CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-539

Generic Name: Tamoxifen Citrate Tablets USP, 10 mg base

Sponsor: Teva Pharmaceuticals USA.

Approval Dates: May 31, 2000

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APPLICATION NUMBER:
74-539

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APPLICATION NUMBER:

74-539

APPROVAL LETTER

ANDA 74-539

MAY 31 2000

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
U.S. Agent for: Pharmachemie B.V.
1510 Delp Drive
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated August 26, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tamoxifen Citrate Tablets USP, 10 mg (base).

Reference is also made to our tentative approval letters dated April 3, 1997, and March 9, 1999, and to your amendments dated April 18, and April 27, 2000.

The listed drug product referenced in your application is subject to a period of patent protection which expires August 20, 2002, (U.S. Patent No. 4,536,516, the "516" patent). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Tamoxifen Citrate Tablets, USP will not infringe on the patent or that the patent is otherwise invalid. You have informed the Agency that Zeneca Pharmaceuticals initiated a patent infringement suit against you in United States District Court for the District of Maryland (Zeneca Limited v. Pharmachemie B.V., Civil Action No. S96-884). You notified the Agency that the litigation was subsequently moved from the District of Maryland to the District of Massachusetts (Civil Action No. 96-12413-RCL), and that the 30-month period provided for under 21 CFR 314.107(b)(3) has expired.

As noted in our tentative approval letter dated March 9, 1999, the agency was precluded from granting final approval to your application because of its response to a Citizens Petition dated March 2, 1999 (Docket No. 98P-0493/PSA1&RC1). In the response, the agency agreed with the petitioner to stay the effective date of approval of any ANDA for this drug product other than the ANDA submitted by Barr Laboratories, Inc., until 180 days after the date of the first commercial marketing of the drug product under Barr's ANDA, or the date of a decision of a court holding the

tamoxifen patent to be invalid or not infringed. However, in a subsequent decision, Mylan Pharmaceuticals, Inc. v. Henney, No. 99-cv-862, slip op. at 33 (D.D.C. March 31, 2000), the court rejected FDA's interpretation of 314.94(a)(12)(viii) as described in its March 2, 1999 response. The court remanded the issue to the Agency to reinterpret the effect of the regulation on Barr's change from a paragraph IV to a paragraph III certification to U.S. Patent No. 4,536,516. The Agency has determined that Barr's change in certification makes it ineligible for 180-day exclusivity under Section 505(j)(5)(B)(iv) of the Federal Food Drug and Cosmetic Act. Barr's was the first substantially complete ANDA for Tamoxifen Citrate Tablets containing a paragraph IV certification. Please note that because Barr is no longer eligible for 180-day exclusivity, FDA will give final approval to any ANDA for Tamoxifen Citrate Tablets that is otherwise eligible for final approval.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tamoxifen Citrate Tablets USP, 10 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Nolvadex Tablets®, 10 mg (base) of Astrazeneca Pharmaceuticals, L.P.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 5/31/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

TENTATIVE APPROVAL LETTER

ANDA 74-539

APR 3 1997

Pharmachemie USA, Inc.
Attention: Hellen de Kloet
U.S. Agent for Pharmachemie B.V
323 Davis Street
Northborough, Massachusetts 01532

Dear Madam:

This is in reference to your abbreviated new drug application dated August 26, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tamoxifen Citrate Tablets USP, 10 mg (base).

Reference is also made to your amendments dated September 10, October 23, November 1 and 13, and December 30, 1996, and February 19, March 21, and April 2, 1997.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on August 20, 2002 [Patent No. 4,536,516 (the '516 patent)]. However, litigation is underway in the United States District Court for the District of Maryland, involving a challenge to the patent (Zeneca Limited V. Pharmachemie BV, Civil Action No. S96-884). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(I), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

b. the date of court decision [505(j)(4)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under Section 501 of

the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Sheila M. O'Keefe, Consumer Safety Officer, at (301) 594-0370, for further instructions.

Sincerely yours,

/S/

4/3/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

Final Printed Labeling

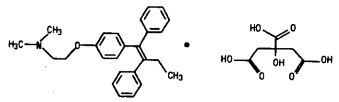
TAMOXIFEN CITRATE TABLETS USP, 10 m

DESCRIPTION

Tamoxifen Citrate Tablets USP, a nonsteroidal antiestrogen, are for oral administration. Each tablet contains 15.2 mg of tamoxifen citrate (equivalent to 10 mg of tamoxifen).

In addition, each tablet contains as inactive ingredients: colloidal silicon dioxide; lactose, monohydrate; magnesium stearate; microcrystalline cellulose; potato starch; povidone.

Chemically, tamoxifen citrate is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)-2-[*p*-(1,2-Diphenyl-1-butenyl) phenoxy]-*N*, *N*-dimethylethylamine citrate (1:1). The structural and molecular formulas are:



$C_{32}H_{37}NO_8$

Tamoxifen citrate has a molecular weight of 563.62, the pKa of 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C it is 0.2 mg/mL.

CLINICAL PHARMACOLOGY

Tamoxifen is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.

In cytosols derived from human breast adenoc nomas, tamoxifen competes with estradiol for e gen receptor protein.

Tamoxifen is extensively metabolized after administration. Studies in women receiving 20 of ^{14}C tamoxifen have shown that approxim 65% of the administered dose is excreted from body over a period of 2 weeks with fecal excre the primary route of elimination. The drug is excr mainly as polar conjugates, with unchanged and unconjugated metabolites accounting for than 30% of the total fecal radioactivity.

N-desmethyl tamoxifen is the major metab found in patients' plasma. The biological activity N-desmethyl tamoxifen appears to be similar to of tamoxifen. 4-Hydroxytamoxifen and a side c primary alcohol derivative of tamoxifen have b identified as minor metabolites in plasma.

Following a single oral dose of 20 mg tamoxifen average peak plasma concentration of 40 ng/ (range 35 to 45 ng/mL) occurred approximate hours after dosing. The decline in plasma conc trations of tamoxifen is biphasic with a term elimination half-life of about 5 to 7 days. The av age peak plasma concentration of N-desmet tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chro administration of 10 mg tamoxifen given twice d for 3 months to patients results in average stea state plasma concentrations of 120 ng/mL (ran 67-183 ng/mL) for tamoxifen and 336 ng/mL (ran 148-654 ng/mL) for N-desmethyl tamoxifen. T average steady-state plasma concentrations tamoxifen and N-desmethyl tamoxifen after admi istration of 20 mg tamoxifen once daily for thr months are 122 ng/mL (range 71-183 ng/mL) a 353 ng/mL (range 152-706 ng/mL), respective

TEVA

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Duration of Therapy —In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy.

In the NSABP B-14 trial, in which patients were randomized to tamoxifen 20 mg/day for 5 years versus placebo and were disease-free at the end of this 5-year period were offered rerandomization to an additional five years of tamoxifen or placebo. With four years of follow-up after this rerandomization, 92% of the women that received 5 years of tamoxifen were alive and disease-free, compared to 86% of the women scheduled to receive 10 years of tamoxifen (p=0.003). Overall survivals were 96% and 94%, respectively (p=0.08). Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit.

A Scottish trial of five years of tamoxifen versus indefinite treatment found a disease-free survival of 70% in the five-year group and 61% in the indefinite group, with 6.2 years median follow-up (HR=1.27, 95% CI 0.87-1.85).

In a large randomized trial conducted by the Swedish Breast Cancer Cooperative Group of adjuvant tamoxifen 40 mg/day for 2 or 5 years, overall survival at ten years was estimated to be 80% in the patients in the five-year tamoxifen group, compared with 74% among corresponding patients in the two-year treatment group (p=0.03). Disease-free survival at ten years was 73% in the five-year group and 67% in the two-year group (p=0.009). Compared with two years of tamoxifen treatment, five years of treatment resulted in a slightly greater reduction in the incidence of contralateral breast cancer at ten years, but this difference was not statistically significant.

Contralateral Breast Cancer —The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving tamoxifen compared to placebo. Data on contralateral breast cancer are available from 32,422 out of 36,689 patients in the 1995 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). In clinical trials with tamoxifen of 1 year or less, 2 years, and about 5 years duration, the proportional reductions in the incidence rate of contralateral breast cancer among women receiving tamoxifen were 13% (NS), 26% (2p = 0.004) and 47% (2p < 0.00001), with a significant trend favoring longer tamoxifen duration (2p = 0.008). The proportional reduction in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor. Treatment with about 5 years of tamoxifen reduced the annual incidence rate of contralateral breast cancer from 7.6 per 1000 patients in the control group compared with 3.9 per 1000 patients in the tamoxifen group.

In a large randomized trial in Sweden (the Stockholm Trial) of adjuvant tamoxifen 40 mg/ day for 2-5 years, the incidence of second primary breast tumors was reduced 40% (p < 0.008) on tamoxifen compared to control. In the NSABP B-14 trial in which patients were randomized to tamoxifen 20 mg/day for 5 years versus placebo, the incidence of second primary breast cancers was also significantly reduced (p < 0.01). In NSABP B-14, the annual rate of contralateral breast cancer was 8.0 per 1,000 patients in the placebo group compared with 5.0 per 1,000 patients in the tamoxifen group, at 10 years after first randomization.

INDICATIONS AND USAGE

Metastatic Breast Cancer: Tamoxifen is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen therapy.

Adjuvant Treatment of Breast Cancer: Tamoxifen is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some tamoxifen adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

Tamoxifen is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. Data are insufficient to predict which women are most likely to benefit and to determine if tamoxifen provides any benefit in women with tumors less than 1 cm.

Tamoxifen reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen therapy for breast cancer.

Current data from clinical trials support five years of adjuvant tamoxifen therapy for patients with breast cancer.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen therapy is likely to be beneficial.

CONTRAINDICATIONS

Tamoxifen is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Effects in Metastatic Breast Cancer Patients: As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported some breast cancer patients with bone metastas within a few weeks of starting treatment with tamo ifen. If hypercalcemia does occur, appropriate mea ures should be taken and, if severe, tamoxife should be discontinued.

Effects on the Uterus-Endometrial Cancer: As wit other additive hormonal therapy (estrogens), a increased incidence of endometrial cancer has bee reported in association with tamoxifen treatment The underlying mechanism is unknown, but may b related to the estrogen-like effect of tamoxifen. An patients receiving or having previously receive tamoxifen, who report abnormal vaginal bleedin should be promptly evaluated. Patients receiving o having previously received tamoxifen should hav routine gynecological care and they should prompt ly inform their physician if they experience an abnormal gynecological symptoms, e.g., menstrua irregularities, abnormal vaginal bleeding, changes i vaginal discharge, or pelvic pain or pressure.

In a large randomized trial in Sweden of adjuvant tamoxifen 40 mg/day for 2-5 years, an increased incidence of uterine cancer was noted. Twenty three of 1,372 patients randomized to receive tamoxifen versus 4 of 1,357 patients randomized to the observation group developed cancer of the uterus [RR = 5.6 (1.9-16.2), p<.001]. One of the patients with cancer of the uterus who was randomized to receive tamoxifen never took the drug. After approximately 6.8 years of follow-up in the NSABP B-14 trial, 15 of 1,419 women randomized to receive tamoxifen 20 mg/day for 5 years developed uterine cancer and 2 of the 1,424 women randomized to receive placebo, who subsequently were treated with tamoxifen, also developed uterine cancer. Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine

After initiation of therapy, steady state concentrations for tamoxifen are achieved in about 4 weeks and steady state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite.

In a 3-month crossover steady-state bioavailability study with tamoxifen citrate tablets, 10 mg twice a day versus tamoxifen citrate tablets, 20 mg given once daily, tamoxifen citrate tablets, 20 mg taken once daily had similar bioavailability to tamoxifen citrate tablets, 10 mg taken twice a day.

Clinical Studies—Metastatic Breast Cancer

Premenopausal Women (Tamoxifen Citrate Tablets vs. Ablation) —Three prospective, randomized studies (Ingle, Pritchard, Buchanan) compared tamoxifen citrate tablets to ovarian ablation (oophorectomy or ovarian irradiation) in premenopausal women with advanced breast cancer. Although the objective response rate, time to treatment failure, and survival were similar with both treatments, the limited patient accrual prevented a demonstration of equivalence. In an overview analysis of survival data from the three studies, the hazard ratio for death (tamoxifen/ovarian ablation) was 1.00 with two-sided 95% confidence intervals of 0.73 to 1.37. Elevated serum and plasma estrogens have been observed in premenopausal women receiving tamoxifen, but the data from the randomized studies do not suggest an adverse effect of this increase. A limited number of premenopausal patients with disease progression during tamoxifen therapy responded to subsequent ovarian ablation.

