AZ) reviewed the topic of myalgia following a potential safety signal identified by "routine internal pharmacovigilance internal processes." Literature search did not permit definition of a relationship between anastrozole and muscle pain. Review of the ATAC trial clinical database showed an incidence of myalgia of 5.8% for the anastrozole arm (of N=3092) and 5.2% (of N=3094) for the tamoxifen arm. A search of AZ's total safety database revealed 920 myalgia cases, with 84 cases showing positive dechallenge, and 11 of these case also reporting positive rechallenge. The average time to onset was 168 days after

starting anastrozole (median 33 days, range 1-1095 days). The average time to recovery/improvement after stopping anastrozole was 31 days (median 14 days, range 2-122 days).

### Hypercalcemia

AZ reviewed the topic of hypercalcemia due to a safety signal identified from a literature article by Jarhult in 2011. A patient was treated with Arimidex 1 mg daily starting Oct. 2005, following laparotomy for lobular breast cancer found to be metastatic to abdominal lymph nodes. In Nov. 2008, the patient underwent neck exploration for hypercalcemia believed due to hyperparathyroidism. All 4 parathyroid glands appeared normal (2 removed, 1 biopsied). Hypercalcemia persisted at high levels until 2 weeks after discontinuation of Arimidex in July 2009. Upon rechallenge, serum calcium and parathyroid hormone levels rose. Upon dechallenge, levels fell more slowly, but normalized after 8 weeks. Another published report (Kuroi 2011) also suggested an association between hypercalcemia and aromatase inhibitor therapy (letrozole). In the ATAC trial, the incidence of hypercalcemia for the Arimidex treatment arm was 0.6%, and 0.2% for the tamoxifen treatment arm. Search of AZ's total safety database revealed 84 cases of hypercalcemia and/or hyperparathyroidism, of which 14 cases were reported with both. In addition to the original literature case (Jarhult 2011), there were 6 cases with positive dechallenge. Interpretation was confounded by the presence of metastatic disease in 4 subjects and concomitant therapy directed against hypercalcemia.

### **Recommended Action:**

- Section 6.2 of the PI should be amended to include hypercalcemia and myalgia as adverse events observed post-market.
- Extensive updates to the PPI recommended by DMPP (Division of Medical Policy Programs) should be incorporated. (Hypercalcemia and myalgia will not be added to the PPI because they do not reach the threshold incidence of 10% for common events.)
- Section 17 (Patient Counseling Information) should be revised to incorporate new language to be included in the PPI:
  - 17.3 Ischemic cardiovascular events
  - 17.7 Missed dose.

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

/s/  
-----

NANCY S SCHER  
04/19/2013

PATRICIA CORTAZAR  
04/19/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20541Orig1s027**

**OTHER REVIEW(S)**

# REGULATORY PROJECT MANAGER LABELING REVIEW

## Division of Oncology Products 1

**Application Number:** NDA 020541/SLR-027  
**Name of Drug:** Arimidex® (anastrozole) Tablets, 1 mg  
**Sponsor:** AstraZeneca Pharmaceuticals LP

### Material Reviewed

**Submission Date:** November 1, 2012  
**Receipt Date:** November 2, 2012

### Background and Summary

NDA 020541 is approved for the treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy. SLR-027 provides for:

1. Revision to Section 6.2 Post-Marketing Experience to modify the text for trigger finger to include hypercalcemia (with or without an increase in parathyroid hormone).
2. Added myalgia to Section 6.2 Post-Marketing Experience.
3. In addition to reviewing the patient package insert, the FDA revised the text throughout the entire patient package insert.

This supplement has been reviewed by Nancy Scher, M.D., Clinical Reviewer; Patricia Cortazar, M.D., Clinical Team Leader; Karen Dowdy, Ph.D., DMPP Reviewer; and Sharon Mills, Ph.D., DMPP Team Leader.

### Recommendations for Regulatory Action

The attached labeling is the agreed upon labeling between FDA and AstraZeneca Pharmaceuticals LP and the above listed supplement should be approved.

---

Amy Tilley  
Regulatory Project Manager

Supervisory Concurrence:

---

Alice Kacuba, RN, MSN, RAC  
Chief, Project Management Staff

**Review**

Package Insert and Patient Package Insert

The labeling deletions are shown as ~~strike through~~ and additions are shown as double underlined.

