1.5 Product Information

1.5.1 Prescribing Information

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

ANATERO (Anastrozole Tablets 1mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

White colored, round shaped, biconvex film coated tablets, debossed with '1' on one side and 'H' on the other side.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant Treatment

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

First-Line Treatment

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

Second-Line Treatment

ANATERO 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 ANATERO.

4.2 Posology and method of administration

Recommended Dose

The dose of ANATERO is one 1 mg tablet taken once a day. For patients with advanced breast cancer, ANATERO should be continued until tumor progression. ANATERO 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, ANATERO was administered for five years.

No dosage adjustment is necessary for patients with renal impairment or for elderly patients.

Patients with Hepatic Impairment

No changes in dose are recommended for patients with mild-to-moderate hepatic impairment. ANATERO has not been studied in patients with severe hepatic impairment

4.3 Contraindications

Pregnancy and Premenopausal Women

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

Hypersensitivity

ANATERO 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.

4.4 Special warnings and precautions for use

Ischemic Cardiovascular Events

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

Bone Effects

Results from the ATAC trial bone sub study at 12 and 24 months demonstrated that patients receiving ANATERO 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 ANATERO.

Cholesterol

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ANATERO 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.

Estrogen

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

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.

Cytochrome P450

Based on in vitro and in vivo results, it is unlikely that co-administration of ANATERO 1 mg will affect other drugs as a result of inhibition of cytochrome P450

4.6 Fertility, pregnancy and lactation

Pregnancy

PREGNANCY CATEGORY X

ANATERO may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. ANATERO 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 ANATERO use in pregnant women. If ANATERO 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/m2 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 (AUC0-24hr 9 times higher). In rabbits, Anastrozole caused pregnancy failure at doses equal to or greater than 16 times the recommended human dose on a mg/m2 basis.

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.

Fertility

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 ANATERO 1 mg or placebo. After 6 months of treatment there was no statistically significant difference in the percentage of patients who experienced a ≥50% reduction in Gynecomastia (primary efficacy analysis). Secondary efficacy analyses (absolute change in

breast volume, the percentage of patients who had any reduction in the calculated volume of Gynecomastia, breast pain resolution) were consistent with the primary efficacy analysis. Serum estradiol concentrations at Month 6 of treatment were reduced by 15.4% in the ANATERO 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 ANATERO-treated patients and 8.1% of the placebo-treated patients with the most frequent being acne (7% ANATERO and 2.7% placebo) and headache (7% ANATERO and 0% placebo); all other adverse reactions showed small differences between treatment groups. One patient treated with ANATERO discontinued the trial because of testicular enlargement. The mean baseline-subtracted change in testicular volume after 6 months of treatment was + 6.6 ± 7.9 cm3 in the ANATERO-treated patients and + 5.2 ± 8.0 cm3 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 ANATERO. The trial duration was 12 months. Patients were enrolled on the basis of a diagnosis of typical (27/28) or atypical (1/27) McCune-Albright Syndrome, precocious puberty, history of vaginal bleeding, and/or advanced bone age. Patients' baseline characteristics included the following: a mean chronological age of 5.9 ± 2.0 years, a mean bone age of 8.6 ± 2.6 years, a mean growth rate of 7.9 ± 2.9 cm/year and a mean Tanner stage for breast of 2.7 ± 0.81. Compared to pre-treatment data there were no on-treatment statistically significant reductions in the frequency of vaginal bleeding days, or in the rate of increase of bone age (defined as a ratio between the change in bone age over the change of chronological age). There were no clinically significant changes in Tanner staging, mean ovarian volume, mean uterine volume and mean predicted adult height. A small but statistically significant reduction of growth rate from 7.9 ± 2.9 cm/year to 6.5 ± 2.8 cm/year was observed but the absence of a control group precludes attribution of this effect to treatment or to other confounding factors such as variations in endogenous estrogen levels commonly seen in McCune-Albright Syndrome patients.

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

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

Serious adverse reactions with ANATERO 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.

Common adverse reactions (occurring with an incidence of ≥10%) in women taking ANATERO included: hot flashes, asthenia, arthritis, pain, arthralgia, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, 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 ANATERO 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.

Clinical Trials Experience

Adjuvant Therapy

Adverse reaction data for adjuvant therapy are based on the ATAC trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving ANATERO 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.