Male Breast Cancer —Published results from 122 patients (119 evaluable) and case reports in 16 patients (13 evaluable) treated with tamoxifen have shown that tamoxifen is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to tamoxifen which constitutes a 50% objective response rate.

Clinical Studies—Adjuvant Breast Cancer

Overview —The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, and again in 1995. In 1998, 10-year outcome data were reported for 36,689 women in 55 randomized trials of adjuvant tamoxifen using doses of 20-40 mg/day for 1-5+ years. Twenty-five percent of patients received one year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER) positive (>10 fmol/mg), 21% were ER poor (<10 fmol/l), and 31% were ER unknown. Among 29,441 patients with ER positive or unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node positive disease and 46% had node negative disease.

Among women with ER positive or unknown breast cancer and positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (logrank $2p < 0.00001$). At ten years, the recurrence rate was 59.7% for tamoxifen vs. 44.5% for control (logrank $2p < 0.00001$). Among women with ER positive or unknown breast cancer and negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (logrank $2p < 0.00001$). At ten years, the recurrence rate was 79.2% for tamoxifen versus 64.3% for control (logrank $2p < 0.00001$).

The effect of the scheduled duration of tamoxifen may be described as follows. In women with ER positive or unknown breast cancer receiving 1 year or less, 2 years or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at $2p < 0.003$). The corresponding reductions in breast cancer recurrence were 21%, 29% and 47% (trend significant at $2p < 0.00001$).

Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% ($2p = 0.007$) for all durations taken together, or 9% ($2p = 0.02$) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (NS). The effects of about 5 years of tamoxifen on recurrence and mortality were similar regardless of age and concurrent chemotherapy. There was no indication that doses greater than 20 mg per day were more effective.

Node Positive—Individual Studies —Two studies (Hubay and NSABP B-09) demonstrated an improved disease-free survival following radical or modified radical mastectomy in postmenopausal women or women 50 years of age or older with surgically curable breast cancer with positive axillary nodes when tamoxifen was added to adjuvant cytotoxic chemotherapy. In the Hubay study, tamoxifen was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, tamoxifen was added to melphalan [L-phenylalanine mustard (P)] and fluorouracil (F).

In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50-59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonstatistically significant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60-70 years, there was a trend toward a beneficial effect of tamoxifen without any clear relationship to estrogen or progesterone receptor status.

Three prospective studies (ECOG-1178, Toronto, NATO) using tamoxifen adjuvantly as a single agent demonstrated an improved disease-free survival following total mastectomy and axillary dissection for postmenopausal women with positive axillary nodes compared to placebo/no treatment controls. The NATO study also demonstrated an overall survival benefit.

Node Negative—Individual Studies —NSABP B-14, a prospective, double-blind, randomized study, compared tamoxifen to placebo in women with axillary node-negative, estrogen-receptor positive (≥ 10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

One additional randomized study (NATO) demonstrated improved disease-free survival for tamoxifen compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of tamoxifen appeared to be independent of estrogen receptor status.

surgery, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540 tamoxifen; 483 placebo; RR=1.13, 95% CI 1.00-1.28) was observed. Among these same women, tamoxifen was associated with an increased risk of having cataract surgery (101 tamoxifen; 63 placebo; RR=1.62, 95% CI 1.17-2.25). (See Table 2 in **CLINICAL PHARMACOLOGY**). Among all women on the trial (with or without cataracts at baseline), tamoxifen was associated with an increased risk of having cataract surgery (201 tamoxifen; 129 placebo; RR=1.51, 95% CI 1.21-1.89). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

Pregnancy Category D: Tamoxifen may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen and should use barrier or nonhormonal contraceptive measures if sexually active. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups when compared to historical controls. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.3 to 2.4-fold the human maximum recommended dose on a mg/m^2 basis) caused changes in both sexes that are similar to those caused by estradiol, ethynylestradiol and diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol in utero and who have a 1 in 1,000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, in utero exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen in utero, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long term risk of a DES-like syndrome.

PRECAUTIONS

General: Decreases in platelet counts, usually to 50,000-100,000/mm^3 , infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe.

Information for Patients:

Monitoring During Tamoxifen Therapy: Women taking or having previously taken tamoxifen should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take tamoxifen.

Women taking tamoxifen as adjuvant breast cancer therapy should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking tamoxifen as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

Laboratory Tests: Periodic complete blood counts, including platelet counts, and periodic liver function tests should be obtained.

Drug Interactions: When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen.

Tamoxifen, N-desmethyl tamoxifen and 4-hydroxytamoxifen have been found to be potent inhibitors of hepatic cytochrome p-450 mixed function oxidases. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known.

One patient receiving tamoxifen with concomitant phenobarbital exhibited a steady state serum level of tamoxifen lower than that observed for other patients (i.e., 26 ng/mL vs. mean value of 122 ng/mL). However, the clinical significance of this finding is not known.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

Drug/Laboratory Testing Interactions: During postmarketing surveillance, T_4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given tamoxifen.

In the postmarketing experience with tamoxifen, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with preexisting hyperlipidemias.

of approximately 6.8 years) showing adverse events more common on tamoxifen than on placebo. The incidence of hot flashes (64% vs. 48%), vaginal discharge (30% vs. 15%), and irregular menses (25% vs. 19%) were higher with tamoxifen compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events, a higher incidence was seen in tamoxifen-treated patients (through 5 years, 1.7% vs. 0.4%). Two of the patients treated with tamoxifen who had thrombotic events died.

NSABP B-14 Study

	% of Women	
Adverse Effect	TAMOXIFEN (n=1422)	PLACEBO (n=1437)
Hot Flashes	64	48
Fluid Retention	32	30
Vaginal Discharge	30	15
Nausea	26	24
Irregular Menses	25	19
Weight Loss (>5%)	23	18
Skin Changes	19	15
Increased SGOT	5	3
Increased Bilirubin	2	1
Increased Creatinine	2	1
Thrombocytopenia*	2	1
Thrombotic Events		
Deep Vein Thrombosis	0.8	0.2
Pulmonary Embolism	0.8	0.2
Superficial Phlebitis	0.4	0.0

* Defined as a platelet count of <100,000/mm^3

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, tamoxifen or placebo was administered for 2 years to women following mastectomy. When compared to placebo, tamoxifen showed a significantly higher incidence of hot flashes (19% versus 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for tamoxifen was 10% versus 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and Tamoxifen Adjuvant Trial Organization (NATO), women received either tamoxifen or no therapy. In the Toronto study, hot flashes were observed in 29% of patients, for tamoxifen versus 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8%, and 2.0% of women, respectively, for tamoxifen versus 0.2% for each in the untreated group.

Postmarketing experience: Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome and bullous pemphigoid have been reported with tamoxifen therapy.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of tamoxifen in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3-5 days of beginning tamoxifen and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after tamoxifen was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to tamoxifen therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of tamoxifen given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of tamoxifen given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg tamoxifen tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10 mg tamoxifen tablet was given twice a day for at least five years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see **CLINICAL PHARMACOLOGY**). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg per day were more effective. Current data from clinical trials support five years of adjuvant tamoxifen therapy for patients with breast cancer.

HOW SUPPLIED

Tamoxifen Citrate Tablets (equivalent to 10 mg of tamoxifen) are round, biconvex, uncoated, white tablets identified with TAM 10 debossed on one side and PCH debossed on the other side and are supplied in bottles of 60s and 250s. The tablets are unscored.

Store at controlled room temperature 15° to 30° C (59° to 86°F). Protect from light.

MANUFACTURED BY
PHARMACHEMIE BV
Haarlem, The Netherlands
DATE
May 2000

cancer have been reported.

In the NSABP P-1 trial, among participants randomized to tamoxifen there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo (RR 2.48, 95% CI 1.27-4.92). This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo (RR 4.50, 95% CI 1.78-13.16). Among women ≤ 49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR 0.94, 95% CI 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants ≤ 49 randomized to tamoxifen compared to 2 among participants randomized to placebo (RR 2.21, 95% CI 0.4-12.0). For women ≥ 50 at the time of diagnosis, there were 29 cases among participants randomized to tamoxifen compared to 12 among women on placebo (RR 2.5, 95% CI 1.3-4.9). The risk ratios were similar in the two groups, although fewer events occurred in younger women. Most (29 of 33 cases in the tamoxifen group) endometrial cancers were diagnosed in symptomatic women; although 5 of 33 cases in the tamoxifen group occurred in asymptomatic women. Among women receiving tamoxifen the events appeared between 1 and 61 months (average=32 months) from the start of treatment.

Among participants receiving tamoxifen, there were 33 cases of FIGO stage I [20 IA, 12 IB, and 1 IC] endometrial cancer. Among participants receiving placebo, there were 13 FIGO stage I cases [8 IA and 5 IB]. There was a single FIGO Stage IV endometrial cancer in a participant receiving placebo. (See Table 2 in **CLINICAL PHARMACOLOGY**). The distribution of FIGO stage was similar between participants receiving tamoxifen and placebo. Five women receiving tamoxifen and 1 receiving placebo with FIGO Stage IB disease received postoperative radiation therapy in addition to surgery.

Endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus.

Non-Malignant Effects on the Uterus: An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of tamoxifen.

There have been a few reports of endometriosis and uterine fibroids in women receiving tamoxifen. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen.

Thromboembolic Effects of Tamoxifen: For treatment of breast cancer, the risks and benefits of tamoxifen should be carefully considered in women with a history of thromboembolic events.

Data from the P-1 trial show that participants receiving tamoxifen without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-tamoxifen, 6-placebo, RR=3.01, 95% CI: 1.15-9.27). Three of the pulmonary emboli, all in the tamoxifen arm, were fatal. Eighty-seven percent of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving tamoxifen, the events appeared between 2 and 60 months (average=27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the tamoxifen group (30-tamoxifen, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women ≤ 49 and in women ≥ 50, although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on tamoxifen) and were at risk for complication of the event and its treatment (0/25 on placebo, 4/48 on tamoxifen). Among women receiving tamoxifen, deep vein thrombosis events occurred between 2 and 57 months (average=19 months) from the start of treatment.

There was a non-statistically significant increase in stroke among patients randomized to tamoxifen (24-placebo; 34-tamoxifen; RR 1.42; 95% CI 0.82-2.51). Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen group were categorized as hemorrhagic. Seventeen of the 34 strokes in the tamoxifen group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes 3 strokes in the placebo group and 4 strokes in the tamoxifen group were fatal. Eighty-eight percent of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving tamoxifen, the events occurred between 1 and 63 months (average=30 months) from the start of treatment.

Effects on the liver: Liver cancer: In the Swedish trial using adjuvant tamoxifen 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the tamoxifen-treated group versus 1 case in the observation group (See **PRECAUTIONS – Carcinogenesis**). In other clinical trials evaluating tamoxifen, no cases of liver cancer have been reported to date.

No cases of liver cancer were reported in NSABP P-1 with a median follow-up of 4.2 years.

Effects on the liver: Non-malignant effects: Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to tamoxifen is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on tamoxifen). Serum lipids were not systematically collected.

Other cancers: A number of second primary tumors, occurring at sites other than the endometrium, have been reported following the treatment of breast cancer with tamoxifen in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving tamoxifen. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated.

Effects on the Eye: Ocular disturbances, including corneal changes, cataracts, the need for cataract

Carcinogenesis: A conventional carcinogenesis study in rats (doses of 5, 20, and 35 mg/kg/day for up to 2 years) revealed hepatocellular carcinoma at all doses, and the incidence of these tumors was significantly greater among rats given 20 or 35 mg/kg/day (69%) than those given 5 mg/kg/day (14%). The incidence of these tumors in rats given 5 mg/kg/day (29.5 mg/m^2) was significantly greater than in controls.

In addition, preliminary data from 2 independent reports of 6-month studies in rats reveal liver tumors which in one study are classified as malignant (See **WARNINGS**).

Endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving tamoxifen, but not in the controls.

Mutagenesis: Although no genotoxic potential was found in a conventional battery of *in vivo* and *in vitro* tests with pro- and eukaryotic test systems with drug metabolizing systems present, increased levels of DNA adducts have been found in the livers of rats exposed to tamoxifen. Tamoxifen also has been found to increase levels of micronucleus formation *in vitro* in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for two weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was obtained by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See **WARNINGS**.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tamoxifen, 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.

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

ADVERSE REACTIONS

Adverse reactions to tamoxifen are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with tamoxifen as compared to placebo.

Metastatic Breast Cancer: Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting tamoxifen and generally subside rapidly.

In patients treated with tamoxifen for metastatic breast cancer, the most frequent adverse reaction to tamoxifen is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, lightheadedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

Premenopausal Women: The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared tamoxifen therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

Adverse Reactions*	TAMOXIFEN All Effects % of Women n=104	OVARIAN ABLATION All Effects % of Women n=100
Flush	33	46
Amenorrhea	16	69
Altered Menses	13	5
Oligomenorrhea	9	1
Bone Pain	6	6
Menstrual Disorder	6	4
Nausea	5	4
Cough/Coughing	4	1
Edema	4	1
Fatigue	4	1
Musculoskeletal Pain	3	0
Pain	3	4
Ovarian Cyst(s)	3	2
Depression	2	2
Abdominal Cramps	1	2
Anorexia	1	2

* Some women had more than one adverse reaction.

Male Breast Cancer: Tamoxifen is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

Adjuvant Breast Cancer: In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of tamoxifen 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up

Dispense in well-closed,
light-resistant container.

Rx only

250 Tablets

TAMOXIFEN CITRATE TABLETS, USP

Equivalent to 10 mg tamoxifen

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM HOLLAND

Usual dosage:
See package insert.

Keep out of the reach of children.

Batch no.:

Exp. date:

Store at controlled room temperature
15 - 30°C (59 - 86°F).
Protect from light.

Dispense in well-closed,
light-resistant container.

Rx only

60 Tablets

TAMOXIFEN CITRATE TABLETS, USP
Equivalent to 10 mg tamoxifen

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM HOLLAND

Keep out of the reach of children.

Batch no.:

Exp. date:

Store at controlled
room temperature
15 - 30°C (59 - 86°F).
Protect from light.

Dispense in well-closed,
light-resistant container.

Rx only

250 Tablets

TAMOXIFEN CITRATE TABLETS, USP

Equivalent to 10 mg tamoxifen

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM HOLLAND

Usual dosage:
See package insert.

Keep out of the reach of children.

Batch no.:

Exp. date:

60 Tablets

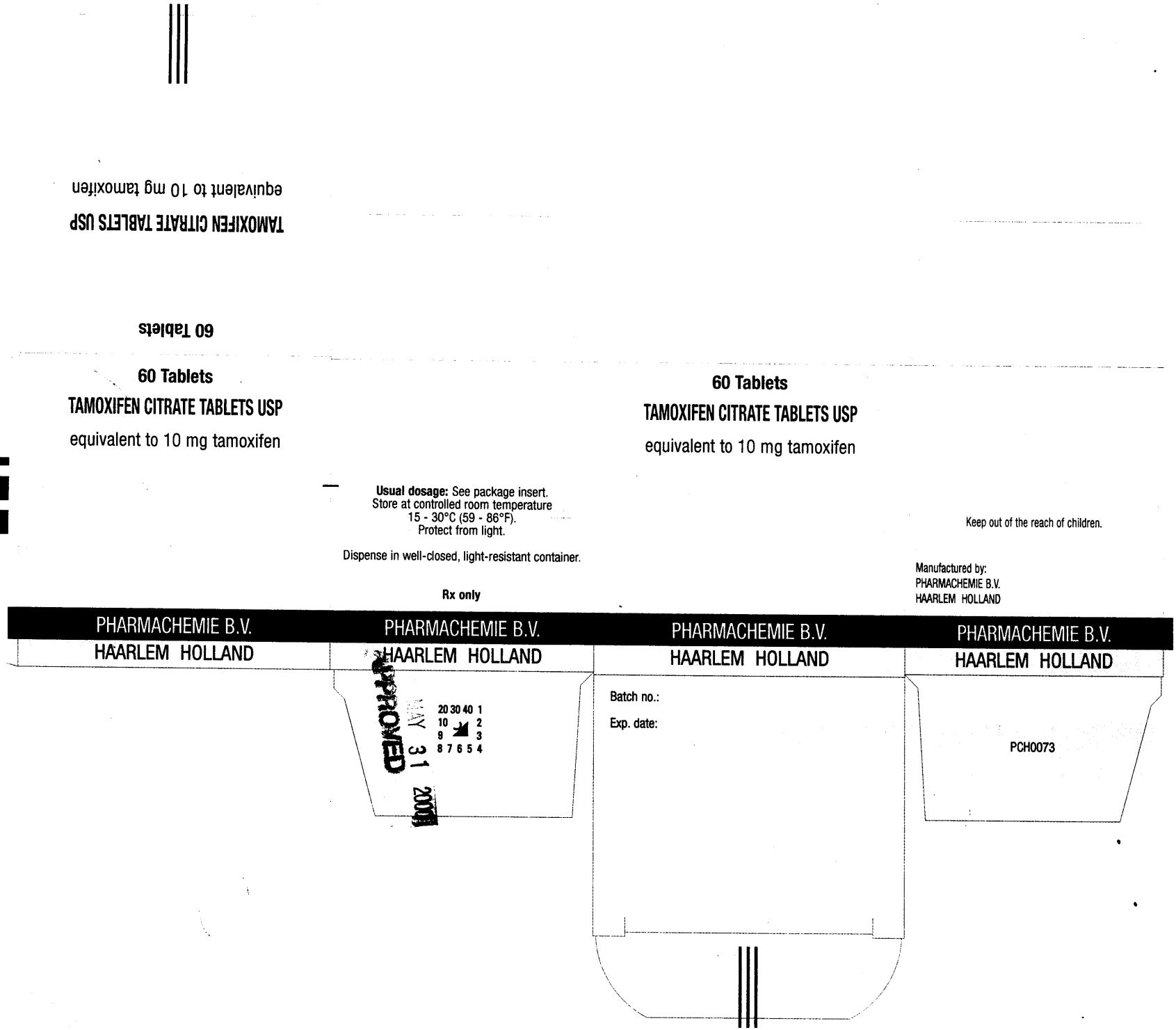
TAMOXIFEN CITRATE TABLETS, USP
Equivalent to 10 mg tamoxifen

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM HOLLAND

Keep out of the reach of children.

Batch no.:

Exp. date:


60 Tablets
TAMOXIFEN CITRATE TABLETS USP
equivalent to 10 mg tamoxifen
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15 - 30°C (59 - 86°F).
Protect from light.
Dispense in well-closed, light-resistant container.
Rx only
Keep out of the reach of children.
Manufactured by:
PHARMACHEMIE B.V.
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Exp. date:
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APPROVED MAY 31 2007

TAMOXIFEN CITRATE TABLETS USP
equivalent to 10 mg tamoxifen

250 Tablets

250 Tablets

TAMOXIFEN CITRATE TABLETS USP

equivalent to 10 mg tamoxifen

250 Tablets

TAMOXIFEN CITRATE TABLETS USP

equivalent to 10 mg tamoxifen

Usual dosage: See package insert.
Store at controlled room temperature
15 - 30°C (59 - 86°F).
Protect from light.

Dispense in well-closed, light-resistant container.

Rx Only

Keep out of the reach of children.

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM HOLLAND

PHARMACHEMIE B.V.
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HAARLEM HOLLAND

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HAARLEM HOLLAND

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Batch no.:
Exp. date:

PCH0075

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

CHEMISTRY REVIEW(S)

Div

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: No. 1

2. **ANDA**: 74-539

3. **NAME AND ADDRESS OF APPLICANT**:
Pharmachemie USA, Inc.
Attn: J. David Hayden
U.S. Agent for Pharmachemie B.V.
P.O. Box 145
Oradell, NJ 07649

4. **LEGAL BASIS FOR ANDA SUBMISSION**:
The firm has stated with regard to the patent Certification and Exclusivity Status that:

"After approval of our ANDA for Tamoxifen Citrate Tablets USP, PHARMACHEMIE B.V. will not market this product in the United States until the date on which Zeneca's patent will expire.

According to the 14th edition of the 'Approved Drug Products', Zeneca is entitled to marketing exclusivity until August 20, 2002."

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**:
Tamoxifen Citrate Tablets USP, 10 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
Firm:

08/26/94	ANDA submission (received on 08/30/94)
10/14/94	ANDA Update response to the 9/22/94 RTF letter.
12/5/94	ANDA Update response to the 11/10/94 RTF letter.
12/28/94	Revised Certification Statement.

FDA:

09/22/94	Refuse to File letter
11/10/94	Refuse to File Letter #2
1/11/95	Acknowledge of submission

10. **PHARMACOLOGIC CATEGORY**: Tamoxifen is effective in delaying recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection and breast irradiation in women with axillary node-negative

breast cancer. Tamoxifen is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer. Tamoxifen is effective in the treatment of metastatic breast cancer in women.

11. **HOW DISPENSED:** Rx

12. **RELATED INDs, NDAs and DMFs:**
Name of Listed Drug: Nolvadex®

Holder of NDA: Zeneca (NDA 17-970)

DMF listed in FDA 356h:
DMF — (Pharmachemie B.V.)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Tablets/oral administration

14. **STRENGTH:**
10 mg

15. **CHEMICAL STRUCTURE AND NAME:**
Refer to insert labeling. As per current USP.

16. **RECORDS AND REPORTS:**
N/A

17. **COMMENTS:**

18. **CONCLUSIONS/RECOMMENDATIONS:**
Not approvable (MAJOR AMENDMENT).

19. **REVIEWER:**
Kenneth J. Furnkranz

DATE COMPLETED/REVISED:
5/26/95

cc: ANDA #74-539
DUP Jacket
ANDA #74-539/Division File
Field Copy

Endorsements:

HFD-625/K.Furnkranz/5-26-95
HFD-625/M.Smela/5-26-95
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F/T by MM 5-30-95
Not Approvable - Major

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: No. 2

2. **ANDA**: 74-539

3. **NAME AND ADDRESS OF APPLICANT**:
Pharmachemie USA, Inc.
Attn: J. David Hayden
U.S. Agent for Pharmachemie B.V.
P.O. Box 145
Oradell, NJ 07649

4. **LEGAL BASIS FOR ANDA SUBMISSION**: The firm has revised their patent Certification and Exclusivity Statement:

   A. They deleted the prior certification dated 7/5/95 indicating that they will not market until after expiration of the patent, and
   B. They have certified that U.S. Patent #4,536,516 owned by Zeneca Limited is invalid or uninforceable.

   Pharmachemie has indicated that, according to the Orange Book, the reference listed drug is not entitled to a period of exclusivity under 505(j)(4)(D) of the Act.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**:
Tamoxifen Citrate Tablets USP, 10 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:

Firm:

08/26/94	ANDA submission (received on 08/30/94)
10/14/94	ANDA Update response to the 9/22/94 RTF letter.
12/5/94	ANDA Update response to the 11/10/94 RTF letter.
12/28/94	Revised Certification Statement.
12/6/95	O/NC - Bioavailability information
*1/26/96	ANDA Amendment. Response to N/A letter #1
*2/12/96	O/NC - Revised Patent Certification; Patent is invalid
*5/13/96	O/NC - Revised Patent Certification information.

FDA:

09/22/94	Refuse to File letter
11/10/94	Refuse to File Letter #2
1/11/95	Acknowledge of submission
6/6/95	N/A #1; Chem./Label deficiencies; MAJOR Amend.

10. **PHARMACOLOGIC CATEGORY**: Tamoxifen is effective in delaying

recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection and breast irradiation in women with axillary node-negative breast cancer and in postmenopausal women with breast cancer. Tamoxifen is effective in the treatment of metastatic breast cancer in women.

11. **HOW DISPENSED**: Rx

12. **RELATED INDs, NDAs and DMFs**:
Name of Listed Drug: Nolvadex®
Holder of NDA: Zeneca (NDA 17-970)

DMF listed in FDA 356h:
DMF [redacted] (Pharmachemie B.V.)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**:
Tablets/oral administration

14. **STRENGTH**:
10 mg

15. **CHEMICAL STRUCTURE AND NAME**: See insert. As per USP.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

[redacted]

18. **CONCLUSIONS/RECOMMENDATIONS**:
Not approvable (MINOR AMENDMENT).