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

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

/s/  
-----

AMY R TILLEY  
04/30/2013

ALICE KACUBA  
04/30/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: April 10, 2013

To: Robert Justice, MD  
Director  
**Division of Oncology Products 1 (DOP1)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Patient Package Insert  
(PPI)

Drug Name (established name): ARIMIDEX (anastrozole)

Dosage Form and Route: tablet, for oral use

Application Type/Number: NDA 20-541

Supplement Number: S-027

Applicant: AstraZeneca UK LTD c/o AstraZeneca Pharmaceuticals LP



## 1 INTRODUCTION

On November 2, 2012, AstraZeneca Pharmaceuticals LP submitted for the Agency's review a Changes Being Effected (CBE) Labeling Supplement to their New Drug Application (NDA) 20-541/S-027 for ARIMIDEX (anastrozole) tablets. The purpose of this submission is to update the approved product labeling with new post-marketing safety data, to correct the frequency of occurrence for a previously approved adverse event, and to add corresponding revisions to the Patient Package Insert (PPI). ARIMIDEX (anastrozole) tablets was initially approved on December 27, 1995. ARIMIDEX (anastrozole) tablets is 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

On November 6, 2012, the Division of Oncology Products 1 (DOP1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ARIMIDEX (anastrozole) tablets.

This review is written in response to a request by DOP1 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for ARIMIDEX (anastrozole) tablets.

## 2 MATERIAL REVIEWED

- Draft ARIMIDEX (anastrozole) tablets Patient Package Insert (PPI) received on November 2, 2012, and received by DMPP on November 6, 2012.
- Draft ARIMIDEX (anastrozole) tablets Prescribing Information (PI) received on November 2, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 28, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- performed a comprehensive review to ensure that the PPI is consistent with current Patient Labeling Team practices, as agreed to with DOP1 on March 28, 2013
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

/s/  
-----

KAREN M DOWDY  
04/10/2013

SHARON R MILLS  
04/10/2013

LASHAWN M GRIFFITHS  
04/10/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20541Orig1s027**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**From:** Tilley, Amy  
**Sent:** Thursday, April 18, 2013 3:31 PM  
**To:** 'Valas, E Jane' [jane.valas@astrazeneca.com](mailto:jane.valas@astrazeneca.com)  
**Cc:** Troise, Nicholas J [Nicholas.troise@astrazeneca.com](mailto:Nicholas.troise@astrazeneca.com)  
**Subject:** \*Time Sensitive\* NDA 20541-SLR-027 Arimidex - FDA Revised PI

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Monday, April 22, 2013 12:00 PM  
**Flag Status:** Flagged

**Attachments:** NS edits 4-18-13 FDA rev PI annotated-draft-label.doc  
[Jane,](#)

Below is the revised PI with revisions to Section 6.2 as follows:

- Put in the introductory language currently used in the Post-Marketing Section.
- Changed the sentence fragments to a bulleted list.
- (b) (4) "hepatitis" under hepatobiliary events, since hepatitis encompasses more than just elevated LFTs.



NS edits  
-13 FDA rev F

We respectfully request your response to this email **no later than 12 noon on April 22, 2013.**

Regards.

*Amy Tilley*

---

Amy Tilley | Regulatory Project Manager | Division of Oncology Products  
1,  
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,  
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ [amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)



consider the environment before printing this e-mail

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

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

/s/  
-----

AMY R TILLEY  
04/18/2013

**From:** Tilley, Amy  
**Sent:** Monday, April 15, 2013 3:22 PM  
**To:** 'Valas, E Jane'  
**Cc:** Troise, Nicholas J  
**Subject:** RE: \*Time Sensitive\* NDA 20541-SLR-027 Arimidex – FDA Revised PI & PPI  
Division of Medical Policy Programs (DMPP) ...

**Importance:** High  
Jane,

Below is the language we inadvertently left out of the PI we sent you on April 11th.

Section 17.3 in the PI should read as follows so that it will match the language in the PPI.

### **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. *If patients have new or worsening chest pain or shortness of breath they should seek medical attention immediately.*

If you have any further questions please contact me.

Thanks.

*Amy*

---

**From:** Valas, E Jane [mailto:jane.valas@astrazeneca.com]  
**Sent:** Monday, April 15, 2013 10:58 AM  
**To:** Tilley, Amy  
**Cc:** Troise, Nicholas J  
**Subject:** FW: \*Time Sensitive\* NDA 20541-SLR-027 Arimidex - FDA Revised PI & PPI Division of Medical Policy Programs (DMPP) ...

Amy,

I am seeking clarification on comment DMPP6 found in the PPI. Please would you confirm that the blue text “have new or worsening” adequately addresses the request for *what symptoms may occur* and the “highlighted” “right away” (get medical help right away) addresses *the actions patients should take*. Please can you also confirm that the last part of the comment : “include this information in the PI” has also been addressed?

We are meeting tomorrow morning as part of the team is in the UK to prepare response to FDA as requested by noon April 17.