Table1: Adverse reactions occurring with an incidence of at least 5% in either treatment group during treatment, or within 14 days of the end of treatment in the ATAC trial

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

Hemic and lymphatic		
Lymphedema	304 (10)	341 (11)
Anemia	113 (4)	159 (5)
Metabolic and nutritional		
Peripheral edema	311 (10)	343 (11)
Weight gain	285 (9)	274 (9)
Hypercholesterolemia	278 (9)	108 (3.5)
Musculoskeletal		
Arthritis	512 (17)	445 (14)
Arthralgia	467 (15)	344 (11)
Osteoporosis	325 (11)	226 (7)
Fracture	315 (10)	209 (7)
Bone pain	201 (7)	185 (6)
Arthrosis	207 (7)	156 (5)
Joint Disorder	184 (6)	160 (5)
Myalgia	179 (6)	160 (5)
Nervous system		
Depression	413 (13)	382 (12)
Insomnia	309 (10)	281 (9)
Dizziness	236 (8)	234 (8)
Anxiety	195 (6)	180 (6)
Paresthesia	215 (7)	145 (5)
Respiratory		
Pharyngitis	443 (14)	422 (14)
Cough increased	261 (8)	287 (9)
Dyspnea	234 (8)	237 (8)
Sinusitis	184 (6)	159 (5)

Bronchitis	167 (5)	153 (5)
Skin and appendages		
Rash	333 (11)	387 (13)
Sweating	145 (5)	177 (6)
Special Senses		
Cataract Specified	182 (6)	213 (7)
Urogenital		
Leukorrhea	86 (3)	286 (9)
Urinary tract infection	244 (8)	313 (10)
Breast pain	251 (8)	169 (6)
Breast Neoplasm	164 (5)	139 (5)
Vulvovaginitis	194 (6)	150 (5)
Vaginal Haemorrhage¶	122 (4)	180 (6)
Vaginitis	125 (4)	158 (5)

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

† COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

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

§ N=Number of patients receiving the treatment.

¶ Vaginal Hemorrhage without further diagnosis.

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

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

	ANATERO N=3092 (%)	**Tamoxifen N=3094 (%)**	**Odds-ratio**	**95% CI**

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

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

Ischemic Cardiovascular Events

Between treatment arms in the overall population of 6186 patients, there was no statistical difference in ischemic cardiovascular events (4% ANATERO vs. 3% tamoxifen). In the overall population, angina pectoris was reported in 71/3092 (2.3%) patients in the ANATERO arm and 51/3094 (1.6%) patients in the tamoxifen arm; myocardial infarction was reported in 37/3092 (1.2%) patients in the ANATERO 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 ANATERO and 10% in patients on tamoxifen. In this patient population, angina pectoris was reported in 25/216 (11.6%) patients receiving ANATERO and 13/249 (5.2%) patients receiving tamoxifen; myocardial infarction was reported in 2/216 (0.9%) patients receiving ANATERO and 8/249 (3.2%) patients receiving tamoxifen.

Bone Mineral Density Findings

Results from the ATAC trial bone sub study at 12 and 24 months demonstrated that patients receiving ANATERO 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 ANATERO lowers circulating estrogen levels it may cause a reduction in bone mineral density.

A post-marketing trial assessed the combined effects of ANATERO 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 ANATERO 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 ANATERO 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 ANATERO on lipid profile. In the primary analysis population for lipids (ANATERO 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 (ANATERO+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 ANATERO alone had a neutral effect on lipid profile. Combination treatment with ANATERO 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 ANATERO 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 ANATERO had an increase in joint disorders (including arthritis, arthrosis and arthralgia) compared with patients receiving tamoxifen. Patients receiving ANATERO 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 ANATERO 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 ANATERO-treated patients 317 (10%) versus 167 (5%), respectively.

Patients receiving ANATERO 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 ANATERO (50%) and tamoxifen (51%).

• Cardiovascular events were consistent with the known safety profiles of ANATERO and tamoxifen.

• The cumulative incidences of all first fractures (both serious and non-serious, occurring either during or after treatment) was higher in the ANATERO 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 ANATERO 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 ANATERO 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 ANATERO 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

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

Body system Adverse Reaction*	**Number (%) of subjects**	
	ANATERO (N=506)	**Tamoxifen (N=511)**
Whole body		
Asthenia	83 (16)	81 (16)
Pain	70 (14)	73 (14)
Back pain	60 (12)	68 (13)
Headache	47 (9)	40 (8)
Abdominal pain	40 (8)	38 (7)
Chest pain	37 (7)	37 (7)
Flu syndrome	35 (7)	30 (6)
Pelvic pain	23 (5)	30 (6)
Cardiovascular		
Vasodilation	128 (25)	106 (21)
Hypertension	25 (5)	36 (7)
Digestive		
Nausea	94 (19)	106 (21)
Constipation	47 (9)	66 (13)
Diarrhea	40 (8)	33 (6)
Vomiting	38 (8)	36 (7)
Anorexia	26 (5)	46 (9)
Metabolic and Nutritional		
Peripheral edema	51 (10)	41 (8)
Musculoskeletal		
Bone pain	54 (11)	52 (10)
Nervous		
Dizziness	30 (6)	22 (4)
Insomnia	30 (6)	38 (7)

Depression	23 (5)	32 (6)
Hypertonia	16 (3)	26 (5)
Respiratory		
Cough increased	55 (11)	52 (10)
Dyspnea	51 (10)	47 (9)
Pharyngitis	49 (10)	68 (13)
Skin and appendages		
Rash	38 (8)	34 (8)
Urogenital		
Leukorrhea	9 (2)	31 (6)