19. **REVIEWER**:
Kenneth J. Furnkranz

DATE COMPLETED/REVISED:
5/28/96

cc: ANDA #74-539
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Field Copy

Endorsements:
HFD-625/K.Furnkranz/5-29-96
HFD-625/M.Smela/5-31-96
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F/T by: bc/6-11-96
Not Approvable - MINOR

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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: 3

2. **ANDA**: 74-539

3. **NAME AND ADDRESS OF APPLICANT**:
Pharmachemie USA, Inc.
Attn: J. David Hayden
U.S. Agent for Pharmachemie B.V.
P.O. Box 145
Oradell, NJ 07649

4. **LEGAL BASIS FOR ANDA SUBMISSION**: **Refer to the Chemistry Review #2.** Pharmachemie has revised their patent certification and exclusivity statement in this amendment to correct an error in the date for the prior Paragraph III Certification. The correct date is October 10, 1994.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**:
Tamoxifen Citrate Tablets USP, 10 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:

Firm:

08/26/94	ANDA submission (received on 08/30/94)
10/14/94	ANDA Update response to the 9/22/94 RTF letter.
12/5/94	ANDA Update response to the 11/10/94 RTF letter.
12/28/94	Revised Certification Statement.
12/6/95	O/NC - Bioavailability information
1/26/96	ANDA Amendment. Response to N/A letter #1
2/12/96	O/NC - Revised Patent Certification; Patent is invalid
5/13/96	O/NC - Revised Patent Certification information.
*9/10/96	ANDA Amendment. Response to N/A letter #2
*11/1/96	Bio Data
*10/23/96	ANDA Amendment. Response to Telephone Amendment Request.
*11/13/96	ANDA Amendment. Response to Telephone Amendment Request.

FDA:

09/22/94	Refuse to File letter
11/10/94	Refuse to File Letter #2
1/11/95	Acknowledge of submission
6/6/95	N/A #1; Chem./Label deficiencies; MAJOR Amend.
6/18/96	N/A #2; Chem/Labeling deficiencies; MINOR AMEND.
9/13/96	N/A Letter; Additional labeling changes resulting

from changes in the labeling of the listed drug: Nolvadex; Zeneca Pharmaceuticals.

*9/25/96 Labeling review.

10. **PHARMACOLOGIC CATEGORY:** See previous review.

11. **HOW DISPENSED:** Rx

12. **RELATED INDs, NDAs and DMFs:**
Name of Listed Drug: Nolvadex®
Holder of NDA: Zeneca (NDA 17-970)

DMF listed in FDA 356h:
DMF (Pharmachemie B.V.)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Tablets/oral administration

14. **STRENGTH:**
10 mg

15. **CHEMICAL STRUCTURE AND NAME:** See insert. As per USP.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

[redacted]

18. **CONCLUSIONS/RECOMMENDATIONS:**
Chemistry Closed. Awaiting Bio and Labeling resolution.

19. **REVIEWER:**
Kenneth J. Furnkranz

DATE COMPLETED/REVISED:
19-Nov-1996

cc: ANDA #74-539
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-625/K.Furnkranz/11-19-96
HFD-625/M.Smela
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Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: 4

2. **ANDA**: 74-539

3. **NAME AND ADDRESS OF APPLICANT**:
Pharmachemie USA, Inc.
Attn: Ms. Hellen de Kloet, V.P.
U.S. Agent for Pharmachemie B.V.
323 Davis Street
Northborough, MA 01532

4. **LEGAL BASIS FOR ANDA SUBMISSION**: **Refer to the Chemistry Review #2.** Pharmachemie has certified that the relevant patent (#4,536,516) was invalid and unenforceable and the patent holder brought suit for patent infringement within 45 days of receipt of the notice, and, according to 21 CFR 314.107(b)(3), approval may be made effective 30 months after the date of receipt of the notice of certification. Accordingly, Pharmachemie believes that their ANDA #74-539 can now be given final approval.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**:
Tamoxifen Citrate Tablets USP, 10 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
Firm:

08/26/94	ANDA submission (received on 08/30/94)
10/14/94	ANDA Update response to the 9/22/94 RTF letter.
12/5/94	ANDA Update response to the 11/10/94 RTF letter.
12/28/94	Revised Certification Statement.
12/6/95	O/NC - Bioavailability information
1/26/96	ANDA Amendment. Response to N/A letter #1
2/12/96	O/NC - Revised Patent Certification; Patent is invalid
5/13/96	O/NC - Revised Patent Certification information.
9/10/96	ANDA Amendment. Response to N/A letter #2
11/1/96	Bio Data
10/23/96	ANDA Amendment. Response to Telephone Amendment Request.
11/13/96	ANDA Amendment. Response to Telephone Amendment Request.
12/30/96	ANDA Amendment. Response to Sept 13, 1996 and October 10, 1996 letters.
2/19/97	ANDA Amendment. Response to Labeling Deficiency FAX of 1/13/97.

	3/14/97	O/NC: Change of US Agent.
	3/21/97	ANDA Amendment. Response to a Telephone Amendment dated 3/19/98
*	8/18/98	ANDA Amendment. Request for Final Approval.
*	9/4/98	FAX Amendment: Certification that there have been no changes in the CMC information in the ANDA since the date of tentative approval

* Items reviewed this cycle.

FDA:

09/22/94	Refuse to File letter
11/10/94	Refuse to File Letter #2
1/11/95	Acknowledge of submission
6/6/95	N/A #1; Chem./Label deficiencies; MAJOR Amend.
6/18/96	N/A #2; Chem/Labeling deficiencies; MINOR AMEND.
9/13/96	N/A Letter; Additional labeling changes resulting from changes in the labeling of the listed drug: Nolvadex; Zeneca Pharmaceuticals.
9/25/96	Labeling review/NA Letter.
12/11/96	MV Satisfactory as per the Northeast Regional Laboratory.
1/13/97	Labeling FAX/Request for Telephone Amendment.
2/28/98	Labeling Approval Summary
3/6/97	Chemistry Approval Summary
4/3/97	Tentative Approval Letter
9/3/98	Telephone request; Additional certification that no CMC changes have occurred since tentative approval on 4/3/97.

10. **PHARMACOLOGIC CATEGORY:** See Chemistry Review #2.

11. **HOW DISPENSED:** Rx

12. **RELATED INDs, NDAs and DMFs:**
Name of Listed Drug: Nolvadex®
Holder of NDA: Zeneca (NDA 17-970)

DMF listed in FDA 356h:
DMF [redacted] (Pharmachemie B.V.)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM:**
Tablets/oral administration

14. **STRENGTH:**
10 mg

15. **CHEMICAL STRUCTURE AND NAME:** See insert. As per USP.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**:
    1. Bioequivalence Signoff complete 1/15/97.
    2. An EER was found acceptable 4/3/97. EER update requested 8/26/98. Awaiting results.
    3. Impurity specifications are satisfactory.

18. **CONCLUSIONS/RECOMMENDATIONS**: Approve pending labeling review and EER FUR.

19. **REVIEWER**: Kenneth J. Furnkranz

DATE COMPLETED/REVISED: 31-Aug-1998

cc: ANDA #74-539
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-625/K.Furnkranz
HFD-625/M.Smela
HFD-617/D.Huie, P.M./9/8/98
HFD-613/CHolquist
HFD-613/JGrace
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F/T by: gp/9/11/98
Approve ANDA

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: 5

2. **ANDA**: 74-539

3. **NAME AND ADDRESS OF APPLICANT**:
Pharmachemie USA, Inc.
Attn: Ms. Hellen de Kloet, V.P.
U.S. Agent for Pharmachemie B.V.
323 Davis Street
Northborough, MA 01532

4. **LEGAL BASIS FOR ANDA SUBMISSION**: **Refer to the Chemistry Review #2.** Pharmachemie has certified that the relevant patent (#4,536,516) was invalid and unenforceable and the patent holder brought suit for patent infringement within 45 days of receipt of the notice, and, according to 21 CFR 314.107(b)(3), approval may be made effective 30 months after the date of receipt of the notice of certification. Accordingly, Pharmachemie believes that their ANDA #74-539 can now be given final approval.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**:
Tamoxifen Citrate Tablets USP, 10 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
Firm:

08/26/94	ANDA submission (received on 08/30/94)
10/14/94	ANDA Update response to the 9/22/94 RTF letter.
12/5/94	ANDA Update response to the 11/10/94 RTF letter.
12/28/94	Revised Certification Statement.
12/6/95	O/NC - Bioavailability information
1/26/96	ANDA Amendment. Response to N/A letter #1
2/12/96	O/NC - Revised Patent Certification; Patent is invalid
5/13/96	O/NC - Revised Patent Certification information.
9/10/96	ANDA Amendment. Response to N/A letter #2
11/1/96	Bio Data
10/23/96	ANDA Amendment. Response to Telephone Amendment Request.
11/13/96	ANDA Amendment. Response to Telephone Amendment Request.
12/30/96	ANDA Amendment. Response to Sept 13, 1996 and October 10, 1996 letters.
2/19/97	ANDA Amendment. Response to Labeling Deficiency FAX of 1/13/97.

	3/14/97	O/NC: Change of US Agent.
	3/21/97	ANDA Amendment. Response to a Telephone Amendment dated 3/19/98
	8/18/98	ANDA Amendment. Request for Final Approval.
	9/4/98	FAX Amendment: Certification that there have been no changes in the CMC information in the ANDA since the date of tentative approval
	4/15/99	O/NC: Notice of Address Change
	11/1/99	O/NC: Designation of New Agent; Ms. Deborah A. Jaskot; TEVA
*	4/18/00	ANDA Amendment; Request for 90 Day Amendment
*	4/27/00	Exclusivity Statement

* Items reviewed this cycle.

FDA:

09/22/94	Refuse to File letter
11/10/94	Refuse to File Letter #2
1/11/95	Acknowledge of submission
6/6/95	N/A #1; Chem./Label deficiencies; MAJOR Amend.
6/18/96	N/A #2; Chem/Labeling deficiencies; MINOR AMEND.
9/13/96	N/A Letter; Additional labeling changes resulting from changes in the labeling of the listed drug: Nolvadex; Zeneca Pharmaceuticals.
9/25/96	Labeling review/NA Letter.
12/11/96	MV Satisfactory as per the Northeast Regional Laboratory.
1/13/97	Labeling FAX/Request for Telephone Amendment.
2/28/98	Labeling Approval Summary
3/6/97	Chemistry Approval Summary
4/3/97	Tentative Approval Letter
9/3/98	Telephone request; Additional certification that no CMC changes have occurred since tentative approval on 4/3/97.
3/9/99	2nd Tentative Approval

10. PHARMACOLOGIC CATEGORY: See Chemistry Review #2.

11. HOW DISPENSED: Rx

12. RELATED INDs, NDAs and DMFs:

Name of Listed Drug: Nolvadex®
Holder of NDA: Zeneca (NDA 17-970)

DMF listed in FDA 356h:
DMF —— (Pharmachemie B.V.)
DMF
DMF
DMF
DMF

13. DOSAGE FORM:
Tablets/oral administration

14. STRENGTH:
10 mg

15. **CHEMICAL STRUCTURE AND NAME:** See insert. As per USP.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
    1. Bioequivalence Signoff complete 1/15/97.
    2. An EER was found acceptable 4/3/97. EER update requested 8/26/98. Acceptable for all firms 9/98.
    3. DMF's are current and acceptable

18. **CONCLUSIONS/RECOMMENDATIONS:** Approve

19. **REVIEWER:** Kenneth J. Furnkranz

DATE COMPLETED/REVISED: 5-May-2000

cc: ANDA #74-539
DUP Jacket
Division File
Field Copy

/S/ 5/12/00

Endorsements:
HFD-625/K.Furnkranz/5/5/00
HFD-625/M.Smela, T.L./5/9/00
X:\new\firmsnz\pharmach\ltrs&rev\74539A05.fkf.doc
F/T by:
Approve ANDA

/S/ 5/12/00

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-539 SPONSOR: Pharmachemie B.V.
DRUG: Tamoxifen Citrate
DOSAGE FORM: Tablets
STRENGTH(s): 10 mg
TYPE OF STUDY: Single/~~Multiple~~ ~~Fasting~~/~~Fed~~
STUDY SITE:

STUDY SUMMARY: The Single-dose bioequivalence study under fasting conditions conducted by Pharmachemie B.V. on its Tamoxifen Citrate 10 mg Tablets is acceptable. Dissolution testing is acceptable.

DISSOLUTION:

PRIMARY REVIEWER: Moneto H. Mallary BRANCH: ~~III~~

INITIAL: /S/ DATE: 1/6/97

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 1/7/97

Acting DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 1/28/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

JAN 7 1997

Tamoxifen Citrate
10 mg Tablets
ANDA #74-539
Reviewer: Moheb H. Makary
WP. 74539SD.N96

Pharmachemie B.V.
Haarlem, Holland
Submission Date:
November 1, 1996

Review of An Amendment to Bioequivalence Study, and Dissolution Data

I. Objective:

The firm has replied to the reviewer's comments made in the review of the August 26, 1994 and December 6, 1995 submissions (a bioequivalence study on Tamoxifen Citrate 10 mg Tablet and dissolution data).

II. Comment

The firm was asked to submit data to support the long term stability of tamoxifen and N-desmethyltamoxifen, i.e., the stability in frozen study samples for the period equal to the time from the day the plasma samples were collected to the day the last sample was analyzed (3 months).

The firm submitted the results of the long-term stability experiments for tamoxifen and N-desmethyltamoxifen. The results indicated that no signs of deterioration of tamoxifen and N-desmethyltamoxifen in spiked plasma pools during storage period of three months at -20°C.

Reply to Comment

The firm's response to the comment is acceptable.

Recommendations:

The single-dose bioequivalence study under fasting conditions conducted by Pharmachemie B.V., on its Tamoxifen Citrate 10 mg Tablets, lot #92Z0702, comparing it to Nolvadex® 10 mg Tablets manufactured by Zeneca., has been found acceptable by the Division of Bioequivalence. The study demonstrates that Pharmachemie's Tamoxifen Citrate Tablets, 10 mg is bioequivalent

to the reference product, Nolvadex® Tablets, 10 mg manufactured by Zeneca.

2. The dissolution testing conducted by the firm on its Tamoxifen Citrate 10 mg Tablets, lot #92Z0702 is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.02N HCl at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than ~ of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE.
FT INITIALLED RMHATRF /S/ Date: 1/7/97

Concur: /S/ Date: 1/7/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-6-97 wp 74539SD.N96
cc: ANDA #74-539, original, HFD-658 (Makary), Drug File, Division File.

MAR 26 1996

Tamoxifen Citrate
10 mg Tablets
ANDA #74-539
Reviewer: Moheb H. Makary
WP. 74539SD.D95

Pharmachemie B.V.
Haarlem, Holland
Submission Date:
December 6, 1995

Review of An Amendment to Bioequivalence Study, and Dissolution Data

I. Objective:

The firm has replied to the reviewer's comments made in the review of the August 26, 1994 submission (a bioequivalence study on Tamoxifen Citrate 10 mg Tablet and dissolution data).

II. Comment #1

The firm was asked to calculate AUC_{0-t} for tamoxifen and N-desmethyltamoxifen, up to time t, where t is the last measurable (quantifiable) time point for tamoxifen and N-desmethyltamoxifen for each subject.

The firm submitted the values of AUC_{0-t} and AUCinf of each subject for tamoxifen, and N-desmethyltamoxifen on a 3.5" Diskette. The firm also submitted a copy of analysis of variance (ANOVA) on Cmax, AUC_{0-t} and AUCinf for tamoxifen, and N-desmethyltamoxifen.

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to submit the arithmetic mean of the plasma concentrations for each sampling time point for tamoxifen and N-desmethyltamoxifen.

The firm submitted arithmetic mean of the plasma concentrations at each sampling time point for tamoxifen and N-desmethyltamoxifen.

The plasma concentrations for tamoxifen and N-desmethyltamoxifen are shown below:

Mean Tamoxifen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 20 mg (2x10 mg Tablets) Tamoxiofen Citrate Under Fasting Conditions
(N=38)

Time (hr)	Pharmachemie Test product Lot #92Z0702 ug/L (SD)	Zeneca Reference product Lot #5146M ug/L (SD)
0	0.30*	0.30*
1	6.28 (5.98)	7.44 (6.09)
2	16.22 (7.79)	18.83 (7.96)
3	22.58 (7.53)	24.44 (8.37)
4	24.55 (7.27)	25.96 (6.91)
5	26.76 (6.19)	26.58 (6.39)
6	23.60 (5.99)	22.96 (5.25)
7	22.55 (5.82)	21.93 (4.30)
8	21.17 (4.74)	20.58 (4.05)
10	19.59 (4.62)	19.73 (3.76)
12	18.00 (4.28)	17.95 (3.72)
16	13.67 (3.14)	14.01 (2.81)
20	12.52 (2.86)	12.29 (2.22)
24	12.52 (2.91)	11.96 (2.14)
30	10.71 (2.56)	10.24 (2.02)
36	9.40 (2.39)	9.09 (1.77)
48	8.50 (2.19)	8.09 (1.81)
72	6.85 (1.94)	6.62 (1.92)
96	5.63 (1.91)	5.38 (1.44)
120	4.72 (1.69)	4.68 (1.47)
144	3.97 (1.41)	4.02 (1.28)
168	3.56 (1.31)	3.48 (1.23)
216	2.67 (1.16)	2.58 (0.90)
264	2.03 (1.09)	2.05 (0.83)
336	1.42 (0.84)	1.44 (0.69)
408	1.00 (0.69)	0.97 (0.55)
480	0.66 (0.53)	0.68 (0.40)
576	0.48 (0.40)	0.44 (0.25)
672	0.40 (0.30)	0.34 (0.11)

* Values below the lower limit of quantitation (0.5 ug/L)

Table II

Mean N-Desmethyltamoxifen Plasma Concentrations and Pharmacokinetic Parameters Following An Oral Dose of 20 mg (2x10 mg Tablets) Tamoxifen Citrate Under Fasting Conditions
(N=38)

Time (hr)	Pharmachemie Test product Lot #92Z0702 ug/L (SD)	Zeneca Reference product Lot #5146M ug/L (SD)
0	0.30*	0.30*
1	0.78 (0.73)	0.89 (0.71)
2	2.93 (1.75)	3.15 (1.53)
3	5.17 (2.22)	5.47 (2.30)
4	6.85 (2.53)	7.15 (2.48)
5	9.21 (2.51)	8.85 (2.34)
6	9.21 (2.43)	8.94 (2.32)
7	9.75 (2.73)	9.25 (2.15)
8	9.82 (2.74)	9.13 (2.23)
10	10.20 (2.75)	9.82 (2.01)
12	10.45 (2.85)	9.87 (2.36)
16	9.09 (2.25)	9.16 (2.09)
20	9.77 (2.75)	9.41 (2.08)
24	10.20 (2.87)	9.47 (2.01)
30	10.04 (2.66)	9.28 (2.03)
36	9.90 (2.74)	9.34 (2.08)
48	10.19 (2.47)	9.64 (2.21)
72	10.60 (2.63)	9.99 (2.93)
96	10.13 (3.13)	9.56 (2.28)
120	9.77 (3.04)	9.38 (2.54)
144	9.18 (2.87)	9.01 (2.42)
168	8.96 (2.62)	8.58 (2.57)
216	7.89 (2.68)	7.38 (2.14)
264	6.81 (2.28)	6.78 (2.23)
336	5.72 (1.96)	5.75 (1.90)
408	4.82 (2.13)	4.56 (1.67)
480	3.81 (1.79)	3.60 (1.35)
576	2.95 (1.52)	2.72 (1.13)
672	2.30 (1.58)	2.03 (0.97)

* Values below the lower limit of quantitation (0.5 ug/L)

Reply to Comment #2

The firm's response to the comment is acceptable.

Comment #3

The firm was asked to submit the ———————— for One-fifth (20%)

of the subjects completed the study for tamoxifen and N-desmethyltamoxifen.

The firm submitted the chromatograms for the following subjects #8, 11, 13, 19, 21, 47, 50, 51, 54, 58, 59, 62, 65 and 74.

Reply to Comment #3

The firm's response to the comment is acceptable.

Comment #4

The firm was asked to submit a copy of the analytical raw data for all subjects in the study for tamoxifen and N-desmethyltamoxifen.

The firm submitted the analytical raw data for all subjects in the study for tamoxifen and N-desmethyltamoxifen.

Reply to Comment #4

The firm's response to the comment is acceptable.

Comment #5

The firm was advised to submit 3.5" Diskettes, in ASCII code, which contain all pharmacokinetic data for tamoxifen and N-desmethyltamoxifen.

The firm submitted a 3.5" Diskette contains all pharmacokinetic data for tamoxifen and N-desmethyltamoxifen.

Reply to Comment #5

The firm's response to the comment is acceptable.

Comment #6

The firm was advised to use the following model in the statistical analysis of the study:

Y = Group Trt Group*Trt

The firm submitted the statistical analysis using the above model. The 90% confidence intervals resulting from the above model are:

Tamoxifen

LnAUC(0-t)	91.1-115.1%
LnAUCinf	90.9-114.6%
LnCmax	89.2-107.1%

N-desmethyltamoxifen

LnAUC(0-t)	92.6-115.2%
LnAUCinf	89.6-116.4%
LnCmax	96.8-116.7%

The 90% confidence intervals for the above pharmacokinetic parameters calculated using the above model remain within the acceptable range of 80-125%.

However, the Division of Biometrics has indicated that if the Group term in the above model is significant (which it is) the following model

Y = Group trt;

is advised to be used.

The above model employed by the reviewer in the statistical analysis of the study resulted in the following 90% confidence intervals:

Tamoxifen

LnAUC(0-t)	90.7-113.7%
LnAUCinf	90.4-113.1%
LnCmax	88.8-105.8%

N-desmethyltamoxifen

LnAUC(0-t)	92.2-113.8%
LnAUCinf	89.1-114.7%
LnCmax	96.8-116.0%

The 90% confidence intervals for the above pharmacokinetic parameters calculated using the second model remain within the acceptable range of 80-125%.

Reply to Comment #6

The firm's response to the comment is acceptable.

Comment #7

The firm was asked to submit data to support the long term stability of tamoxifen and N-desmethyltamoxifen (i.e., their stability in frozen study samples for the period equal to the time from the day the plasma samples were collected to the day the last sample was analyzed).

The firm indicated that during the assay validation and the

bioanalysis of the study samples, no formal assessments have been made concerning long-term stability of the analytes in study samples. At that time, long-term stability in biological samples was only considered in the validation of an assay method for a registered drug if the literature indicated that stability could be a problem. For tamoxifen, there was no such indication.

The firm stated that the maximum period between sample collection and analysis was three months and for many subjects this period was less than two months. The firm submitted the 15% duplicate assays as information concerning the long-term stability. The maximum time interval between the first and second assay of a duplicate was seven weeks.

Reply to Comment #7

The firm did not demonstrate the long-term stability of tamoxifen and N-desmethyltamoxifen.

The firm's response to the comment is unacceptable.

The firm should submit data to support the long term stability of tamoxifen and N-desmethyltamoxifen [i.e., their stability in frozen study samples for the period equal to the time from the day the plasma samples were collected to the day the last sample was analyzed (3 months)].

Comment #8

The firm was asked to submit the expiration date for the reference product and the content uniformity for the test and reference products.

The firm submitted the following information:

Test product:	Tamoxifen Citrate Tablets, 10 mg (Pharmachemie B.V.), lot #92Z0702, Exp. 8/94, content uniformity 97.9% (%CV=1.0).
Reference product:	Nolvadex^{R} Tablets, 10 mg(Zeneca), lot # 5146M, Exp. 6/95, Content uniformity 98.2% (%CV=1.9).

Reply to Comment #8

The firm's response to the comment is acceptable.

Comment #9

The firm was advised to resubmit the comparative dissolution testing using 1000 ml of 0.02N HCl (instead of 900 mL). The dissolution profiles should be determined at 15, 30, 45 and 60 minutes.

The firm indicated that the mentioning of dissolution volume of 900 mL was an error. The dissolution volume used was 1000 mL 0.02 N HCl according to USP dissolution conditions.

Reply to Comment #9

The firm's response to the comment is acceptable.

Recommendations:

The single-dose bioequivalence study under fasting conditions conducted by Pharmachemie B.V., on its Tamoxifen Citrate 10 mg Tablets, lot #92Z0702, comparing it to Nolvadex® 10 mg Tablets manufactured by Zeneca., has been found to be incomplete by the Division of Bioequivalence for the reason given in comment# 7.

The firm should be informed of the deficiency comment and recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 3/26/96

H/I See memo dated 11-17-97 /S/

Concur:_____ Date:_____
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/3-25-96 wp 74539SD.D95
cc: ANDA #74-539, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

JUN 29 1995

Tamoxifen Citrate Tablets
10 mg
ANDA #74-539
Reviewer: Moheb H. Makary
WP. 74539SD.894

Pharmachemie B.V.
Haarlem, Holland
Submission Date:
August 26, 1994

Review Of Bioequivalence Study and Dissolution Data

I. Objective:

The firm has submitted a bioequivalence study under fasting conditions for its 10 mg Tamoxifen Citrate Tablets, and dissolution data to compare the bioavailability of Pharmachemie B.V., and Zeneca (Nolvadex®) 10 mg Tamoxifen Citrate Tablets following a single 20 mg dose administered as 2x10 mg tablets. The formulation for Tamoxifen Citrate 10 mg Tablets (Pharmachemie B.V.) was also submitted.

II. Introduction:

Tamoxifen citrate is a nonsteroidal agent which has demonstrated potent antiestrogenic properties. In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein. It is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

Tamoxifen is metabolized by cytochrome P-450. These enzymes can be inhibited by tamoxifen and its metabolites. Therefore, a long elimination half-life is observed. Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug was excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.
N-desmethyl tamoxifen was the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to tamoxifen. 4-hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma.
Chronic administration of 10 mg tamoxifen given twice daily for three months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. After initiation of therapy, steady state concentrations for tamoxifen are achieved in about 4 weeks and steady state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite.

Tamoxifen citrate is commercially available as tablets of 10 mg, Nolvadex®, manufactured by Zeneca Pharmaceuticals, (ICI). In women and men with metastatic breast cancer, one or two 10 mg tablets are administered twice a day (morning and evening).

III. Protocol #PBP-931102-6 For Single-Dose, Parallel group Bioavailability Study of Tamoxifen Citrate 10 mg Tablet Under Fasting Conditions:

Clinical site: [redacted]

Analytical site: [redacted]

Sponsor: Pharmachemie B.V.
The Netherlands

Investigators: [redacted]

Study design: single-dose, open label, parallel design, randomized study, under fasting conditions. The study was a one period of 29 days.

Subjects: Seventy-six (38 per treatment) healthy adult male volunteers were selected to participate in this study. All subjects successfully completed the study in six groups:

Group 1 subjects #1-12 were dosed on March 19, 1993.
Group 2 subjects #13-24 were dosed on March 22, 1993.
Group 3 subjects #25-36 were dosed on March 26, 1993.
Group 4 subjects #37-48 were dosed on March 31, 1993.
Group 5 subjects #49-57 were dosed on April 7, 1993.
Group 6 subjects #58-76 were dosed on April 14, 1993.

Inclusion criteria: The subjects were between 21 and 45 years old. All subjects were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983), except subject #23 was 0.5 kg above the upper limit of the 15%. Each subject received a complete physical examination and laboratory

tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and negative urine drug and alcohol were enrolled in the study.

Exclusions: Subjects with history or presence of:
- evidence of clinically relevant pathology;
- history of relevant drug and/or food allergies;
- illness within five days prior to the start of the study;
- positive screen on five (groups of) drugs of abuse, benzodiazepines, barbiturates and tricyclic antidepressants;
- positive screen on HIV;
- participation in a drug study within 90 days prior to the start of the study;
- participation in another tamoxifen study during the preceding two years;
- donating of blood within 90 days prior to the start of the study;
- mental handicap;

were excluded from the study.

Restrictions: The consumption of alcohol beverages, xanthine and caffeine containing foods were prohibited for 48 hours before and during the first 48 hours of the study. Subjects were instructed to take no medication for 14 days prior to the study start and during the study.

Dose and treatments: All subjects completed an overnight fast before any of the following drug treatments:

Test product: A. 2x10 mg Tamoxifen Citrate Tablets (Pharmachemie B.V.), lot #92Z0702, Exp. N/A, lot size ——— Tablets, content uniformity not reported, potency 97.8%.

Reference product: B. 2X10 mg Nolvadex^{R} Tablets(Zeneca), lot # 5146M, Exp. not reported. Content uniformity not reported, potency 99.5%.

Food and fluid intake: On day 1 single, oral 20 mg (2 TabletS) dose was administered with 200 mL of water. Subjects stayed in the clinical facility for 48 hours following drug administration and

left at 9.00 AM on day 3. On days 4, 5, 6, 7, 8, 10, 12, 18, 21, 25 and 29 the subjects returned to the clinical facility for collection of a blood sample. Meals were provided at 8:30 AM (breakfast, not on day 1), 12.30 PM (lunch) and 18:30 PM (dinner), and 10 hours after dosing.

Blood samples: 10 mL blood samples were collected just before and at: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36, 48, 72, 96, 120, 144, 168, 216, 264, 336, 408, 480, 576 and 672 hours after dosing on day 1.

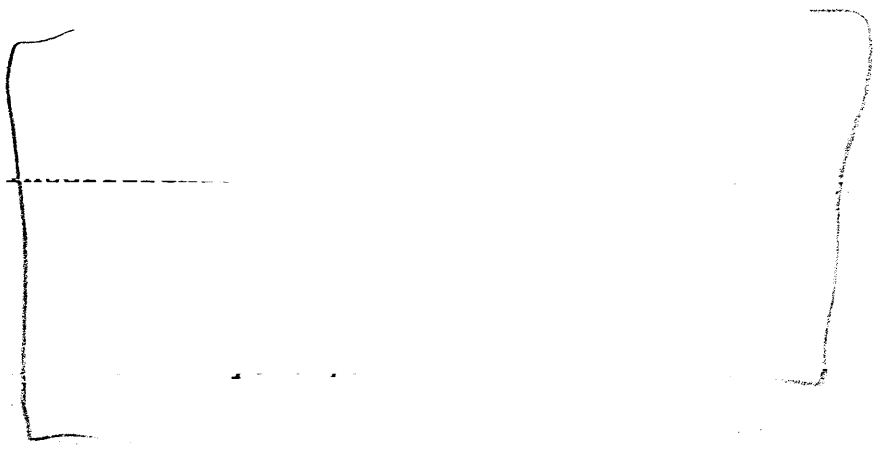
It should be noted that during the night of March 27 to March 28, 1993 the official time changed from winter-time to summer-time. The blood-sampling schedules for the subjects who commenced the study before this date were not adjusted. Therefore, all blood samples which were collected after this date for all subjects in groups 1, 2 and 3 were collected one hour earlier than the schedule time. For group 1 (subjects 1-12) was on day 10 at 216 hours blood sample. For group 2 and 3 were on day 7 at 144 hours and on day 3 48 hours blood samples, respectively.

Safety assessments: During the entire study blood pressure, heart rate and oral body temperature were measured regularly as vital sign on day 1, 2 and 3. Hematology tests were performed on days 7, 15, 21 and 29.

Assay methodology

Specificity:

Recovery:



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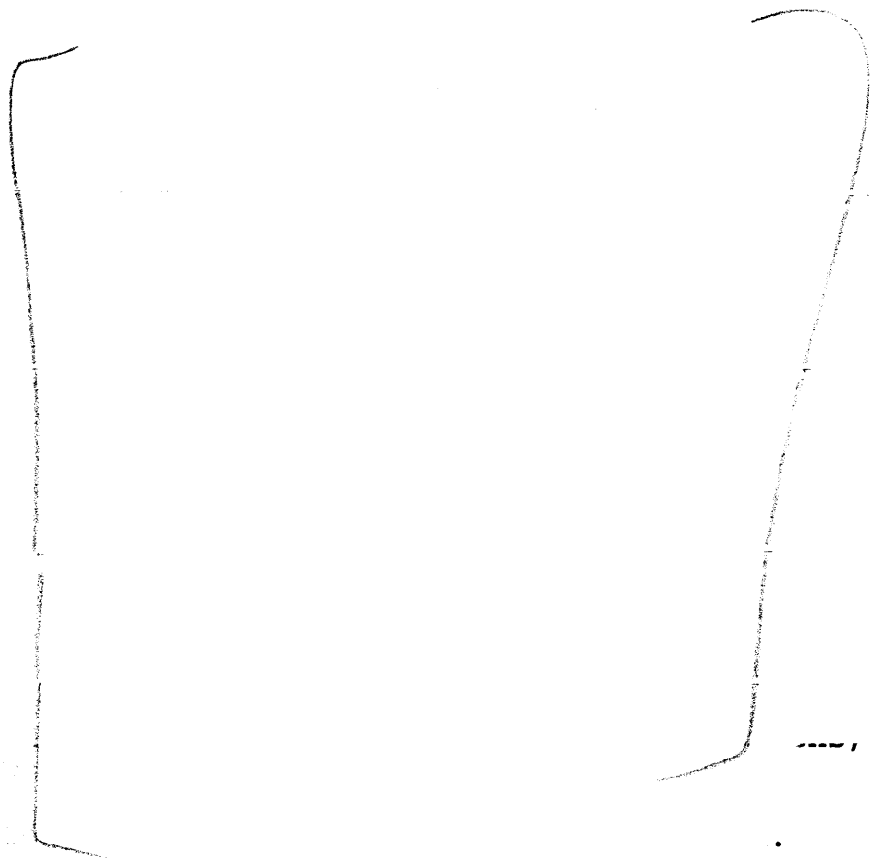

Pharmacokinetics:

Pharmacokinetic parameters determined for tamoxifen and N-desmethyltamoxifen after dosing were the maximum plasma concentration (Cmax), the time to attain the maximum concentration (tmax), the terminal elimination rate constant (Kel), the corresponding terminal elimination half-life (t1/2), the area under the plasma concentration-time curve from 0 to 216 hours (AUC_{0-216}) for tamoxifen and from 0 to 576 hours (AUC_{0-576}) for N-desmethyltamoxifen and the area under the plasma concentration-time curve from 0 to infinity (AUCinf) for both compounds.
Concentrations of 4-hydroxytamoxifen were low and in most cases below the limit of detection. Therefore, no pharmacokinetic parameters could be calculated for 4-hydroxytamoxifen.

Statistical Analysis:

The individual Cmax and AUC were compared after logarithmic transformation. An ANOVA model with the treatment as source of variation was performed at an alpha = 0.05. The 90% confidence intervals (2 one-sided t-test method) were calculated for LnAUC and LnCmax.

IV. In Vivo Results:

The study was conducted during months of March up to May 1993. Seventy-six (76) subjects were selected in this study, all successfully completed the study in six groups. Group 1-4 consisted of 12 subjects each. Due to recruitment problems group 5 consisted of 9 subjects. Consequently group 6 consisted of 19 subjects.
No severe adverse experiences were reported by the subjects. Very few adverse experiences were reported and those reported were of a mild intensity. The adverse events are summarized in Table I. Vital signs measurements, ECG and clinical laboratory test results did not reveal clinically relevant changes. However, subject #9 AB hematology tests, as performed on day 7, 9, 11, 15, 21 and 29, showed a transient neutropenia. This serious adverse event was immediately reported to the sponsor. The relation to the medication (B) was rated as possible. All investigations concerning this event, performed thereafter did not reveal any evidence of pathology.

The geometric mean of the plasma concentrations and pharmacokinetic parameters for tamoxifen and N-desmethyltamoxifen are summarized in Table II and Table III.

Table II

Geometric Mean Tamoxifen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 20 mg (2x10 mg Tablets) Tamoxiofen Citrate Under Fasting Conditions
(N=38)

Time (hr)	Pharmachemie Test product Lot #92Z0702 ug/L	Zeneca Reference product Lot #5146M ug/L
0	0.30*	0.30*
1	3.99	5.62
2	13.49	17.17
3	20.84	23.13
4	23.35	25.07
5	26.09	25.92
6	22.91	22.46
7	21.85	21.56
8	20.66	20.22
10	19.08	19.41
12	17.53	17.61
16	13.34	13.74
20	12.22	12.11
24	12.20	11.79
30	10.41	10.07
36	9.12	8.93
48	8.25	7.92
72	6.60	6.37
96	5.36	5.22
120	4.45	4.48
144	3.76	3.85
168	3.36	3.29
216	2.46	2.43
264	1.81	1.90
336	1.25	1.30
408	0.83	0.81
480	0.53	0.58
576	0.41	0.39
672	0.35	0.33

* Values below the lower limit of quantitation (0.5 ug/L)

	Test	Reference	90% CI
	Arithmetic Mean(CV)	Arithmetic Mean(CV)	
AUC(0-216)(ug.hr/L)	1432(27.0)	1406(23.5)	
AUCinf (ug.hr/L)	1957(37.3)	1917(28.8)	
Cmax (ug/L)	27.9(22.9)	28.8(25.3)	
Tmax (hr)	4.52(24.5)	4.29(21.6)	
Kel (1/hr)	0.00606	0.00585	
Half-life (hr)	123(26.8)	125(22.4)	
LnAUC (0-216)			92.2-110.7%
LnAUCinf			89.6-112.6%
LnCmax			89.0-106.5%

Table III

Geometric Mean N-Desmethyltamoxifen Plasma Concentrations and Pharmacokinetic Parameters Following An Oral Dose of 20 mg (2x10 mg Tablets) Tamoxifen Citrate Under Fasting Conditions
(N=38)

Time (hr)	Pharmachemie Test product Lot #92Z0702 ug/L	Zeneca Reference product Lot #5146M ug/L
0	0.30*	0.30*
1	0.56	0.68
2	2.32	2.79
3	4.58	5.00
4	6.32	6.71
5	8.84	8.55
6	8.88	8.65
7	9.36	9.01
8	9.43	8.87
10	9.82	9.61
12	10.06	9.60
16	8.81	8.93
20	9.41	9.18
24	9.80	9.25
30	9.70	9.07
36	9.51	9.11
48	9.91	9.41
72	10.27	9.59
96	9.68	9.30
120	9.29	9.06
144	8.76	8.71
168	8.60	8.22
216	7.46	7.10
264	6.45	6.46
336	5.40	5.47
408	4.38	4.29
480	3.42	3.37
576	2.59	2.51
672	1.85	1.84

* Values below the lower limit of quantitation (0.5 ug/L)

	Test	Reference	90% CI
	Arithmetic Mean(CV)	Arithmetic Mean(CV)	
AUC(0-576)(ug.hr/L)	3839.0(29.3)	3683.0(26.6)	
AUCinf (ug.hr/L)	4789.0(35.6)	4663.0(32.0)	
Cmax (ug/L)	12.3(25.2)	11.4(22.8)	
Tmax (hr)	58.31(115.3)	57.47(83.4)	
Kel (1/hr)	0.00318	0.00308	
Half-life (hr)	236.0(30.1)	235.0 (22.1)	
LnAUC (0-576)			92.7-114.9%
LnAUCinf			89.0-115.0%
LnCmax			97.9-118.1%

1. For tamoxifen, Pharmachemie's test product had an AUC(0-216) of 1432 ug.hr/L and AUCinf of 1957 ug.hr/L, which were 1.8% and 2.0%, higher, respectively, than their reference product values. The differences were not statistically significant. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-216) and AUCinf. The ratios of AUC(0-216)/AUCinf were 73.2% and 73.34% for the test and the reference products, respectively.