Your timely attention to this matter would be appreciated,

Thank you,  
Jane

**E. Jane Valas, Ph.D.**

---

**AstraZeneca Pharmaceuticals LP**  
**Research and Development | Regulatory Affairs**  
C4C-218 1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355  
Tel 302 886-2122 Fax 302 886-2822  
jane.valas@astrazeneca.com

 Please consider the environment before printing this e-mail

---

**Confidentiality Notice:** This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

**From:** Tilley, Amy [mailto: Amy.Tilley@fda.hhs.gov]  
**Sent:** Thursday, April 11, 2013 5:26 PM  
**To:** Troise, Nicholas J  
**Cc:** Valas, E Jane  
**Subject:** \*Time Sensitive\* NDA 20541-SLR-027 Arimidex - FDA Revised PI & PPI Division of Medical Policy Programs (DMPP) ...

Nicholas and/or Jane,

Below are the FDA Revised PI and PPI for NDA 20541-SLR-027 Arimidex.

Please check all the cross references as they should be in *italics*.

We have extensively revise the PPI and have sent it in a separate document. Also, please note the comment in the beginning of the PPI regarding the formatting issues.

We respectfully request your response **by Noon on April 17, 2013.**


Please confirm receipt of this email.

Regards.

*Amy Tilley*

---

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,  
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD  
20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs



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

/s/  
-----

AMY R TILLEY  
04/15/2013

**From:** Tilley, Amy  
**Sent:** Thursday, April 11, 2013 5:26 PM  
**To:** 'Troise, Nicholas J'  
**Cc:** 'Valas, E Jane'  
**Subject:** \*Time Sensitive\* NDA 20541-SLR-027 Arimidex - FDA Revised PI & PPI

**Follow Up Flag:** Follow up  
**Due By:** Wednesday, April 17, 2013 12:00 PM  
**Flag Status:** Flagged

**Attachments:** Arimidex FDA label rev 4-11-13.doc; anastrozole (ARIMIDEX) 20541 S-027  
FDA DMPP PPI Apr 11 2013 marked.doc

Nicholas and/or Jane,

Below are the FDA Revised PI and PPI for NDA 20541-SLR-027 Arimidex.

Please check all the cross references as they should be in *italics*.

We have extensively revise the PPI and have sent it in a separate document.  
Also, please note the comment in the beginning of the PPI regarding the  
formatting issues.



Arimidex  
abel rev 4-11



anastrozole  
MIDEX) 20541

We respectfully request your response **by Noon on April 17, 2013.**

Please confirm receipt of this email.

Regards.

*Amy Tilley*

---

Amy Tilley | Regulatory Project Manager | Division of Oncology Products  
1,  
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,  
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



consider the environment before printing this e-mail

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

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

/s/  
-----

AMY R TILLEY  
04/11/2013



NDA 020541/S-027

**CBE SUPPLEMENT –  
ACKNOWLEDGEMENT**

AstraZeneca Pharmaceuticals LP  
Attention: Nicholas J. Troise  
Director, Regulatory Affairs  
1800 Concord Pike, PO Box 8355  
Wilmington, DE 19803-8355

Dear Mr. Troise:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 020541  
**SUPPLEMENT NUMBER:** 027  
**PRODUCT NAME:** Arimidex (anastrozole) Tablets 1 mg  
**DATE OF SUBMISSION:** November 1, 2012  
**DATE OF RECEIPT:** November 2, 2012

This supplemental application, submitted as a Changes Being Effected supplement, proposes the following changes in Section 6.2 Post-Marketing Experience: the addition of Trigger finger and hypercalcemia (with or without an increase in parathyroid hormone) have been reported ( $\geq 0.1\%$  and  $< 1\%$ ) in patients receiving ARIMIDEX. Myalgia has been reported ( $\geq 1\%$  and  $< 10\%$ ) in patients receiving ARIMIDEX. Also, in the Patient Information Section “What are possible side effects of ARIMIDEX?” muscle pain and abnormally high levels of calcium in blood have been added.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 1, 2013 in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be May 2, 2013.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 1  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-3994.

Sincerely,

*{See appended electronic signature page}*

Amy R. Tilley  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

/s/  
-----

AMY R TILLEY  
11/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>			
TO: <b>CDER-DMPP-PatientLabelingTeam</b>			FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Tilley/RPM/OHOP/DOP1/301-796-3994		
REQUEST DATE: November 6, 2012		NDA/BLA NO.: NDA 20541 SLR-027	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)		
NAME OF DRUG: Arimidex	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)	
SPONSOR: AstraZeneca			PDUFA Date: May 2, 2013		
<b>TYPE OF LABEL TO REVIEW</b>					
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b> EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA020541\020541.enx">\\CDSESUB1\EVSPROD\NDA020541\020541.enx</a> eCTD Sequence Number: 0045					
<b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>					
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  A copy of the sponsor's proposed patient labeling in Word format will be sent via email to DMPP along with this consult.  Labeling Meetings: TBS					
SIGNATURE OF REQUESTER Amy Tilley <i>{See appended electronic signature page}</i>					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS		

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

/s/  
-----

AMY R TILLEY  
11/06/2012