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

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

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

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

	Number (n) and Percentage of Patients	
Adverse Reaction*	ANATERO 1 mg (N=506) n (%)	NOLVADEX 20 mg (N=511) n (%)
Depression	23 (5)	32 (6)
Tumor Flare	15 (3)	18 (4)
Thromboembolic Disease†	18 (4)	33 (6)
Venous†	5	15

Coronary and Cerebral‡	13	19
Gastrointestinal Disturbance	170 (34)	196 (38)
Hot Flushes	134 (26)	118 (23)
Vaginal Dryness	9 (2)	3 (1)
Lethargy	6 (1)	15 (3)
Vaginal Bleeding	5 (1)	11 (2)
Weight Gain	11 (2)	8 (2)

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

† Includes pulmonary embolus, thrombophlebitis, and retinal vein thrombosis.

‡ Includes myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia and cerebral infarct.

Second-Line Therapy

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

The principal adverse reaction more common with ANATERO 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*	**ANATERO 1 mg (N=262)**		**ANATERO 10 mg (N=246)**		**Megestrol Acetate 160 mg (N=253)**	
	n	**%**	**n**	**%**	**n**	**%**
Asthenia	42	(16)	33	(13)	47	(19)
Nausea	41	(16)	48	(20)	28	(11)
Headache	34	(13)	44	(18)	24	(9)
Hot Flashes	32	(12)	29	(11)	21	(8)
Pain	28	(11)	38	(15)	29	(11)

Back Pain	28	(11)	26	(11)	19	(8)
Dyspnea	24	(9)	27	(11)	53	(21)
Vomiting	24	(9)	26	(11)	16	(6)
Cough Increased	22	(8)	18	(7)	19	(8)
Diarrhea	22	(8)	18	(7)	7	(3)
Constipation	18	(7)	18	(7)	21	(8)
Abdominal Pain	18	(7)	14	(6)	18	(7)
Anorexia	18	(7)	19	(8)	11	(4)
Bone Pain	17	(6)	26	(12)	19	(8)
Pharyngitis	16	(6)	23	(9)	15	(6)
Dizziness	16	(6)	12	(5)	15	(6)
Rash	15	(6)	15	(6)	19	(8)
Dry Mouth	15	(6)	11	(4)	13	(5)
Peripheral Edema	14	(5)	21	(9)	28	(11)
Pelvic Pain	14	(5)	17	(7)	13	(5)
Depression	14	(5)	6	(2)	5	(2)
Chest Pain	13	(5)	18	(7)	13	(5)
Paresthesia	12	(5)	15	(6)	9	(4)
Vaginal Hemorrhage	6	(2)	4	(2)	13	(5)
Weight Gain	4	(2)	9	(4)	30	(12)
Sweating	4	(2)	3	(1)	16	(6)
Increased Appetite	0	(0)	1	(0)	13	(5)

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

Other less frequent (2% to 5%) adverse reactions reported in patients receiving ANATERO 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 ANATERO. 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

	ANATERO 1 mg (N=262)		ANATERO 10 mg (N=246)		Megestrol Acetate 160 mg (N=253)	
Adverse Reaction Group	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gastrointestinal Disturbance	77	(29)	81	(33)	54	(21)
Hot Flushes	33	(13)	29	(12)	35	(14)
Edema	19	(7)	28	(11)	35	(14)
Thromboembolic Disease	9	(3)	4	(2)	12	(5)
Vaginal Dryness	5	(2)	3	(1)	2	(1)
Weight Gain	4	(2)	10	(4)	30	(12)

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 ANATERO:

• 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.

• Myalgia, trigger finger and hypercalcemia (with or without an increase in parathyroid hormone)

4.9 Overdose

Clinical trials have been conducted with ANATERO, 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 ANATERO that results in life-threatening symptoms has not been established. There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ANATERO is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Neoplastic

ATC code: L02BG03

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.

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 ANATERO 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, ANATERO 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 ANATERO 1 mg.

The effect of ANATERO 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, ANATERO 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 ANATERO. ANATERO does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

5.2 Pharmacokinetic properties

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 Cmax of Anastrozole decreased by 16% and the median Tmax 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 ANATERO. Plasma concentrations approach steady-state levels at about 7 days of once daily dosing. Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Metabolism

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

Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 in vitro with Ki values which were approximately 30 times higher than the mean steady-state Cmax 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/1.73m2) compared to controls. Total clearance was only reduced 10%. No dosage adjustment is needed for renal impairment.

Effect of Hepatic Impairment

Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of Anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, these plasma concentrations were still with the range of values observed in normal subjects. The effect of severe hepatic impairment was not studied. No dose adjustment is necessary for stable hepatic cirrhosis

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate

Povidone

Sodium starch glycolate

Isopropyl alcohol

Magnesium stearate

Opadry white-Y-1-7000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

30's HDPE Container and 3x 10's Blister pack (Alu-PVC)

6.6 Special precautions for disposal and other handling No special requirements

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT