Serious Adverse Events	Letrozole 0.5	Letrozole 2.5	Aminoglutethimide
Metabolic / Endocrine			
Hypoadrenalism	1		
Hypercalcemia		3 (1)	
Hypokalemia		1	
Fatigue	2 (2)		1 (1)
Cachexia, Tumor Related			1
Renal			
Acute Renal Insufficiency			1
Urinary Retention			1
Dermatologic			
. Rash			5 (5)
Hematologic			
Neutropenia	1		
Thrombocytopenia		1	
Anemia		2	
Infectious			
Febrile Neutropenia/Sepsis	1	1	3
Septic Shock	1	1	
Pneumonia		1	1
Cellulitis, Lt. Arm			1
Surgical			
Excision Solar Keratosis	1		
Pacemaker Implantation	1		
Gastrointestinal			
Vomiting	1		1 (1)
Jaundice	1		1
Jaundice due to Choledocholithiases	1		
Constipation, Severe		1	
Dysphagia			1
Radiation Enteritis			2
Bowel Obstruction, Large or Small			1
Abdominal / Lower Back Pain			1
Epigastric Pain			1
Mucositis	1 (1)		
Diarrhea			1 (1)
Intercurrent Disease			
Rectal Adenocarcinoma	1		
Colon Cancer		1	
Edema, Lt. Arm		1	
Breast Cancer, Contralateral		1	
Gastric Cancer		1	

Serious Adverse Events	Letrozole 0.5	Letrozole 2.5	Aminoglutethimide
Musculoskeletal			
Bone Pain	2	1	1
Fractures - Wrist	1		
- Hip	1	2	
- Rt. Femur		1	
- Sternal			1
- Clavicular			1
Neurological			
Headache	1		
Seizures	2 (?1)		
Subdural Hematoma		1	
Quadriplegia		1	
Dizziness associated with Nausea & Vomiting		1	
Behavioral Disorder / Anxiety Reaction			2
Parkinson's Disease			1
Peripheral Facial Nerve Paralysis			1
Stupor / Coma			1
Allergic			
Conjunctivitis	1 (1)		
Death, ? Cause		1	

Deaths on Study

Two hundred eighteen patients had died since initiation of study. Case report forms for eleven deaths were reviewed. In seven patients) death was due to cancer progression. Three patients died from other causes: one from complications of a pleurodiesis procedure, one from unknown causes, and one from acute pulmonary edema. One patient died at home two months after initiation of study medication. The cause of death was thought to be progression but no information is available to confirm this impression. (Patient is included in the SAE table.)

Clinical Monitors of Safety

Blood Pressure, Pulse Rate, ECG Monitoring

At baseline no difference in median systolic or diastolic blood pressure or median pulse rate were observed in the arm. No changes in the median systolic blood pressure, diastolic blood pressure, or pulse rate were observed. About 35% of the patients had a rise in systolic blood pressure $\geq$ 30 mm Hg and about the same percentage on all three treatment arms had a $\geq$ 20 mm Hg rise in diastolic blood pressure at one or more visits. About 15% of the patients treated with letrozole 0.5 mg had at least one diastolic reading over 100 mg Hg, while 7.6% of the patients on letrozole 2.5 mg and 7.3% of the patients on aminoglutethimide had at least one diastolic reading greater

than 100 mg Hg. No consistent abnormalities in ECG tracings were noted for any of the three treatment groups.

Weight

No relevant significant changes in weight were observed in any treatment arm over the duration of the study. Weight gain was reported in 6.3% of the patients on the letrozole 0.5 mg arm, on 4.9% of the patients on the letrozole, and on 7.3% of the patients treated with aminoglutethimide. Weight loss was reported in 4.7% of the patients treated with letrozole 0.5 mg, in 5.9% of the patients treated with letrozole, but only in 1.1% of the patients treated with aminoglutethimide.

Age

Systolic blood pressure, diastolic blood pressure, and weight gain were analyzed with respect to age: $\leq$ age 55, age 56 - 69, and age $\geq$ 70. More patients $\leq$ age 55 in the letrozole arms had elevations of systolic blood pressure (13.2% in L0.5 and 17.4% in L2.5) than on the aminoglutethimide arm (3.3%). In the other age groups, differences in systolic blood pressure were less pronounced. Diastolic blood pressure elevation (> 100 mg Hg) occurred more frequently in all age groups treated with letrozole 0.5 mg. Weight gain occurred most often in patients $\leq$ age 55 and $\geq$ age 70 treated with aminoglutethimide. No differences in weight gain were noted in any of the other treatment groups.

Laboratory Evaluations for Safety

Hematology Parameters

Five patients, three on the letrozole 0.5 mg arm and two on the letrozole 2.5 mg arm, had abnormalities in hemoglobin. In no case was the abnormality related to study drug. One patient on letrozole 0.5 mg had a decrease in granulocytes due another medication. Four patients on the aminoglutethimide arm developed grade 3/4 granulocytopenia, three for unclear reasons. Thrombocytopenia was noted in two patients, one on letrozole 0.5 mg and one on letrozole 2.5 mg, and was attributed to underlying disease. A decrease in lymphocyte counts at study entry was noted for twenty-two patients on letrozole 0.5 mg. twenty-nine patients on letrozole 2.5 mg, and twenty-two patients on aminoglutethimide. Sixteen patients with grade 3 lymphocytopenia shifted to grade 4 during the course of the study (one on the letrozole 0.5 mg arm, nine on the letrozole 2.5 mg arm, and six on aminoglutethimide). Since the baseline lymphocytopenia is reported across treatment groups, the most obvious cause would seem to be underlying disease. Worsening of the lymphocyte counts on the aminoglutethimide arm can be associated with concurrent use of steroids.

Liver Function Studies

The following table (AR/BC3 - S8) provides information on the number of patients developing

grade 3/4 liver toxicity during the study on each treatment arm. The number in parenthesis is the number of patients in each group known to have liver metastases. Most of the non-cancer related abnormalities were in gamma-GT. Not included in the table are three patients, one on each treatment arm, with missing baseline GT measurements. All three had gamma-GT elevations to grade 3/4 during the study. No serious adverse events which could definitely be related to abnormalities in hepatic function were reported. The data indicates that a small number of patients do develop abnormalities of liver function studies which may be related to study drug. These abnormalities are not serious in nature. Patients treated with aminoglutethimide are more likely to develop gamma GT abnormalities than patients treated with letrozole.

Table AR/BC3- S8 : Number of Patients with Gr. 3/4 Liver Function Test Abnormalities

Parameter	Letrozole 0.5	Letrozole 2.5	Aminoglutethimide
Bilirubin	6 (4)	4 (3)	1 (1)
SGOT	5 (4)	4 (4)	2 (2)
SGPT	2 (1)	1 (1)	4 (2)
Gamma - GT	18 (14)	11 (9)	28 (20)

Creatinine, Electrolytes

No patients developed grade 3/4 abnormalities of creatinine during study. Seven patients had creatinine elevations to grade 2 level, none related to trial medication. One patient, included in the SAE section, had an increase in creatinine which was considered to be related to aminoglutethimide therapy. Renal function returned to normal when study drug was removed. No significant abnormalities were noted in electrolyte values over time on any study arm. A significant decrease in serum sodium value in one patients on the letrozole 0.5 mg arm was due to laxative abuse. One patient on the letrozole 2.5 mg arm had a decrease to a serum Na = 121 mEq/l probably due to SIADH. Six abnormal potassium values were reported. These abnormal values occurred randomly across treatment arms and were not related to study treatment.

SUMMARY - AR/BC3

AR/BC3 is an open, randomized multicenter phase II trial which compared the efficacy of letrozole 0.5 mg, letrozole 2.5 mg, and aminoglutethimide (with adrenocorticoid replacement) in postmenopausal women with advanced breast cancer of receptor positive or receptor unknown status previously treated with antiestrogens. The study, which enrolled five hundred fifty seven women included one hundred ninety-three patients on the letrozole 0.5 mg arm, one hundred eighty-five patients on the letrozole 2.5 mg arm, and one hundred seventy-eight patients on the aminoglutethimide arm, commenced on September 16, 1993 and patient accrual was completed on May 31, 1996. The study population was well balanced with regard to baseline demographic characteristics. A confounding factor in the study design for AR/BC3 was the failure to allow an adequate period (six weeks) for possible withdrawal response after discontinuation of

antiestrogens prior to the initiation of the study drug in patients who had had a response to antiestrogen therapy (CR, PR, or SD for > 6 months). About eight per cent of responders with hormonally sensitive breast cancers will have a withdrawal response to discontinuation of a hormonal therapy.

Response rates (CR + PR) as determined by the FDA were similar in both letrozole arms (L0.5 - 17.6%, L2.5 - 18.3%) and slightly less on the aminoglutethimide arm (12.3%). Odds ratio for the comparison of the response rate of letrozole 0.5 to letrozole 2.5 is 0.95 (95% CI: 0.56, 0.94) which is not significant (p=0.85, two-sided). Odds ratio for the comparison of the response rate for letrozole 0.5 to aminoglutethimide is 1.53 (95% CI: 0.86, 2.73) favoring letrozole and tending toward significance (p = 0.15, two-sided). The odds ratio for the comparison of the response rate for letrozole 2.5 with aminoglutethimide is 1.61 (95% CI: 0.9, 2.87) favoring letrozole and tending toward significance (p= 0.11, two-sided). Median duration of response is 706 days for letrozole 2.5 mg (95% CI: 522, -), 619 days (95% CI: 532, -) for letrozole 0.5 mg and 450 days (95% CI: 350, -) for aminoglutethimide. Significance testing has not been performed since it would be inaccurate as most patients are censored for progression. Response rates in the population subset not at risk for antiestrogen withdrawal response are as follows: letrozole 0.5 - 17.5%, letrozole 2.5 - 17.5%, and aminoglutethimide -7.8%. No difference is detected when response rates for the two letrozole arms are compared. Odds ratio for comparison of the response rate for this subpopulation treated on the L0.5 arm as compared the response rate for the same population treated with AG is 2.50 (95% CI: 1.09, 5.72; p = 0.03, two-sided). Odds ratio for the comparison of the response rate for the L2.5 subpopulation with the response rate for the AG subpopulation is 2.49 (95% CI: 1.07, 5.77; p = 0.03, two-sided). This information suggests that letrozole may more effective than aminoglutethimide in the population for which this therapy is intended (i.e. postmenopausal hormonal responsive breast cancer patients who have failed antiestrogen therapy).

Median time to progression is 103 days (95% CI: 96, 179 days) for patients on the letrozole 0.5 mg arm, 121 days (95% CI: 93, 258 days) for the letrozole 2.5 mg arm, and 112 days (95% CI: 92, 171 days) on the aminoglutethimide arm. The relative risk of progression when letrozole 0.5 is compared to letrozole 2.5 is 1.16 (95% CI: 0.91, 1.49) which favors the letrozole 2.5 mg arm but is not significant (p = 0.24, two-sided). The relative risk of progression in a comparison of the time to progression on the letrozole 0.5 arm to aminoglutethimide is 0.85 (95% CI: 0.67, 1.08) which favors the letrozole arm but not significant (p=0.18, two-sided). The relative risk of progression for the letrozole 2.5 mg arm compared to the aminoglutethimide arm is 0.73 (95% CI: 0.57, 0.91) which indicates that the letrozole 2.5 mg arm is superior to the aminoglutethimide arm in terms of delaying progression (p=0.01, two-sided). In the subset of patients not at risk for antiestrogen withdrawal response the median time to progression was 101 days (95% CI: 90, 181) for the L0.5 arm, 101 days (95% CI: 90, 180) for the L2.5 arm, and 92 days (95% 86, 130) for the AG arm. No difference was detected in a comparison between the letrozole 0.5 and the letrozole 2.5 arm in the risk of progression (RR - 1.06; 95% CI: 0.77, 1.45; p=0.72, two-sided). When L0.5 is compared to AG the relative risk of progression is 0.76 (95% CI: 0.56, 1.02) in favor of less risk of progression with letrozole (p=0.07, two-sided). When L2.5 is compared to

AG the relative risk of progression is 0.73 (95% CI: 0.53, 0.90) indicating a statistically significant (p = 0.05) reduction in risk of progression in favor of letrozole 2.5 mg.

Median time to treatment failure for each study arm is: 98 days (95% CI: 91, 159) for the letrozole 0.5 mg arm, 102 days (95% CI: 92, 180) for the letrozole 2.5 mg arm, and 96 days (95% CI: 90, 163) for the aminoglutethimide arm. The median time to treatment failure is less than the time to progression in all three study arms. The shorter time to treatment failure is due to the fact that many patients on each arm were removed for progression and a few for other reasons within the first 100 days of study. The relative risk of treatment failure in a comparison of letrozole 0.5 with letrozole 2.5 mg is 1.17 (95% CI: 0.92, 1.48; p = 0.20, two-sided); in a comparison of letrozole 0.5 mg with aminoglutethimide is 0.84 (95% CI: 0.67, 1.06; p = 0.14, two-sided) which tends toward significance in favor of letrozole; and, in a comparison of letrozole 2.5 with aminoglutethimide is 0.72 (95% CI: 0.57, 0.82; p = 0.007). The risk of treatment failure is significantly less with letrozole 2.5 mg in this study population.

Median survival (in days) by treatment arm is 636 days (95% CI: 494, 761) in the letrozole 0.5 mg arm, 792 days (95% CI: 610, +) in the letrozole 2.5 mg arm, and 592 days (95% CI: 504, 845) in the aminoglutethimide arm. No significant differences in the relative risk of death was observed in comparisons between the treatment arms. However, less than 50% of the patients on each arm have died so comparison of the relative risk is survival is premature.

In summary, no statistically significant differences in response, time to progression, time to treatment failure, or survival are detected in comparison between the two letrozole doses although the numerical values and p values tend to favor letrozole 2.5 mg. In comparisons of letrozole 0.5 or letrozole 2.5 with aminoglutethimide, the odds of response are in favor of letrozole, but do not reach statistical significance. When time to progression is examined, the median time to progression is shorter (103 days) on the letrozole 0.5 arm compared to aminoglutethimide (112 days), but the relative risk of progression is less with letrozole (although not significantly so). Risk of progression is statistically significantly less with letrozole 2.5 mg when compared to aminoglutethimide. The risk of treatment failure is less for treatment with letrozole 0.5 and the risk of treatment failure is significantly less with letrozole 2.5 mg as compared to aminoglutethimide. In terms of survival (relative risk of death) the treatments are equivalent but the data is not mature since less than 50% of the patients are dead. Efficacy data indicate that letrozole 2.5 mg is similar to aminoglutethimide in terms of response, has a longer median duration of response, and poses significantly less risk of progression or failure treatment when compared to aminoglutethimide.

The clinical safety profile for letrozole included monitors such as pulse rate, blood pressure, ECGs, and weight. No abnormalities in any of aforementioned were observed with letrozole therapy. No deaths attributable to letrozole or aminoglutethimide therapy occurred during the course of this study. About 3-4% of the patients discontinued study due to serious adverse events. On the letrozole 0.5 arm one serious adverse event, an allergic reaction, which lead to study discontinuation was definitely related to study drug. Another serious AE, a DVT, was

considered to probably be due to study drug. No. One episode of stroke on the letrozole 2.5 arm may possibly be related to study drug usage. (See Table AR/BC3-S6).Other serious adverse events which may possibly be related to letrozole include aggravation of preexisting hypertension, increased fatigue, and hypercalcemia. (See Table AR/BC3). Most serious adverse events which occurred on either letrozole arm did not appear to have any relationship to study drug.

The ten most frequent adverse events reported in this study which were related to letrozole therapy included: (1) nausea in 7.3 - 10.3% of patient; (2) vomiting in 3.6 - 3.8%; (3) somnolence in 2.6 - 3.2%; (4) hot flushes in 2.6 - 4.9%; (5) fatigue in 2.6 - 3.2%; (6) asthenia in 1.6 - 3.6%; (7) headache in 1.1 - 3.1%; (8) dizziness in 1.1 - 3.1%; (9) rash in 1.0 - 2.7%; and, (10) abdominal pain in 0.5 - 1.6%. No increase in adverse events related to study drug was observed in association with impaired renal or hepatic function. No difference in the frequency of adverse events was noted when the patient population was stratified by age. About 2.4% of patients treated with letrozole on this study demonstrated a transient increase in SGOT, SGPT, and gamma-GT to grade 3/4 toxicity levels which may possibly be related to drug. No patient had letrozole therapy discontinued temporarily or permanently due to drug induced liver function abnormalities. Decreases in lymphocyte count were noted at study initiation in 73 (13.2%) of patients and worsened in sixteen patients (21.9%) on treatment and are probably related to the underlying disease.

Conclusion

Study AR/BC3, which compared the use of letrozole 0.5 mg, letrozole 2.5 mg, and aminoglutethimide in postmenopausal women with receptor positive or receptor unknown advanced breast cancer previously treated with antiestrogen therapy, demonstrates that letrozole has similar if not improved efficacy when compared to aminoglutethimide, a standard but not FDA approved treatment for breast cancer. Letrozole when compared to aminoglutethimide has a similar numbers of adverse events and serious adverse events. The safety profile for letrozole, as demonstrated in this study, is very acceptable.

Appendix I:

PROTOCOL REVIEW: AR/BC3

Title: Open, randomized, multicenter, phase II Trial comparing once daily doses of 0.5 mg and 2.5 mg CGS 20 267 with twice daily 250 mg aminoglutethimide plus daily 30 mg hydrocortisone or 37.5 mg cortisone acetate as second-line endocrine therapy in postmenopausal patients with advanced breast cancer

Aims of Trial:

1)Primary: To assess the antitumor efficacy as evaluated by objective response rate and duration of response, time to treatment failure (TTF), and time to progression (TTP) in three treatment arms (daily doses of 0.5 mg CGS 20 267, 2.5 mg CGS 20 267, or twice daily 250 mg aminoglutethimide plus HC or CA) and compare them to each other

2) Secondary:
-To determine the effects of daily doses of 0.5 mg CGS 20 267, 2.5 mg CGS 20 267, and twice daily 250 mg aminoglutethimide plus HC or CA on plasma estrogen levels (E1, E1S, and E2)
-To assess the trough plasma drug concentration level during treatment with daily doses of 0.5 mg CGS 20 267 and 2.5 mg CGS 20 267

Design:

Open, randomized, multicenter phase II trail in postmenopausal women with advanced breast cancer who have previously progressed with antiestrogen therapy given as adjuvant therapy and/or first-line treatment for advanced disease. CGS 20 267 0.5 mg or 2.5 mg will be taken in between 8-9 AM daily. For the first fourteen days of study aminoglutethimide 125 mg (½ tablet) will be taken in between 8-9 AM and in the afternoon between 4-6 PM. Hydrocortisone 20 mg or cortisone acetate 25 mg will be taken with the morning dose of aminoglutethimide and hydrocortisone 10 mg or cortisone acetate 12.5 mg will be taken with the afternoon dose. No washout period for antiestrogens is seen. Antiestrogens as well as other anticancer drugs should be stopped before the patient enters the study. Patient should have recovered from any reversible toxicity due to previous anticancer treatment. Randomized will be done by country using a fixed block design.

Examinations are scheduled before the start of treatment, at two weeks, at one month, two months, three months, and every three months thereafter until withdrawal from trial. Survival data will be collected every three months.

Patient Population:

Inclusion Criteria:

Histologic or cytologic documentation of breast cancer
ER and/or PR positive or unknown
Documented measurable and/or evaluable disease (Bony metastases must show enlarging existing lytic lesions, positive bone scan and pain are not acceptable measures of disease)
Progressive locally advanced disease, loco-regional recurrence not curable by surgery or radiotherapy or progressive metastatic disease
Postmenopausal women with the postmenopausal state defined as:

-No spontaneous menses for five years or
-Amenorrhea for at least twelve months with LH and FSH > 40 IU/L or
-Bilateral oophorectomy or
-Radiation castration and amenorrhea for at least three months

Evidence of progression on adjuvant antiestrogen therapy given for more than six months or within twelve months of discontinuation of antiestrogen therapy or progression with antiestrogens as first line therapy for metastatic disease (Chemotherapy may have been used with the antiestrogen therapy, or progression of metastatic disease on chemotherapy prior to therapy with antiestrogens for advanced disease is allowed, but no more than one trial of chemotherapy is allowed.)
WHO PS ≤ 2

Exclusion Criteria:

Rapidly progressive disease including CNS involvement, bilateral diffuse lymphangitic carcinoma of the lung, inflammatory breast cancer, involvement of > one-third of the liver with metastatic disease
Concurrent for previous malignancies except contralateral breast cancer, cone biopsied in-situ carcinoma of the cervix or adequately treated basal or squamous cell carcinoma of the skin
Sole manifestation of disease: hilar enlargement (unless measured on CT scan), pleural effusion, and ascites
Blastic (sclerotic) bone lesions or mixed blastic and lytic bone metastases with no other measurable / evaluable disease
Concurrent Diseases:

Uncontrolled cardiac or unstable angina (Class IV NYHA)
Uncontrolled diabetes mellitus
Porphyria
History of Peptic Ulcer Disease

More than one chemotherapy regimen for advanced disease
Previous adjuvant or first line therapy for metastatic disease with other than antiestrogen therapy, ovariectomy, or radiation castration (ie. use of progestins or aromatase inhibitors)
Persistent toxicity from previous cancer chemotherapies
Bisphosphonate therapy initiated within six months of start of trial with bony disease as the sole manifestation of advanced disease
Failure to discontinue antiestrogen therapy
Concurrent use of other investigational drugs, chemotherapies, immunotherapy or biologic

response modifiers, or endocrine therapy including steroids except as an aerosol for obstructive airway disease, topical application for dermatologic condition, or use for intra-articular injection

Measures of Efficacy:
(Scans and x-rays should be carried out within fourteen days of scheduled visit.)

History at baseline evaluation
Performance status at all visits
Pain measurement evaluation at all visits
Quality of Life using the EORTC questionnaire
Direct measurement of superficial or palpable lesions at baseline and every three months
Color photographs of visible lesions at baseline and every three months
Hematology[9] and blood chemistry[10] within two week of study entry
Chest x-ray within four weeks prior to study entry and every three months while on study
EKG at baseline, three months, one year and at removal from study
Bone scan at baseline and if negative repeat at six months; if positive, x-rays of involved areas at baseline and every three months while on study or oftener with increasing symptomatology
Liver ultrasound or CT scan at study entry, every three months if abnormal at study entry or if liver function studies become abnormal
FSH and LH if indicated prior to study
Tumor response assessments every three months while on trial
Estrogens (E1, E1S, and E2) will be measured at each visit prior to daily study drug ingestion
CGS 20 267 levels will be measured at every examination prior to daily study drug ingestion

Measures of Tolerability

Tolerability will be assessed starting with the second examination and will include grading of all adverse events, measurement of weight, blood pressure, pulse rate, and evaluation of hematology. Chemistry data will be evaluated at the third and subsequent visits. ECG will be done at baseline, 3 and 12 month. Abnormal laboratory tests should be validated or repeated prior to patient's removal from study. Concurrent medication should be recorded at each visit. Pill counts will be done from examination 2 onward. All adverse events will be graded for relationship to study drug using the following grading: not related, unlikely, possible, probable, or highly probable

Serious adverse events include:
- deaths on study
- hospitalizations resulting from adverse events

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[1]CBC includes hemoglobin, hematocrit, white blood count, differential and platelet count.

[2] Chemistry includes: sodium, potassium, total and/or ionized calcium, phosphate, cholesterol, urea, creatinine, total protein and/or albumin, total bilirubin, SGOT, SGPT, SGGT, and alkaline phosphatase.

events which result in persistent disability or incapacity
events which result in cancer, overdose, a significant hazard, contraindication, or need for a new precautionary statement due to serious vital organ dysfunction.

Evaluation of Efficacy and Tolerability:

Main criterion for efficacy will be evaluation of tumor response using the UICC Criteria. In patients on bisphosphonate therapy, objective response will no be included in the assessment of overall tumor response, except for progression which will be considered as criterion for patient's removal from study. Blastic (sclerotic) and mixed bone lesions will not be evaluated for response. Confirmed corrected hypercalcemia during the trial requiring bisphosphonate therapy will be considered as bony progression.

Main criterion for tolerability is the occurrence of adverse experiences, the severity of which will be classified using the NIH Common Toxicity Criteria. The relationship of adverse reactions to study medication will be recorded in the CRF.

Premature Discontinuations from Trial:

Adverse experiences
Abnormal laboratory values
Abnormal test procedure results
Unsatisfactory therapeutic effect
Patient's condition no longer requires trial treatment
Patient does not meet protocol criteria
Patient withdraws consent
Patient is lost to follow-up
Administrative problems
Death

Statistical Considerations and Analysis of Data:

The primary goal of AR/BC3 is to determine the more appropriate dose of CGS 20 267 in the treatment of advanced breast cancer in postmenopausal women. Primary endpoints include: overall tumor response and duration of response, time to progression, time to treatment failure, and time to death if > 100 deaths are observed. Secondary endpoints include: performance status, quality of life, endocrine response, pharmacokinetic measurements (trough levels), and tolerability. No interim analyses are planned. Primary analysis to be performed is "intent to treat".

Sample size has been calculated on the basis of overall tumor response as well as on the time to progression (or time to treatment failure). For sample size based on tumor response the overall objective response (CR and PR) was assumed to be 20% in the treatment arms with a minimum

response rate of 10%. With $a = 0.05$, two-sided level of significant and with the power = 0.90 the ability to detect a 15% absolute difference between the two treatment would require a sample size of 146 patients per arm. Allowing for simultaneous comparison of the three treatment arms, loss to follow-up, and nonevaluability a total sample size of 540 patients is needed. To detect a 50% difference in the median time (i.e. detection of a hazard ratio of 1.5) to progression (to treatment failure) between any two of the three treatment arms when comparing the three arms simultaneously with $a = 0.05$, two-side and power = 0.90 a sample size of 154 per arm (total sample of 456 patients) is needed. Allowing for a 15% failure rate to reach any endpoint the total sample size should be 544 patients. Randomization will be stratified by country and each country will be taken into account in the analysis. In addition to the intent to treat analysis, analysis of evaluable and eligible and evaluable patients will be done.

For those variables concerned with time to event or duration of response the Kaplan-Meir product-limit method will be applied to estimate the survival function. Time to progression will be from the first day of treatment until documented progression. TTP will be right censored for patients withdrawing from trial without progressive disease or for patients still on treatment at time of analysis and who have no evidence of progression. Deaths due to unknown cause will be considered as due to progression of disease. Time to treatment failure is defined as the interval from the first day of treatment to diagnosis of progression, withdrawal from trial for any reason, or death from any cause whichever is the earliest event. TTF will be right censored only for patients remaining on trial treatment at the time of analysis and who have no evidence of progressive disease.

Treatments will be compared using the logrank test. If the overall logrank statistic for comparing the three "survival curves" is statistically significant, the two degrees of freedom will be partitioned orthogonally to make the following comparisons: CGS 20 267 vs aminoglutethimide and 0.5 mg/day CGS 20 267 vs 2.5 mg/day CGS 20 267. As the trial is primarily a phase II trial for which the analysis is essentially exploratory, no adjustment of "P-value" is planned to accommodate the multiple endpoints.

For the variables TTP and TTF the stratified logrank test (Mantel-Haenszel) will be applied to selective baseline characteristics to determine their prognostic influence. Baseline characteristics include: performance status, age class (≤ 55, 56 - 69, ≥ 70 years), disease free interval (Stage IV disease, < 2 years, ≥ 2 years), dominant site of disease (soft tissue, bone, visceral), previous chemotherapy, previous response to hormonal therapy, previous/concomitant administration of bisphosphonates, and receptor status. Further identification of additional prognostic factors (ITT analysis only) may be made applying a COX's proportional hazard model.

Overall tumor response will be analyzed applying a non-parametric method for ordered categorical data with 95% confidence intervals for the difference in overall response between CGS 20267 and aminoglutethimide. Prognostic influence of selected baseline characteristics (performance status, age class, disease-free interval, previous chemotherapy, previous response to hormone therapy, previous or concomitant bisphosphonates will be examined using a logistic

regression procedure. Baseline characteristics will be summarized for each treatment group. No significance testing of baseline characteristics will be performed since the treatments were randomly allocated.

Hormone levels and drug levels will be log transformed and descriptive summary statistics for each hormone will be provided. Dependent on the available measurements, a repeated-measures type of analysis will be performed. The influence of baseline characteristics such as age and calculated creatinine clearance on pharmacokinetic data will be examined graphically. For the analysis of hormone measurements and of drug levels only one data set will be analyzed, that of endocrine evaluable patients. The analysis of the EORTC QLQ-C30 will be defined outside of this protocol using the weights for sub-scales as proposed by Aaronson et al. Performance status will be tabulated and summarized in the form of frequency tables with individual changes in performance status tabulated. No formal of analysis of performance status is planned. Adverse events will be tabulated according to patient and will be summarized for each treatment group according to the COSTART body system. No formal analysis is planned. Routine laboratory data will be listed and flagged according to the NIH scale. Key laboratory variables will be summarized in tabular form and in graphical form.

The trial will be performed in accordance with the World Medical Association Declaration of Helsinki. Informed consent (signed by the patient or their representative) must be obtained prior to the patient's participation in the trial.

AMENDMENTS:

Amendment No. 1 (February 17, 1994):

This amendment deals with changes in the eligibility criteria.

1) Patients are considered suitable for another endocrine treatment, i.e. letrozole or aminogluthethimide, when they have disease progression **following chemotherapy given as therapeutic treatment either after failure of first-line antiestrogens for advanced disease, or after failure of adjuvant antiestrogens** is added to the inclusion criteria.

2) **Adrenal insufficiency or Cushing's syndrome** is added to the exclusion criteria.

Amendment No. 2 (August 9, 1994):

This amendment deals with increased knowledge about the adverse events associated with letrozole due to increased patient exposure. The following information was added to the Patient Information Sheet, the Patient Consent Form, and the Witnessed Informed Consent: "Conditions that were reported in one or more persons in clinical trials with letrozole include: nausea, vomiting, dyspepsia (heartburn), constipation, dehydration, hot flushes, vaginal discharge, headache, hair thinning, edema (swelling) anxiety, weakness, fatigue, bone pain, transient

elevations in liver function studies, rash, blood clots obstructing veins (which could lead to blood clots in lungs), allergic reactions including hives and swelling of the mouth, throat and other internal mucous membranes, and interference with functioning of the adrenal gland which can lead to low blood pressure and imbalance in blood salts and symptoms of dizziness, fainting, weakness, nausea, and vomiting. The relationship with letrozole has not always been established."

Amendment No. 3 (August 26, 1994):

This amendment deals with the deletion of Appendices II, III, and IV (the original Patient Information Sheet, Patient Consent Form, and the Witnessed Informed Consent Form which were revised as noted in Amendment No. 2). The amended forms will be provided separately from the protocol and the sheets and any references the original appendices are to be removed from the protocol.

Amendment No. 4 (dated September 9, 1994):

This amendment deals with "Peer Review of Tumor Assessment" and provides instruction on how the information from the peer review process is to be recorded for evaluation by the CRO.

Appendix II: AR/BC 3: Study Discontinuations without Documented Progression on Letrozole 0.5 (A), Letrozole 2.5 mg (B), and Aminoglutethimide (C)

Pt. No.	Rx	Reason For Study Discontinuation if other than Progression	Relationship to Study Drug
	A	AE: Stroke (7/22/94); Remained on study med; Had second AE with drainage of pleural effusion (9/10/94) with talc sclerosis followed by shock and death on removal of chest tube	None
	C	Removed from study for progression not confirmed on PR	15
	A	AE: Severe hip pain due to metastatic disease; RT to area of bony pain: Study med discontinued on 8/5/96 due to persistent pain: pain persisted until death 10/5/95	15
	A	T.F.: Treated with another hormonal agent; not adequately assessed	None
	A	AE: Irritated eyes, fatigue, soreness of oral mucosa, increased bone pain which commenced with study drug and stopped day after study drug D/C; Pt. refused to continue study meads after three months (3/2/94); Noted to have progressed one week later on bone scan (3/9/94)	Yes
	A	AE: D.T.	Yes
	B	T.F.: Pt. had colon cancer with liver meets not metastatic breast cancer	No
	B	T.F.: Pt.. withdrew consent	
	A	T.F.: Removed from study for unclear reasons by PI; Set of images is incomplete on peer review	No
	C	T.F.: Leptomenigeal involvement at time of study enrollment; on-study 2 days when involvement discovered	No
	C	AE: Generalized erythematous pruritus due to study drug	Yes
	B	TF: Ineligible since more than one-third of liver involved with disease	No
	C	TF: Patient noncompliant	
	B	AE: hypercalcemia (Serum calcium not done on study enrollment: Hypercalcemia occurred within six weeks of study drug initiation)	Possibly
	C	TF: Non-compliant	No
	B	TF: More than one-third of liver involved at entry (ineligible)	No
	A	TF: Pt. withdrew consent	No
	A	TF: Did not take study drug	No
	C	TF: Non-compliant	No

	A	TF: Removed from study for increased pain without documented evidence of progression	?
	B	TF: No assessments at time of study removal to prove progression; reason for study removal "progression" unclear	1026
	C	AE: Exanthema, nausea and vomiting, diarrhea associated with study med; Sxs. resolved with discontinuation of the study medication	Yes
	A	TF: Pt. noncompliant	
	C	TF: Pt. noncompliant	
	B	TF: Pt. died on study from acute pulmonary edema:	No
	C	Pt. started study meds on 10/6/94; Pt had gastric biopsy 10/29/94 showing linitis plastica; Jaundice and liver mets on 11/1/94 and study med d/ced: pt. died on 11/14/94: Not evaluate for response: Considered TF	No
	B	TF: Pt. died from unknown causes (? progression) two months after study enrollment; No further information available	No
	C	AE: Acute renal failure; Study drug d/ced on 3/16/94; Progression reported on 3/6/94	Yes
	A	TF: Non-compliant	
	C	TF: Ineligible, did not meet study criteria	No
	C	TF: No documented evidence of progression at time of study removal; ? reason for removal	
	C	TF: Brain mets found at Visit 2; protocol inelibgible	No
	B	AE: Quaddraplegia; study meds discontinued: no documented evidence of disease progression: considered TF	None
	B	AE: CVA (8/4/94) twenty-seven days after starting study medication; died from effects of CVA on 9/6/94: study med d/ced at time of CVA	Possible
	A	TF: Pt. withdrew consent	No
	C	AE: Rash requiring steriods and antihistamines for control; Removed from study due to AE	Yes
	C	Pt developed stupor (7/27/94), became comatose, and died on 8/5/94; No diagnostic tests done to determine eitiology of coma : Response changed from PD to NE; Regarded as a TF since no documentation of progression	No
	A	TF: Pt. withdrew consent	
	C	AE: Pruritic rash which required study removal	Yes
	B	TF: No adequate assessment of progression at time of study removal	
	B	TF: Failure to meet eligibility criteria	

	B	AE: Hypercalcemia	No
	A	AE: Fractured left clavicle: Pt. discontinued therapy: Known to have clavicular lesion at time of study entry: Not evaluable for response	No
	B	TF: Removed from study 6/23/95; died 7/23/95 from melanoma documented by autospy;	No
	C	TF: Lost to followup	
	A	TF: Pt. withdrew consent	
	B	TF: No F/U studies at time of removal from study to prove progression	
	C	TF: Pt. withdrew consent	
	A	Removed from study for progression not confirmed on peer review	
	A	Removed from study for progression not confirmed on peer review	
	A	Removed from study for progression not confirmed on peer review	
	A	Removed from study for progression not confirmed on peer review	
	A	Removed from study for progression not confirmed on peer review	
	A	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	B	Removed from study for progression not confirmed on peer review	
	C	Removed from study for progression not confirmed on peer review	

Appendix III:

AR/BC-3: Changes in Response & Time to Event Data (M.O. Review)

Pt No.	Rx.	Comments / Changes
	A	No F/U assessment; Response changed to 5 (NE): (CVA on 7/12/94) with death due to shock after pleurodiesis with talc sclerosis on 9/10/94; Consider as TF
	A	Offstudy by PI for "bony progression" not confirmed by PR; Response changed to 3 (NC)
	B	Pt. continued on study medication until time of death per review of SAE (collapse w/o loss of consciousness; death due to disease; death on study due to progression)
	A	Study meds d/ced 3/1/94 for severe headache due to pressure of metastatic bone lesion pressing on brain; Pt. also had progression in the liver shown on 3/9/94; Response changed to PD and progression date of 3/1/94 assigned
	A	Correct censoring date : 5/20/96
	C	Pt. died while receiving study drug: Peer review judged progressive disease three months prior to death: Will consider PD and use time to progression
	A	Pt. discontinued study meds after three months due to eye irritation and fatigue both of which disappeared day after study meds were stopped; Was found to have progressed one week later: Pt. should be considered as a treatment failure; Will continue as PD response
	C	Response changed from PD to NC (3) since measurements do not confirm soft tissue progression
	B	Pt. with history of hypercalcemina prior to study therapy controlled with clodronate when enrolled on study (12/2/94) developed hypercalcemia 41 days (1/13/95)after start of therapy; Died from disease progression (1/31/95); Question of hypercalcemic flare is raised- will consider as treatment failure since no docuementation of progression done
	A	Date progression observed in lung: 10/18/95
	B	Pt. found to have colon cancer with liver mets after study enrollment; liver mets used as " site on metastatic disease at enrollment on trial" ; Pt is not evaluable for response (5) and will be considered TF since removed from study due to colon cancer; last date patient took trial medication was 3/6/95
	A	Date of progression, treatment failure: ½/96
	A	Date of progression, treatment failure: 9/4/95
	A	No evidence of progression on peer review for 2/7/96; New bone and liver lesions reported on 5/1/96 so this date assigned for progression and treatment failure
	B	Actual date of progression: 1/12/95
	C	Dates entered for ITT analysis (all patients enrolled counted); Resp = NE (5)
	A	No evidence of progression at time of study removal; Considered NE (5); Died day after study removal, ? cause
	A	Actual date of progression by bone scan: 9/7/95
	A	Overall response on peer review is NC; Response changed from 5 to 3
	B	Soft tissue measurements increased greater than 25% on 9/12/94; date for progression and treatment failure changed to 9/12/94

	B	Bone scan which showed progression was done on 7/21/94
	B	Progression noted on x-rays done on 12/3/93
	A	Bony progression noted on x-ray on 4/27/95
	C	First evidence of progression reported on 3/9/94
	B	Increased size of axillary node on CT scan on /6/94
	B	Bony progression noted on 5/8/95
	C	Progression noted on bone scan done on 5/18/95
	A	Remove from study without evidence of progression
	B	Progression observed on 5/7/96
	B	Pt. ineligible for protocol
	A	Off-study with discovery of brain metastases on day 8
	C	Progression on bone scan on 2/8/94
	C	Progression on skull x-ray performed on 3/4/95
	A	Soft tissue measurements do not reflect a 25% increase on 1/11/95: principal investigator considered soft tissue progression of 2/22/95
	C	X-ray of bony disease done on 11/22/93 which was considered "too early" by peer review. Treatment started on 12/10/93 therefore response changed to "PD".
	C	Original bone scan read as normal by investigator: Peer review considered bony metastatic dz.; response changed from PD based on bone to NE (5)
	B	Not evaluable for response since only site of disease is pleural effusion
	B	Pt. had hypercalcemia prior to study enrollment controlled with clodronate; Started trial meds on 12/2/94: admitted to hospital on 1/13/95 with hypercalcemia; study med dced; Died on 1/31/95 from "disease progression"; no documentation of progression; Hypercalcemia could be due to flare
	B	Date of progression is 7/4/95
	B	Date of progression is 8/24/95
	C	Date of progression : 1/03/94
	A	Date of progression: 3/31/94
	A	Date of progression : 4/7/95
	B	More than one-third of liver evolved at enrollment; no eligible for response evaluation (NE) and is considered a TF since progression not documented when removed due to ineligibility
	B	Stable disease and unconfirmed PR---Best Response in NC
	C	Bony disease only followed per protocol until evidence of progressive disease on pelvic x-ray on 2/9/95 (DOP); Pt had stable disease for eleven months (Response changed)
	B	Date of progression: 10/24/95

	B	Date of progression: 11/15/95
	C	Date of last visit is 5/26/96
	C	Tumor measurement consistent with progression on 1/6/95
	B	Bone scan done 11/25/94 showed progression
	A	Best response was NC until 4/13/94 (Slightly less than six mos. on trial)
	C	Greater than 25% increase in lesions did not occur until 9/29/94
	C	Date of progression is 2/22/95 (line listing)
	A	Bone scan done 2/9/94 shows disease progression (peer review)
	B	No evidence of progression on peer review: censor date removed from study by PI
	A	Reported to be ineligible since more than 1/3 of liver involved at time of study entry; PI reported progression at time of study removal and response changed from NE to PD
	B	Pt started study meds on 1/4/94; Had TIA with hemiplegia on 1/9/94; hemiplegia resolved after 3 days; trail med d/ced on 1/19/94 and patient died from dypsnes due to lung mets on 1/23/94; will consider as PD on basis of chest xray report
	A	Date of progression from line listings is 9/4/94
	B	Incorrectly reported as having soft tissue disease; Dates for progression are correct
	B	Correct date of progression: 8/31/94
	A	Correct date of progression: 11/17/94
	A	Correct date of progression: 10/31/95
	B	Pt given a response of SD since appropriate studies done and no progression in lung lesions examined at time of study removal observed on peer review (PI thought 50% increase.)
	C	Correct date of progression: 3/14/95
	A	Dates added so that patient can be analyzed in an intent to treat analysis; NE for response
	C	Actual date of progression is 9/5/95
	C	Earliest date of progression is 9/6/95 (NMR of spine)
	B	Date of progression: 10/12/95
	A	Date of progression: 4/2/96
	A	Date of progression: 6/6/94
	A	Considered PR by both PI and peer review; Date of first response 2/22/95; End of response 2/19/96 (censored);
	A	Progression on pelvic x-ray done on 7/17/95
	A	Date of progression: 7/3/94
	A	PR response based on soft tissue measurements; Date of response us 8/30/94; Still in response at the last visit on 5/29/95 at which time patient was removed from study

	C	Measurement done by investigator indicate progression on 4/11/96
	C	Date of progression: 4/28/94
	B	Date of progression: ½/95
	B	Date of progression: 3/7/94
	A	Date of first response is 8/30/94; Progression documented on 11/19/95
	A	Date of progression: 2/2/96
	A	Date of progression: 5/11/96
	B	Date of progression: 6/19/95
	C	Date of progression: 8/16/94
	C	Date of progression is 5/29/95 with new lesions on bone scan; NE for response since initial bone lesions not x-rayed
	C	Date of bone scan showing progression is 2/23/95
	A	Date of progression is 4/5/95
	B	No evidence of documentation of progression so censored for progression; Reason for study removal not given so considered TF; response is NE due to lack of assessments at study removal
	B	PD per investigator who noted increased lytic disease on chest x-ray and removed from study; date of progression -1/10/94
	B	Date of progression on bone scan is 12/5/95
	B	Date of progression as evidenced by spine x-ray is 12/15/94
	B	Peer review did not find increased disease in lungs; Called NC; Response changed to NC as indicated by measurements on 11/21/94
	B	Date for bone progression is 4/5/95; no date given for liver progression
	A	Date of progression per listing is 6/14/94
	B	No documentation of progression at time of death on study; Response changed to NE: Died from acute pulmonary edema 7/24/94 while on study: Considered TF
	B	No evidence of bony Involvement on PR so NE for response
	C	Study medication started on 10/4/94: Gastric cancer proven by biopsy on 10/28/94; Jaundice and weight loss reported 11/1/94; Study med d/ced; Pt died on 11/14/94 from gastric Ca; Pt is not evaluable for response; no evidence of breast cancer progression, so is considered a treatment failure; Date of death corrected
	B	Response changed to PD since investigator noted 47% increase in ST lesions with ? new lesions with the date of progression of 11/29/94
	C	Date of progression is 11/9/94
	B	Response changed from PD to NE since no documented evidence of progression; Pt. is a death on study probably due to disease: Will consider as a treatment failure
	A	Progression documented on bone scan done on 3/24/94

	C	Pt started on study med on 2/8/94: Developed acute renal insufficiency on 3/16/94 with other symptoms, study drug D/ced: found to have gastric ulcer on3/20/94; Pt is TF with no evidence of progression at time study med d/ced: response is NE
	A	NE since no evidence of metastatic disease
	B	Progression documented by bone scan on 5/6/94
	C	Response changed from PR to NC as soft tissue CR with stable bony disease reported; Remained in PR at time of last visit
	B	Date of progression in bone is 12/20/94
	C	Response changed to PR based on CR in soft tissue with no evidence of change in pleural effusion
	B	Progression on bone scan done on 11/23/95
	C	New lytic bone lesions seen on x-ray done on 9/8/95
	C	NE since no evidence of metastatic disease
	C	Date of progression is 8/30/94
	B	Bony progression documented on 8/10/95
	A	Called CR on peer review but had evidence of stable pleural effusion per PI and was considered PR by investigator; Response changed to PR
	C	No assessments done at time of study removal (8/26/94) so PD changed to NA
	C	No assessment to document progression at time of study removal due to AE
	B	No documentation of progression at time to study removal: note death within one month of withdrawal from study; assigned NE response and called TF
	C	Actual date of progression: 10/6/94
	C	Date of progression: 8/11/95
	B	Date of progression: 12/15/94
	A	Date of progression: 8/1/95
	C	Pt developed stupor (7/27/94), became comatose, and died on 8/5/94; No diagnostic tests done to determine eitiology of coma : Response changed from PD to NE; Pt. is regarded as a TF since no documentation of progression
	B	Date of progression in line listing is 8/23/94. date of CT Head showing brain met
	A	Progression documented on x-rayed done on 10/12/95
	C	Unable to verify the date of progression (1/4/95) so date changed to 2/20/95
	B	Date of progression by x-ray in 1/17/95
	A	Date of progression by x-ray on 10/31/95
	B	Progression observed on 10/24/95 by investigator and confirmed by peer review
	C	Date of progression: 11/17/94 by x-ray

	A	Date of progression by x-ray is 6/7/95
	C	Date of progression by x-ray is 1/3/96
	B	Progression by x-ray at 4/17/95
	B	Peer review date of progression is 11/22/95
	C	Increased liver size and increased pain per investigator resulted in study removal; response changed from NE to PD and censoring changed
	C	Date of progression is 8/10/95
	A	Date of progression on x-ray is 12/9/94
	B	Date of progression is 3/1/95
	C	Date of progression for ST is 2/15/95
	A	Date of progression: 12/27/94
	C	Date of progression: 2/22/96
	B	Date progression documented is 1/24/95
	A	Date progression documented is 9/7/95
	A	Date of progression is 8/29/95
	B	Date of progression is 11/2/95
	B	Patient died on study, however progression not documented in line listing; considered as TF and censored for progression
	C	Evidence of new blastic lesions on 1/23/96
	B	Removed from study since eligibility criteria not met
	C	Date of progression on x-ray is 5/17/95
	B	Date of progression on x-ray is 7/28/95
	B	No peer review done after 11/5/95, will use investigator assessed response
	B	Date of progression is 6/7/95
	B	Date of progression on x-ray is 5/16/95
	A	Date of progression is 9/20/95
	C	Progression measurements ~ 25%; Peer review called PD
	A	Not assessable since no histological proof of disease
	B	At autospy on 7/23/95 pt. found to have metastatic melanoma; Pt. is reclassified as a TF ; is NE for response since progression may be due to melanoma not breast cancer
	C	Actual date of progression is 3/6/96
	A	Actual date of progression is 3/14/96

	B	Date of progression is 1/30/95
	C	Date of progression on x-ray on 3/2/95
	C	Date of progression is 4/9/96
	A	Date of progression is 1/22/96
	B	Date of progression is 7/5/95
	A	Investigator reported PD but peer review unable to confirm due to poor quality films so response of NE assigned; Changed to PD with progression date of 6/2/95
	C	X-ray evidence of progression on 5/26/95
	C	Date of progression is 5/22/95
	B	Date of progression is 7/6/95
	A	Pt. developed CHF due to lymphangittic lung and pericardial disease on 4/6/95: Removed from study on 4/8/95; Died on 4/10/95: Progression is not documented in the line listings
	C	Date of progression is 3/14/96
	B	Date of progression is 3/13/96
	C	Date of progression: 5/22/95
	B	Date of progression is 5/26/95
	A	Date of progression is 8/3/95
	C	Date of progression is 8/10/95
	C	Actual date of progression is 12/27/95
	C	Mammographic documentation of progression on 11/16/95
	A	Measurements of 11/21/95 consistent with PR; Evaluable disease stable considered PR
	C	Date of progression is 8/8/95
	C	Date of progression is 5/29/95
	A	Date of progression is 8/23/95
	C	Date of progression is 5/30/95
	A	Date of progression is 7/17/95
	C	Date of progression is 8/10/95
	B	Bone and visceral PR with stable soft tissue disease by PI and PR and so response changed to PR
	C	Date of progression in the line listings is 10/19/98
	B	New lytic lesion reported on 10/11/95
	A	Progression date is 3/1/96
	C	Progression date is 11/15/95

	C	Date of progression is 10/19/95
	C	X-ray evidence of progression on 10/25/95
	B	Bony progression on 12/13/95
	A	Date of progression is 10/17/95
	B	Failure to assess lung lesions at time of study removal changes patient from PR to NE; no evidence of progression on any studies at time of study removal; Assigned as TF
	B	Removed from study on 5/7/96 without evidence of progression
	A	Increase in measurements is not 50% but will leave as PD as called by investigator

Appendix IV

Change in Assessment by Study Arm

Table A-IV: ARM A - Change in Assessment

Applicant Assessment	FDA Assessment				
	CR	PR	SD	PD	NE
CR		1355			
PR					
SD		1932, 1002			
PD			743		12, 114, 1026
NE			401	40, 1909	

Table B-IV: ARM B - Change in Assessment

Applicant Assessment	FDA Assessment				
	CR	PR	SD	PD	NE
CR					
PR					570
SD		1009, 1945			
PD			720		68, 573, 718, 762, 1103, 1315, 1328, 1364, 1418, 1807, 2027
NE			796, 1219	1321, 1201, 758	

Table C-IV: ARM C - Change in Assessment

Applicant Assessment	FDA Assessment				
	CR	PR	SD	PD	NE
CR					
PR					
SD		1337, 1342			
PD			70, 721		538, 1315, 1320, 1357, 1361, 1379
NE			15, 1400	524	

APPENDIX V: Listing of the Case Report Forms included in the AR/BC3 Study Report

Pt. No.	Arm	Reason for Inclusion of CRF in the Study Report
	L0.5	Death: Septic shock associated with pleurodiesis
	AG	Death: Nausea and vomiting with bowel obstruction due to disease
	L0.5	AE: Allergic reaction to drug
	L0.5	AE: DVT
	L2.5	AE: Discovery of colon primary with liver mets due to colon primary
	AG	AE: Leptomenigeal involvement
	AG	AE: Total boby erythematous rash due to drug
	L2.5	AE: Hypercalcemia
	L2.5	AE: CVA with death due to CVA
	L0.5	AE: Hypoadrenalism due to brain mets
	L2.5	AE: Nausea, vomiting, diarrhea
	L2.5	AE: Death with history of acute pulmonary edema
	AG	AE: Gastric cancer
	L2.5	Death due to unknown causes
	AG	AE: Renal insufficiency due to study drug
	L2.5	AE: Quadreplegia due to disease
	L2.5	AE: CVA on 8/4/94 with death on 8/6/96
	AG	AE: Rash
	AG	AE: Coma
	AG	AE: Rash
	L2.5	AE: Hypercalcemia
	L2.5	AE: Death due to metastatic melanoma not breast cancer
	AG	Death within thirty days of study removal due to progressive disease

OVERALL SUMMARY OF EFFICACY AND SAFETY:

In the clinical phase I/II trials (AR/PS1; AR/BC2; AR/ST1; 01) at doses varying from 0.1 mg to 5.0 mg letrozole daily, twenty (28.2%) of seventy-one postmenopausal patients with advanced breast cancer no longer responsive to conventional treatment were reported to have objective responses (CR or PR) of greater than 4 weeks duration with letrozole therapy. In all of these studies, aromatase induced suppression of estrogen (estrone and estradiol) levels to less than 95% of baseline estrone / estradiol levels without interference with adrenocortical function was observed. No significant changes in aldosterone levels (adrenal mineralocorticoid function) were observed, although aldosterone levels were consistently about 10% - 12% less than baseline. No adverse physiologic effects due to the decrease in aldosterone concentration were noted (i.e., no change in blood pressure, pulse rate, serum electrolytes, serum glucose). ACTH level and Cortrosyn stimulation testing during these studies did not provide evidence of adrenal malfunction with long term administration of the aromatase inhibitor, letrozole. Thyroid function was not adversely affected. No other hormone abnormalities were detected. Adverse experiences associated with study drug therapy were infrequent and rarely serious.

In a phase II trial (AR/ES1) conducted in a similar population of postmenopausal patients with advanced breast cancer refractory to conventional therapies, forty-six patients were randomized to letrozole 0.5 mg or letrozole 2.5 mg. In this study four (18%) of twenty-two patients on the 0.5 mg arm had objective responses (2 CRs, 2 PRs) and two patients (8%) of twenty-four on the 2.5 mg arm had objective responses (2 PRs). The number of adverse events attributed to study drug were minimal and usually of mild severity. This study provided further evidence that letrozole was efficacious in advanced breast cancer.

Two large (550 + patient) randomized clinical trials which compared letrozole 0.5 mg, letrozole 2.5 mg, and megestrol (AR/BC2) or aminoglutethimide (AR/BC3) were conducted in an attempt to determine the efficacy of letrozole versus a comparator and to determine if a difference in efficacy parameters could be detected using the two doses of letrozole (dose response effect). The study population for both trials included postmenopausal women with receptor positive or receptor unknown breast cancer, locally advanced or metastatic, who had progressed either on adjuvant treatment with antiestrogens (after six months of adjuvant antiestrogen exposure), or progressed within six months (AR/BC2) or one year (AR/BC3) of completion of a course of adjuvant antiestrogen therapy, or progressed while on therapeutic antiestrogens for recurrent disease. In both studies patients on each arm were well matched for demographic and prognostic factors. A confounding factor in both clinical trials was the failure to allow six week to elapse from discontinuation of the antiestrogen therapy to the initiation of study drug to allow for tumor response secondary to antiestrogen withdrawal.

In AR/BC2 the objective response rates for the three arms are as follows: letrozole 2.5 mg - 23.6%, letrozole 0.5 mg - 11.7%, and megestrol - 16.4%. The unadjusted odds ratio (OR = 2.33; 95% CI: 1.32, 4.17) for the comparison of the response rates of letrozole 2.5 mg to letrozole 0.5

mg is statistically significant (p = 0.004, two-sided). The unadjusted odds ratio (OR = 1.57, 95% CI: 0.93, 2.64) for the comparison of the response rates for letrozole 2.5 mg to megestrol tend to favor letrozole (p = 0.09, two sided). Median time to progression for the treatment arms is as follows: letrozole 2.5 mg - 170 days; letrozole 0.5 mg - 154 days; and, megestrol 168 days. Relative risk of progression is significantly less on the letrozole 2.5 mg arm as compared to the megestrol arm (RR = 0.77; 95% CI: 0.60, 0.98; p = 0.03, two-sided). The risk of progression in a comparison of letrozole 2.5 mg to letrozole 0.5 mg tends to favor the 2.5 mg dose (RR = 0.81; 95% CI: 0.63, 1.03, p = 0.09, two sided). Median time to death with about half of the study population dead on each arm is as follows: letrozole - 740 days, letrozole 0.5 mg - 645 days, and megestrol - 659 days. No significant difference in survival has been detected in a comparison of the treatment arms but the data is not mature.

In AR/BC3 objective response rates for each treatment arm are as follows: letrozole 2.5 mg - 18.3%; letrozole 0.5 mg - 17.6 %; and, aminoglutethimide - 12.3%. Comparisons of the odds ratios for response between the various treatment arms does not show any significant difference in the odds of response. Median time to progression on the letrozole 2.5 mg arm was calculated as 121 days, on the letrozole 0.5 mg arm as 103 days, and on the aminoglutethimide arm as 112 days. While no difference in the relative risk of progression is detected in a comparison of letrozole 2.5 mg and letrozole 0.5 mg or in a comparison of letrozole 0.5 mg with aminoglutethimide, a significant difference in the relative risk of progression in favor of letrozole 2.5 mg is observed in a comparison of letrozole 2.5 mg and aminoglutethimide (RR = 0.73; 95% CI: 0.57, 0.94; p = 0.01, two-sided). Median time to death for the letrozole 2.5 mg arm is 792 days, for the letrozole 0.5 mg arm is 636 days, and for the aminoglutethimide is 592 days. No significant difference in the relative risk of survival is detected, however the data is not mature as about two-thirds of the study participants on each arm were alive at the cut-off date.

Data from all clinical studies indicate the letrozole is an effective treatment for receptor positive or unknown breast cancer in postmenopausal patients who have failed antiestrogen therapy in the adjuvant or in the therapeutic setting. In AR/BC2 the response rates for letrozole 2.5 mg were significantly superior to those for letrozole 0.5 mg suggesting that this dose should be the marketed formulation. In AR/BC3 no difference in the odds of response are observed in a comparison between the two dose levels of letrozole. However, the risk of progression is significantly better in both trials for the letrozole 2.5 mg dose with regard to the comparator treatment (megestrol, aminoglutethimide) currently used as second line therapy in postmenopausal breast cancer suggesting the 2.5 mg dose is more likely to be effective.

With regard to symptomatic benefit no significant worsening of performance status was reported on any of the clinical trials with letrozole use. No increase in (worsening of) pain or increase in use of analgesia was reported with continued use of letrozole. Blood pressure, pulse rate, and body temperature remained unchanged with letrozole treatment in all clinical trials. EKG tracings also were unchanged with letrozole treatment.

Estrone production was suppressed to greater than 80% of baseline and estradiol production was

suppressed to greater than 65% of baseline with a daily dose of letrozole 0.5 or 2.5 mg in the clinical trials. In about 40% of the samples obtained while the patient was on letrozole therapy, plasma estrogen levels were below the lower limits of detection of the assays employed to measure estrone, estrone sulfate, and estradiol. As a result no dose effect on estrogen suppression could not be demonstrated in these studies.

Elevations of liver function studies (Grade 3/4) were observed in about 3% of the clinical trial participants which may be related to letrozole treatment since no evidence of hepatic metastases or other liver disease existed when the abnormal liver functions were reported. Other chemistry parameters remained within normal limits. Mild lymphopenia was reported with letrozole treatment which was not associated with increase in viral infection or other immune abnormalities and may well be related to underlying neoplasm rather than drug. Other hematological abnormalities reported on the clinical trials were related to breast cancer or other disease processes.

In the clinical trials no deaths on or within thirty days of letrozole discontinuation were related to letrozole treatment. Thirteen patients (1.7%) out of seven hundred forty breast cancer patients treated with letrozole on the phase III trials discontinued treatment due a serious adverse event which was definitely, probably, or possibly related to letrozole therapy. The number of study discontinuations due to adverse events was significantly increased on the megestrol arm of AR/BC2 as compared to the letrozole arms. However, the number of study discontinuations due to adverse reactions definitely, possibly, or probably related to study drug was not significantly different between the study arms. On AR/BC3 no difference was observed in the number of study discontinuations due to adverse events, whether related to study drug or not.

On study AR/BC2 the incidence of thromboembolic events was significantly less on the letrozole arms as compared to the megestrol arm. The incidence of vaginal bleeding was also significantly less on the letrozole arm as compared to the megestrol arm. On AR/BC3 with the exception of aminoglutethimide related rash and elevation of gamma GGT due to aminoglutethimide no significant differences in the incidence of adverse experiences was noted in the comparator arms. Overall few serious adverse events which were definitely related to letrozole therapy were reported.

The most frequent adverse experiences (usually mild to moderate in severity) reported in comparative clinical trials (AR/BC2; AR/BC3) whether related to study drug or not were: musculoskeletal pain (~ 25.8%); nausea (~11.2%); headache (~ 9.1%); arthralgias (~8.1%); vomiting (~ 6.3%); fatigue (~ 9.3%); dyspnea (~ 11.7%); constipation (~ 7.5%); viral infections (~ 6.4%); hot flushes (~ 4.3%), diarrhea (~ 4.3%); cough (~ 6.6%); chest pain (~ 6.6%); peripheral edema (~ 6.3%); abdominal pain (~ 7.3%); hypertension (~ 5.1%); rash (~ 4.5%); anorexia (~ 4.2%); dyspepsia (~ 4.5%); asthenia (~ 3.2%); somnolence (~ 2.6%); dizziness (~ 4.8%); hypercholesterolemia (~ 1.4%); weight increase (~ 5.2%); and pruritus (~ 3.2%). Many of the adverse experiences reported above are related to the underlying disease. In normal volunteers adverse experiences reported with letrozole included headache and nausea. In the

phase I/II trials adverse experiences related to drug included: nausea, hot flushes, vomiting, diarrhea, and alopecia. Adverse experiences related to more pronounced estrogen deficiency secondary to letrozole therapy could include hot flushes, pruritus, alopecia, and hypercholesterolemia. Weight gain did not appear to be a significant problem with long term letrozole usage.

Letrozole has similar, if not improved efficacy, as compared to other agents used as second line hormonal therapy in the postmenopausal women with receptor positive or receptor unknown breast cancer, ~~cancer~~ which has progressed on adjuvant or therapeutic antiestrogen therapy or within one year of completion of a course of adjuvant antiestrogen therapy. Letrozole is safe and well tolerated with few serious adverse effects.

RECOMMENDED ACTION:

Letrozole should be approved for the treatment of locally advanced or metastatic receptor positive or receptor unknown breast cancer which has progressed despite adequate antiestrogen therapy in the adjuvant or therapeutic setting.

Genevieve A. Schechter 6/20/97

Genevieve A. Schechter, M.D.
Medical Reviewer - DOPD

John R Johnson, MD 6-26-97

John Johnson, M.D.
Team Leader - DOPD

SEP - 6 '96

NDA 20-726: MEDICAL OFFICER FORTY-FIVE DAY REVIEW

NDA: 20-726
DRUG: *Femara*™ (Letrozole)
APPLICANT: Pharmaceuticals Division
Ciba-Geigy Corporation
Summit, NJ 07901
REVIEWER: G. Schechter, M.D.
DATE: September 3, 1996

INTRODUCTION:

NDA 20-726 presents the data to support the use of *Femera*™ (letrozole), an aromatase inhibitor, in "the treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, following antiestrogen therapy".

SUMMARY OF CONTENTS:

I. Overall Description:

NDA 20-726 has been provided as a 131 volume document with Volume 1.1 containing draft labeling, intended uses and benefits, marketing history, and summaries of the chemistry, pharmacology, animal and human pharmacokinetic data, and narrative summaries of individual clinical trials, Volumes 1.071 -1.110 contain AR/BC2 core and update and Volume 1.112 - 1.117 contains the Integrated Safety Summary with individual CRFs in volumes 1.118 - 1.131. A
is available by password on Oracle in a read only mode and on a laptop computer. The
contains the following documents: (1) Proposed Labeling; (2) Trial Protocols for AR/BC2 and AR/BC3; (3) Clinical Trial Reports for AR/BC2 and AR/BC3- letrozole arms ADRs only]; (4) Integrated Summary of Safety [ISS]; (5) Integrated Summary of Efficacy (ISE), and ; (6) NDA Index.

II. Description of Efficacy Studies:

The primary efficacy study is AR/BC2 entitled: "CGS 20267 (non-steroidal oral aromatase inhibitor): Double -blind, randomized, multicenter, comparative, between patient, Phase II trial comparing daily doses of 0.5 mg CGS 20267 versus 2.5 mg CGS 20267 versus 160 gm megestrol acetate as second-line endocrine therapy in patients with advanced breast cancer". Five hundred fifty-two patients were enrolled in this study with 188 on the letrozole 0.5 mg arm, 174 on the letrozole 2.5 mg arm, and 189 on the megestrol acetate arm. Computerized data sets which include all the demographic data, dates for events, and sites of disease, tumor measurements for all patients enrolled in this study are included in the and available in volumes 1.071-1.110. The response and outcome data from this trial will be reviewed with special attention to those patients who had only adjuvant hormonal therapy vs. patients who had

hormonal manipulation for advanced disease +/- adjuvant hormonal therapy. Response will also be evaluated by site(s) of disease and receptor status (known or unknown) as well as disease-free interval after adjuvant treatment. Special attention will be paid to the statistical issues regarding adjusted analyses.

Summary reports for the Phase I efficacy studies are contained in vlume 1.1 and include the following: (1) AR/BC1 ext. (21 patients); (2) AR/PS 1 (14 patients); (3) US01 (23 patients); (4) AR/ES1 (46 patients); (5) AR/ST1 (13 patients); and, (6) NJ0-03 (64 patients). Summary data for these studies is included in Volume 1.001 in the IN. Detailed information for the following clinical studies is included in the following volumes: (1) AR/BC1 ext: vol. 54 - 56; (2) AR/PS1: vol. 57; (3) AR/ST1: vol. 1.57 - 1.61; (4) US01 [Protocol 01]: vol. 62 - 67; (5) NJO-03 [ARI-003] - 1.70. A clinical study report for AR/ES1 could not be located in the NDA and will be requested from the applicant..

III. Description of the Safety Data:

The safety data base is based on data collected on 914 patients treated with letrozole. Six patients were treated at letrozole 5.0 mg/day with three patients treated greater than six months, five hundred thirteen patients were treated at 0.1 - 1.0 mg/day with 94 patients on drug for twelve months or more, while three hundred nifty-five patients were treated with 2.5 mg/day (recommended daily dose in the labeling) with 80 patients on therapy for twelve or more months. Special attention will be given to the safety information from the pivotal trial where two letrozole doses are contrasted with megestrol. Case report forms for serious adverse reactions will be reviewed to determine the relationship to study drug. Attempts will be made to determine if any correlation between sites of disease, drug, and specific adverse events can be made.

III. Brief Description of the Labeling:

Preliminary review indicates that all necessary components of the label are included in the proposed labeling. With regard to the clinical portions of the label the reports of phase II studies can not be verify from information contained in the NDA, the response rate and time to event data will be verified, and the safety information confirmed or corrected. Claims about improved tolerance as compared to megestrol in terms of compliance will be verified or rejected.

ACTION:

The NDA as submitted is filable.

PROBLEM:

In volume 1.1 of the NDA on page 90 of the Clinical Data Summary reference is made (in Table 3: Objective Responses in uncontrolled clinical Trials) to Protocol AR/ES1, an uncontrolled trial in which 46 patients were enrolled. A study report and data for this protocol was not located in

the clinical report sections. Please provide the study report and tabular data for this trial since the clinical study report indicates that efficacy data was collected.

Genevieve A. Schechter, M.D. 9/6/96
Genevieve A. Schechter, M.D.
Medical Reviewer-DOPD

JR Johnson 1-6-96
John Johnson, M.D.
Team Leader - DOPD

Orig.: NDA20726
cc: Div. File / HFD-150
cc. G. Schechter/ HFD-150
cc: G. Williams/ HFD-426
cc .

JUN 20 1997

REVIEW OF SAFETY UPDATE No. 3: NDA 20-726

NDA: 20-726
DOC.: SU (Vol 12.1,12.2)
DOC. DATE: April 14. 1997
DRUG: Letrozole (*Femara™*)
APPLICANT: Novartis
M.O.: G. Schechter, M.D.
DATE: April 25, 1997

SUMMARY: This two volume safety update includes: (1) an updated ISS (Integrated Summary of Safety), (2) correction of grading for hemoglobin, platelet abnormalities, and ionized calcium reported in study AR/BC2; and, (3) revised package insert for *Femara™*.

1. Updated Integrated Summary of Safety:

Updated safety information on AR/BC3 as well as an updated summary of the safety information for all clinical trials is included in this section. Summary data from all trials indicates that the incidence and severity of adverse reactions, whether related to study drug or not, has not changed during this reporting period. No new adverse events were described. The percentage of patients reporting life threatening adverse reactions, whether related to study drug of not, is similar for low dose [0.1 - 1.0 mg] letrozole (2.7%) and for letrozole 2.5 mg (3.8%). For comparison note that on the megestrol arm of AR/BC2, 5.3% of the patients reported life threatening adverse events, while on aminoglutethimide 2.8% of the patients reported life threatening adverse events.

Updated safety information for AR/BC3 showed no significant difference in the incidence of adverse reactions, whether related to study drug or not, for any study arm. The highest severity of adverse events whether reported to study drug or not was higher for severe AEs on both letrozole arms than on the animogluthemide arm while the number of moderate AEs was higher in the aminoglutethimide arm. The "severe" adverse events reported in the letrozole arms were not related to study drug treatment but to intercurrent disease.

When the types of adverse reactions reported on AR/BC3 were reviewed, an increase in adverse events in the Hemic/Lymph and Nervous System categories were noted in the letrozole 0.5 mg as compared to letrozole 2.5 mg. In the Hemic/Lymph System category on the letrozole 0.5 mg arm an increase in the number of anemic patients (anemia related to underlying disease) accounts for the difference in incidence. In the Nervous System category an increased incidence of insomnia, headaches, dizziness, and somnolence were noted on the letrozole 0.5 mg arm. No reported instances of insomnia could be related to study drug. Six of twenty (30%) patients with headache on the letrozole 0.5 mg arm and 11/38 (28.9%) patients with headache on the letrozole 2.5 mg arm claimed that the headaches were drug related. With regard to dizziness 6/9 (67%) of the patients on the letrozole 0.5 mg arm and 2/5 (40%) of the patients on the letrozole 2.5 mg arm were considered related to drug. Somnolence considered to be drug related was reported by 5/6 (83%) patients on the letrozole 0.5 mg arm and in 6/8 (75%) patients on the letrozole 2.5 mg arm.

In a comparison of the adverse events on the letrozole 2.5 mg arm to aminoglutethimide, an increase

incidence of Nervous System and Skin and Appendages adverse events are noted. With regard to headache 5/12 (41.7%) patients on the AG arm and 2/11 (18.2%) on the letrozole 2.5 arm considered the headache drug related. With somnolence 13/16 (81.3%) patients on the AG arm and 6/8 (75%) on the letrozole considered the somnolence drug related. With regard to dizziness 4/6 (66.7%) of patients on the aminoglutethimide arm and 2/5 (40%) on the letrozole 2.5 mg arm were considered drug related. Two of seven (28.6%) of the insomnia cases on the AG arm were related to drug while none on the letrozole arm were considered drug related. With regard to adverse events involving the Skin and Appendages System an increased number of patients reported rash on the aminoglutethimide arm with 19/22 (86.4%) patients claiming the rash was related to drug as compared to 5/7 (71.4%) on the letrozole 2.5 mg arm. On the aminoglutethimide arm three out of the five patients with pruritus considered the pruritus related to drug, while 1/3 on the letrozole 2.5 mg arm was considered drug related. With regard to hot flushes 5/6 (83.3%) patients considered them to be related to aminoglutethimide treatment, while 8/10 (80%) on the letrozole 2.5 mg arm considered the hot flushes to be drug related. The difference in incidence of Skin and Appendage System adverse events is due mainly to increased numbers of patients reporting rash, a well known side effect with aminoglutethimide.

2. Correction of the Laboratory Grading for AR/BC2:

Hemoglobin:

In the the comparison of the Hemoglobin CTC grade at baseline with the final Hemoglobin grade, 134/188 (71.3%) patients on the letrozole 0.5 mg arm, 133/174 (76.4%) patients on the letrozole 2.5 mg arm, and 152/189 (80.4%) patients on the megestrol arm had no change from baseline. Improvement in the Hgb CTC grade was noted for 6/188 (3.2%) patients on the letrozole 0.5 mg arm, for 12/174 (6.9%) patients on the letrozole 2.5 mg arm, and for 5/189 (2.6%) patients on the megestrol arm. A decrease in the CTC Hgb grade $\leq$ one grade was noted for 48/188 (25.5%) of the letrozole 0.5 mg patients, for 29/174 (16.6%) of the letrozole 2.5 mg patients, and for 32/189 (18.1%) of the megestrol treated patients. For the majority of patients no change in hemoglobin was observed with treatment. The worsening grades for the CTC hemoglobin are more likely related to the underlying disease process than to drug effect since the no dose relationship between letrozole doses is noted and the number of grade changes are similar for the letrozole 2.5 mg arm and the megestrol arm.

Platelet Count:

With regard to platelet counts 173/188 (92.0%) patients treated with letrozole 0.5 mg, 156/174 (89.7%) patients treated with letrozole 2.5 mg, and 175/189 (92.6%) of the megestrol treated patients had no change in Platelet Count CTC Grade over the study duration. Improvements were noted in 8/188 (4.2%) of the patients in the letrozole 0.5 mg arm, in 5/174 (2.9%) of patients on the letrozole 2.5 mg arm, and in 11/190 (5.7%) of megestrol treated patients. On the letrozole 0.5 arm one patients had an increase from Grade 0 to Grade 4, but no other grade 3/4 platelet toxicity were reported on any arm. On the letrozole 0.5 mg arm six patients had missing follow-up values. On the letrozole 2.5 mg arm eight patients had a one or two grade decrease from baseline and five patients had no platelet values reported. On the megestrol arm the two patients (1.1%) had a one grade CTC decrease in platelet count and one patient had no information on platelet counts before or during treatment. Decrease in the CTC grade for platelet counts was infrequent and can not be associated with study drug therapy.

Ionized Calcium Values:

Ionized calcium values, which were higher or lower than the normal range using the Ionized Calcium CTC grade at entry onto study, were evaluated for change over the course of study on each treatment. Five patients out of thirteen on the letrozole 0.5 mg arm had worsening of ionized calcium values during study, while seven patients had stabilization of ionized calcium, and one patient's value was improved. Three patients with no pretreatment values had study values of grade II (1 pt.) and grade IV (2 pts.) On the letrozole 2.5 mg arm of eleven patients with high ionized calcium values five had worsening of ionized calcium values and six were stable with treatment. Three patients without pretreatment values were noted to have increased CTC grade: one patient had grade 2 and two patient had grade 4. On the megestrol arm nine of eleven patients had worsening of the CTC ionized calcium grade while two had stabilization. Two patients with no pretreatment values developed grade IV CTC calcium changes.

Ionized calcium values which were below the lower limit of normal at baseline (study initiation) were compared to the highest CTC grade for ionized calcium during study. For thirteen patients who had values measured on the letrozole 0.5 arm no change in grade is noted. For nine patients who had follow-up values on the letrozole 2.5 mg arm no change from baseline was observed. Likewise for eleven patient on the megestrol arm no change was reported. These data indicate letrozole will not normalize low ionized calcium levels. Review of the data in the previous paragraph indicated that high ionized calcium levels on study entry may remain stable or worsen but rarely improve.

3. Revised Package Insert:

An revised package insert has been submitted in this safety update. The labeling review is a separate document.

ACTION:

No action indicated since the review show no new adverse events or increased in the incidence of adverse events for AR/BC3 or for all studies.

Genevieve A Schechter MD

Genevieve A. Schechter, M.D. 4/25/97
Medical Reviewer - DOPD

John R Johnson, MD

John Johnson, M.D.
Team Leader - DOPD 6-20-97

Orig.: NDA ~~20762~~ 20726
cc: wpfiles/letrozo/sfupd3

cc: NDA 20-726
HFD-150/Div Files
/ G Schechter
/ D Spillman

JUN 20 1997

SAFETY UPDATE NO. 2 REVIEW: NDA 20-726

NDA: 20-726
DOC.: SU
DOC. DATE: 1-30-97
DRUG: Letrozole (*Femara™*)
APPLICANT: Ciba-Geigy
M.O.: G. Schechter, M.D.
DATE: April 25, 1997

This submission contained thirty-nine volumes which included the study report, data listings, statistical analyses, and all other information for clinical trial AR/BC3. The contents of this submission were reviewed in the study report for AR/BC3 contained in the NDA. See the Study Report for AR/BC3 for further information.

JR Johnson, MD
6-20-97

cc: NDA 20-726
HFD-150 /Div files
/G. Schechter
/D. Spillman

JUN 20 1997

SAFETY UPDATE REVIEW: NDA20726, LETROZOLE (FEMARA™)

NDA:	20726
DOCUMENT NO.:	SU
CORRES. DATE:	November 27, 1996
DRUG:	Letrozole (Femera™)
APPLICANT:	Ciba-Geigy Corporation Summit, New Jersey 07901
REVIEWER:	G. Schechter, M.D.
DATE:	December 4, 1996

Introduction:

This safety update includes: (1) a Serious Adverse Experience Update which reports new serious adverse events from all ongoing or initiated clinical trials from the period including February 8, 1996 until October 1, 1996; (2) the AR/BC3 Clinical Trial Report which will be submitted separately; and, (3) A General Safety Update.

Clinical trials on which patients are being treated during this period include: (1) AR/BC2, extention; (2) AR/BC3; (3) AR/PK1; (4) NJ-04 ; (5) NJ-05; (6) AR/ET1; (7) Protocol 02; and , (8) Protocol 015. No SAEs have been reported on NJ-05 or Protocol 015. Two additional clinical trials (Protocol 025 and Protocol 026) have been initiated since October 1, 1996.

The following table presents a breakdown of the serious adverse events by letrozole dose only. Information for SAEs for megestrol and aminoglutethimide are reported for interest.

SU-1: Serious Adverse Experiences by Treatment Group

	Letrozole 0.1 - 1.0 mg		Letrozole 2.5 mg		Letrozole 0.5 mg		Megestrol		Aminoglutethimide	
	N	(%)	N	(%)	N	(%)	N	(%)		
No of Patients Treated	557	(100)	435	(100)	13	(100)	189	(100)		
Patients with SAEs	60	(11)	55	(13)	0	(0)	54	(29)	20	(11)
SAERs Cases	65		58		0		60		30	
Discontinued due to SAE	15	(3)	13	(3)	0		19	(10)	5	(3)
Cardiovascular	13	(3)	11	(3)			19	(10)	3	(2)
Digestive	12	(2)	15	(3)			6	(3)	3	(2)
Lab Abnormalities	3	(1)	3	(1)			2	(1)	0	(0)
Hemic/Lymphatic	5	(1)	3	(1)			3	(2)	3	(2)
Metabolic	0	(0)	0	(0)			2	(1)	0	(0)
Infection/Infestation	4	(1)	2	(0.004)			0	(0)	0	(0)

	Letrozole 0.1 - 1.0 mg		Letrozole 2.5 mg		Letrozole 0.5 mg		Megestrol		Aminoglutethimide	
	N	(%)	N	(%)	N	(%)	N	(%)		
Musculo-Skeletal	7	(1)	5	(1)			3	(2)	3	(2)
Nervous System	6	(1)	6	(1)			2	(1)	5	(3)
Respiratory	6	(1)	8	(2)			5	(3)	3	(2)
Special Senses	1	(0)	0	(0)			0	(0)	0	(0)
Surgical Procedure	3	(1)	2	(0.004)			6	(3)	0	(0)
Skin	3	(1)	1	(0)			4	(0)	2	(1)
Endocrine	1	(0)	0	(0)			1	(0.01)	0	(0)
Urogenital	3	(0.5)	2	(0)			8	(4)	2	(1)
Body as a Whole	16	(3)	13	(3)	0		9	(5)	6	(3)

The data from Protocol 002 will not be reviewed as the study is blinded. No information is available as to how many of the SAEs can be contributed to letrozole.

In Trial 944029 one SAE, dyspnea, due to study drug was reported. On Trial 944030 one SAE, angina pectoris, was reported and on trial 940041, one SAE, chest pain, was reported. It is not clear if these serious adverse events reported in the Safety update were ~~not~~ related to study drug or to other disease processes.

In review of the tabular summaries for new and completed trials no new serious adverse events are observed and no appreciable change in the frequency of certain types of adverse events is noted. As is indicated in the table above, the serious adverse events related to study drug did not lead to study discontinuation.

ACTION:

No action is indicated.

Genevieve A Schechter MD 12/4/96
Genevieve A. Schechter, M.D. - Medical Reviewer

John R Johnson, MD
John Johnson, M.D. - Team Leader 6-20-97

20-726
Orig.: NDA ~~20367~~
cc: G. Schechter/HFD-150
HFD-150/DV File
/D. Spillman