2. For tamoxifen, the Cmax of Pharmachemie's test product was 27.9 ug/L which was 3.1% lower than its reference product value. The difference was not statistically significant . The 90% confidence interval of the test mean was within the acceptable range of 80-125% of the reference mean.

3. Based on the geometric mean, tamoxifen plasma levels peaked at 5 hours for both the test and reference products, following their administration under fasting conditions.

4. For N-desmethyltamoxifen, the mean values for AUC(0-576), AUCinf and Cmax were 4.2%, 2.7% and 7.9% higher, respectively, for the test product than for the reference products. The differences were not statistically significant and the 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-576), AUCinf and Cmax. The reviewer's calculations were similar to those submitted by the firm. The ratios of AUC(0-576)/AUCinf were 80.2% and 78.9% for the test and the reference products, respectively.

VI. Formulations:

Pharmachemie's formulation for Tamoxifen Tablets 10 mg is shown below:

Ingredient (amount per tablet)	10 mg
Tamoxifen Citrate*, USP	15.17 mg
Potato Starch NF	[illegible]
Lactose NF	[illegible]
Povidone [illegible], USP	[illegible]
Microcrystalline Cellulose NF	[illegible]
Magnesium stearate NF	[illegible]
Colloidal Silicon Dioxide, NF	[illegible]
	180.00 mg

* Corresponding to Tamoxifen 10 mg

VII. In Vitro Dissolution Testing:

Method:	USP 23 apparatus I (basket) at 100 rpm
Medium:	900 mL of 0.02N HCl
Number of Tablets:	12
Test Product:	Pharmachemie's Tamoxifen Citrate 10 mg Tablets, lot #92Z0702
Reference Product:	Zeneca's Nolvadex® 10 mg Tablets, lot #5146M
Specifications:	NLT [illegible] in 30 minutes

Dissolution testing results are shown in Table IV.

VIII. Comments:

1. For tamoxifen, the 90% confidence intervals for $LnAUC_{0-216}$, LnAUCinf and LnCmax are within the acceptable range of 80-125%.

2. For N-desmethyltamoxifen, the 90% confidence intervals for $LnAUC_{0-576}$, LnAUCinf and LnCmax are within the acceptable range of 80-125%

3. The firm conducted the dissolution testing in 900 mL of 0.02N HCl instead of 1000 mL as recommended by USP.

IX. Deficiency Comments:

1. The firm has calculated area under the plasma concentration-time curve (AUC_{0-t}) up to 216 hours for tamoxifen and up to 576 hours for N-desmethyltamoxifen. AUC_{0-t} should be calculated up to time t, where t is the last measurable (quantifiable) time point for

tamoxifen and N-desmethyltamoxifen for each subject.

2. The firm is advised to submit the arithmetic mean of the plasma concentrations for each sampling time point for tamoxifen and N-desmethyltamoxifen.

3. _____ of the analysis of the unknown samples for tamoxifen and N-desmethyltamoxifen, including all associated standard curves and Q.C. _____ should be submitted for one-fifth (20%) of the subjects, chosen at random.

4. The firm should submit complete analytical raw data for all subjects for tamoxifen and N-desmethyltamoxifen.

5. The firm is advised to submit 3.5" Diskettes, in ASCII code, which contain all pharmacokinetic data for tamoxifen and N-desmethyltamoxifen.

6. There were six groups in the study design, the firm is advised to use the following model in the statisitical analysis of the study:

Y = Group Trt Group*Trt;

7. The firm should submit data to support the long term stability of tamoxifen and N-desmethyltamoxifen (i.e., their stability in frozen study samples for the period equal to the time from the day the plasma samples were collected to the day the last sample was analyzed).

8. The firm is advised to submit the expiration date for the reference product and the content uniformity for the test and reference products.

9. The firm is advised to resubmit the comparative dissolution testing using 1000 mL of 0.02N HCl (instead of 900 mL). The dissolution profiles should be determined at _____

X. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Pharmachemie B.V., on its Tamoxifen Citrate 10 mg Tablets, lot #92Z0702, comparing it to Nolvadex® 10 mg Tablets manufactured by Zeneca., has been found to be incomplete by the Division of Bioequivalence for the reasons given in deficiency comments 1-8.

2. The dissolution testing conducted by Pharmachemie B.V., on its Tamoxifen Citrate 10 mg Tablets, lot #92Z0702, is incomplete. The firm is advised to resubmit the in vitro dissolution testing in accordance with instruction given in deficiency comment #9.

The firm should be informed of the deficiency comments and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE Date: 6/16/95

Concur: /S/ Date: 6/29/95
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/6-16-95 wp 74539SD.894
cc: ANDA #74-539, original, HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

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Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Tamoxifen Citrate Tablets
Dose Strength: 10 mg
ANDA No.:74-539
Firm: Pharmachemie
Submission Date: August 26, 1994
File Name: 74539SD.894

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL 0.02N HCl
Specifications: NLT —, in 30 minutes
Reference Drug: Nolvadex
Assay Methodology: —

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 92Z0702 Strength(mg) 10			Reference Product Lot # 5146M Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	56.7	—	23.2	60.0	—	8.7
20	93.5	—	0.8	77.6	—	7.4
30	93.9	—	0.6	83.7	—	5.4
60	94.4	—	0.6	90.7	—	2.6

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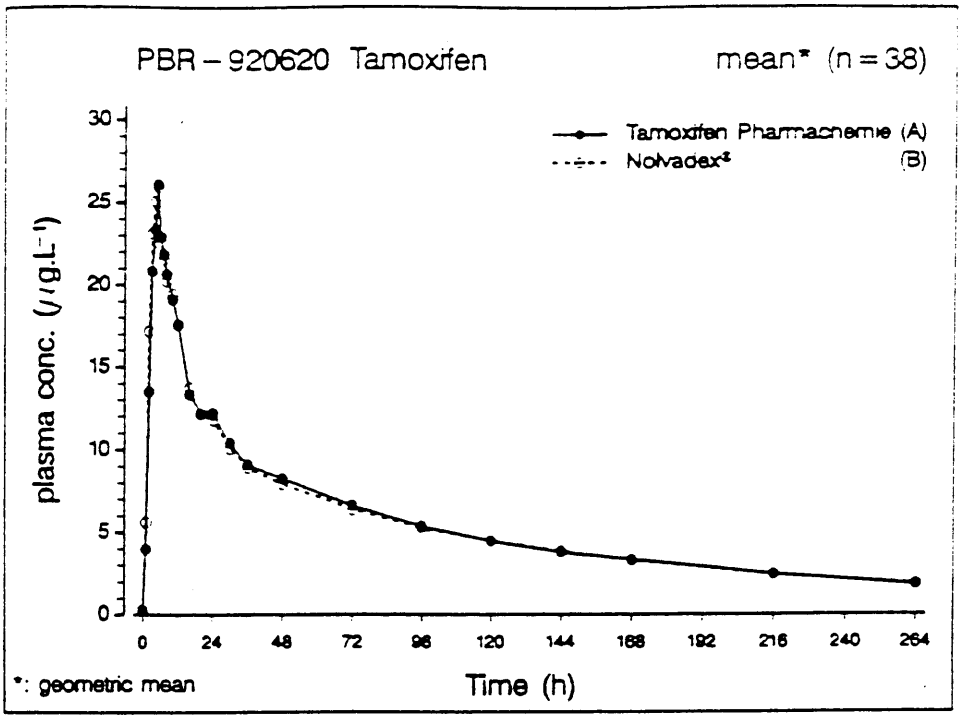
a.



b.

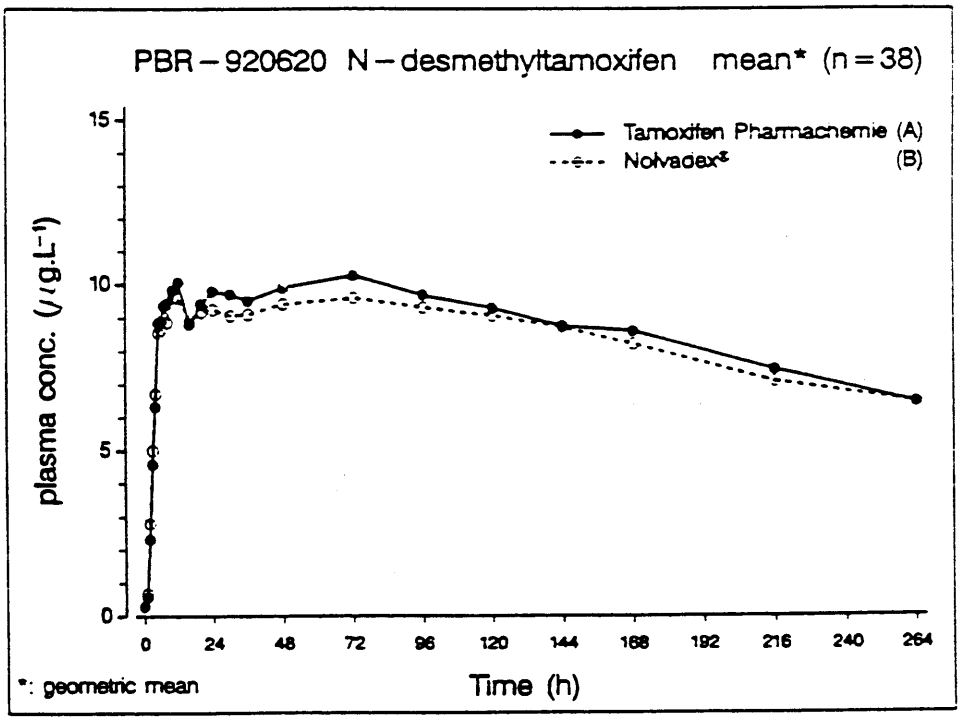


Figure 2. Geometric mean plasma concentration-time profiles of tamoxifen (a) and N-desmethyltamoxifen (b) as observed after single dose oral administration of 20 mg of tamoxifen to two parallel groups of 38 subjects each

A = Tamoxifen Pharmachemie

B = Nolvadex® (ICI Americas Inc., USA)

Table I

Appendix 6.4: Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)

B = Nolvadex® (ICI Americas Inc., U.S.A.)

A

Adverse Experience	Subject	Onset		Duration	Intensity	Relationship
		Day	Scheme time (h)	(h)		
Headache	11 AA	1	1.17	3.00	Mild	Possible
	30 SN	22	505.83	5.00	Mild	Remote
	41 TR	1	2.87	3.00	Mild	Possible
	69 BH	1	6.63	8.50	Mild	Possible
Dizziness	17 GH	4	65.37	6.50	Mild	Remote
Drowsiness	10 JH	1	-0.30	47.17	Mild	None
	12 MA	2	25.63	29.00	Mild	Possible
	32 DP	1	-1.48	749.75	Mild	None
Impaired concentration	12 MA	2	25.63	29.00	Mild	Possible
Feebleness	11 AA	15	N.R.	N.R.	Mild	None
	41 TR	17	N.R.	76 days	Mild	None
Malaise	17 GH	4	65.37	6.50	Mild	Remote
Nausea	11 AA	14	318.67	6.00	Mild	Remote
Nausea, intermittent	76 OB	3	50.40	84.00	Mild	Remote
Abdominal cramps	04 RK	24	558.90	3.00	Mild	Remote
		29	670.90	0.50	Mild	Remote
Vomiting	11 AA	14	N.R.	N.R.	Moderate	Remote
Flatulence	04 RK	1	5.90	49.00	Mild	Possible
	63 EK	1	-2.17	52.00	Mild	None
	64 TJ	1	9.80	1.00	Mild	Possible

N.R. = Not Recorded

Appendix 6.4: (cont.)

Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)
B = Nolvadex® (ICI Americas Inc., U.S.A.)

A

Adverse Experience	Subject	Onset		Duration	Intensity	Relationship
		Day	Scheme time (h)	(h)		
Loose stool	03 KU	1	5.93	114.00	Mild	Possible
	08 WS	3	50.77	72.00	Mild	Remote
	40 AK	2	31.90	0.08	Mild	Possible
Fatigue	63 EK	24	549.83	34.00	Mild	None
	69 BH	1	-0.03	94.67	Mild	None
Influenza	17 GH	14	312.37	N.R.	Moderate	Remote
	41 TR	13	N.R.	N.R.	Moderate	Remote
Cough	08 WS	21	N.R.	N.R.	Mild	None
Sore throat	16 AY	26	N.R.	N.R.	Mild	None
Flushing	41 TR	21	N.R.	28 days	Mild	None
Fever	47 PB	17	385.67	47.00	Moderate	None
Nose congestion	47 PB	17	385.67	47.00	Mild	None
Acute nasopharyngitis (common cold)	10 JH	6	118.70	N.R.	Mild	Remote
		24	N.R.	N.R.	Mild	Remote
	20 RL	9	205.27	83.75	Mild	Remote
	27 HL	26	599.43	168.00	Mild	None
	41 TR	21	N.R.	28 days	Mild	None
	69 BH	1	N.R.	N.R.	Mild	None
Acne increased	20 RL	6	134.27	42.00	Mild	Possible
Tinnitus	41 TR	23	N.R.	N.R.	Mild	None

N.R. = Not Recorded

Appendix 6.4: (cont.)

Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)
B = Nolvadex® (ICI Americas Inc., U.S.A.)

A

Adverse Experience	Subject	Onset		Duration	Intensity	Relationship
		Day	Scheme time (h)	(h)		
Backache	52 GJ	9	N.R.	N.R.	Mild	None
Muscle pain	63 EK	1	-2.17	12.00	Mild	None
Haematoma on site of venepuncture	30 SN	10	216.02	11 days	Mild	None

N.R. = Not Recorded

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Appendix 6.4: (cont.)

Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)

B = Nolvadex® (ICI Americas Inc., U.S.A.)

		B				
Adverse Experience	Subject	Onset Day	Onset Scheme time (h)	Duration (h)	Intensity	Relationship
Headache	39 AV	1	7.93	4.00	Mild	Possible
	42 EW	1	2.83	9.00	Mild	Possible
	56 JR	2	28.27	3.50	Mild	Remote
	60 RE	4	73.93	37.00	Moderate	Remote
		6	121.93	37.00	Moderate	Remote
	72 RI	19	437.52	3.00	Mild	None
Drowsiness	07 ET	2	23.30	48.50	Mild	Remote
	23 TF	2	23.98	23.93	Mild	Remote
	37 EE	1	4.00	9.00	Mild	Remote
	66 AL	5	99.73	54.00	Mild	Remote
	72 RI	4	82.02	1.00	Mild	Remote
Faintness	72 RI	1	-0.03	0.08	Moderate	None
Malaise	25 AW	23	N.R.	N.R.	Mild	None
	62 FL	27	N.R.	N.R.	Mild	None
Nausea	25 AW	23	N.R.	N.R.	Mild	None
Abdominal cramp	39 AV	3	47.93	10.00	Mild	Remote
	42 EW	15	342.83	144.00	Mild	Remote
Flatulence	01 AD	1	4.00	51.00	Mild	Possible
	24 WE	2	33.13	48.00	Mild	Possible
Diarrhoea	01 AD	18	N.R.	N.R.	Mild	Remote
	42 EW	16	N.R.	N.R.	Mild	Remote
Defaecation increased	39 AV	1	4.43	7.50	Mild	Possible

N.R. = Not Recorded

Appendix 6.4: (cont.)

Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)

B = Nolvadex® (ICI Americas Inc., U.S.A.)

B

Adverse Experience	Subject	Onset Day	Onset Scheme time (h)	Duration (h)	Intensity	Relationship
Tingling right hand	71 EH	1	2.57	10.00	Mild	None
Feebleness	05 RB	2	24.37	31.50	Mild	Remote
	72 RI	4	82.02	1.00	Mild	Remote
Fatigue	42 EW	15	N.R.	N.R.	Mild	Remote
Acute nasopharyngitis (common cold)	09 AB	15	335.07	N.R.	Mild	Remote
	15 JM	18	N.R.	N.R.	Mild	Remote
	18 MN	26	N.R.	N.R.	Mild	None
	29 NN	24	552.87	168.00	Mild	None
	39 AV	9	N.R.	N.R.	Mild	Remote
	65 RX	-1	-13.23	N.R.	Mild	None
	71 EH	5	94.23	578.50	Mild	Remote
Sore throat	58 HK	17	387.00	48.00	Mild	None
	71 EH	5	94.23	174.33	Mild	Remote
Pharyngitis	72 RI	32	754.52	N.R.	Moderate	None
Folliculitis left leg	72 RI	26	N.R.	N.R.	Mild	Remote
Pain on site of i.v. cannula	71 EH	1	2.57	10.00	Mild	None
Muscle pain	24 WE	18	N.R.	N.R.	Mild	None
Earache	72 RI	32	754.52	N.R.	Mild	None
Neck stiffness	42 EW	1	-1.25	73.08	Mild	None

N.R. = Not Recorded

Appendix 6.4: (cont.)

Adverse Experiences

Adverse experiences as reported after single dose administration of 20 mg tamoxifen as two 10 mg tablets

A = Tamoxifen Pharmachemie (Pharmachemie B.V., The Netherlands)
B = Nolvadex® (ICI Americas Inc., U.S.A.)

		B				
Adverse Experience	Subject	Onset		Duration	Intensity	Relationship
		Day	Scheme time (h)	(h)		
Toothache	25 AW	23	N.R.	N.R.	Mild	None
Acne increased	18 MN	9	N.R.	N.R.	Mild	Possible
Haematoma on site of venepuncture	25 AM	10	216.00	264.00	Mild	None

N.R. = Not Recorded

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-539
FIRM: Pharmachemic USA
Attention: Deborah A. Jaskot
U.S. Agent for Pharmachemie B.V.
TEVA Pharmaceuticals, USA
650 Cathill Road
Sellersville, PA 18960
DOSAGE FORM: Tablet
STRENGHT: 10 mg
DRUG: Tamoxifen Citrate

EER for acceptable 9/98 /S/

CGMP STATEMENT/EIR UPDATED STATUS:
An EER update was issued on August 30, 1994 for the listed firms. EER was found acceptable as per OC on April 3, 1997. An EER update has been submitted on or about August 26, 1998.

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:
Pharmachemie BV
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

The Tamoxifen Citrate nds is ——— by:

The ——— DMF #—— was most recently updated on 15-March-2000. The DMF Amendment was reviewed by this reviewer on 5-May-2000, and was found satisfactory.. No updates to the DMF have been received since the last review.

BIOEQUIVALENCY STATUS: Satisfactory. Office level Bioequivalence signoff occurred on 1/7/97.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Method validation by the District Laboratory is not required for the approval of the application. Pharmachemie's methods for drug product release (as indicated in the COA) are those described in the USP for the drug product.

Pharmachemie has submitted validation information for the —— method submitted for the drug product (refer to pp. 1152 - 1168) which included reproducibility, linearity, accuracy precision and limit of quantitation determinations.

The stability indicating nature of the —— Method #2 for the determination of impurities was assessed by stress testing of the drug product, and subsequent analysis. Detection and quantitation of ———

[redacted] testing was performed. Included in the validation studies were evaluations of linearity, precision, accuracy, reproducibility, resolution and stability.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? The product will be marketed in [redacted] bottles of 60 and 250 tablets as well as [redacted] holding prior to packaging.

Container/closure for 60s: [redacted] white, [redacted] bottle [redacted] #93200332) manufactured using [redacted]. Closure ([redacted] is a white, [redacted] (#93201264) using [redacted]

Container/closure for 250s [redacted] white, [redacted] bottle [redacted] #93200332) manufactured using [redacted] and [redacted] Closure ([redacted] is white, [redacted] (#93201264) using [redacted]

A [redacted] #93215025) inside a [redacted], #93400230). Pharmachemie uses the [redacted]

LABELING: The current labeling has been found satisfactory (refer to the 5/1/2000 Labeling Approval Summary of T. Watkins.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Pharmachemie has submitted a translation of the original Batch Manufacturing Record for Tamoxifen Citrate Tablets Exhibit Batch; Lot #92Z0702. The batch is a [redacted] tablet) batch size. The batch size meets the requirements of OGD. Pharmachemie has also submitted a blank Manufacturing Batch Record for a [redacted] tablet batch, which is identified as the production batch size. The exhibit batch was manufactured 8/4/92 and was used for the bio study and stability studies.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
The bioequivalence batches manufactured in support of these ANDA's were as described above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The production batch sizes for the 10 mg tablet will be ——— tablets.

Manufacturing process for intended production size batch is same as for the exhibit batch.

cc: ANDA #74-539
HFD-600/Reading File

Endorsements:
HFD-625/K.Furnkranz/5/5/00
HFD-625/M.Smela/5/9/00
x:\new\firmsnz\pharmach\ltrs&rev\74539a05.fkf
F/T by: gp/5/9/00

/S/ 5/12/00

/S/ 5/12/00

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:9/3/98

NAME/TITLE OF INDIVIDUAL(S): Hellen de Kloet
FIRM:Pharmachemie
PRODUCT NAME: Tamoxifen Citrate
TEL #: 5083930973
Reference:ANDA 74539

Notes of Conversation: I phoned in regard to the minor amendment dated 8/18/98. I referred to the T/A letter which stated that for full approval any CMC changes need to be included or a statement that no changes have been made and that the amendment did not have either of these. She referred to the "Release Statement" about updating before distribution of commercial batches. I stated this would not do and the information was needed before approval.

She agreed to address this issue in a Telephone Amendment with a fax copy to Ken Furnkranz within a day or two.

SIGNATURE OF OGD REPRESENTATIVES: /S/

Location of Electronic Copy:
X:\new\firmsnz\pharmach\telecons\090398

APPEARS THIS WAY
ON ORIGINAL

PHARMACHEMIE B.V.
HOLLAND

AUG 18 1998

Minor Amendment #11 - ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

TPL

NDA CMC AMENDMENT

Am

General Introduction

On April 3, 1997 the FDA granted tentative approval for ANDA 74-539 for Tamoxifen Citrate Tablets USP, 10 mg. A copy of this letter is included in this amendment.

Pharmachemie B.V. ("Pharmachemie") certified in its ANDA under 21 CFR §314.94 (a) (12) that the relevant patent (Patent No 4,536,516) was invalid and unenforceable and the patent holder brought suit for patent infringement within 45 days of receipt of the notice.

According to 21 CFR §314.107 (b)(3) approval of an ANDA may be made effective 30 months after the date of the receipt of the notice of certification by the patent holder unless the court has extended this period. No such extension has been obtained.
The patent holder received the notice on February 14, 1996.
As FDA is aware, Barr Laboratories, Inc. has asserted a claim to 180-day exclusivity for its own ANDA for this product under section 505(j)(5)(B)(iv) of the Act (Docket No. 98P/0493). Barr's claim, however, is without merit, as explained in the detailed comments submitted by Pharmachemie on the Barr petition.
Accordingly, and given the fact that the 30-month stay of final approval under 21 CFR §314.107(b)(3) expired on August 14, 1998, Pharmachemie believes that its ANDA No 74-539 can now be given final approval effective immediately.

Notice to the PO, Zeneca Limited was rec'd 2/27/96. cl
Calculate the 30 month period to expire 8/27/98.

/S/
8/25/98

Draft approval letter, application will be held until General Counsel can give opinion on Barr's claim to 180 day exclusivity.

RECEIVED
AUG 19 1998
GENERIC

/S/
8/25/98

/S/
8/25/98

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-539

FIRM: Pharmachemic USA
Attention: Mr. J. David Hayden
P.O.Box 145
Oradell, NJ 07649

DOSAGE FORM: Tablet

STREGHTH: 10 mg

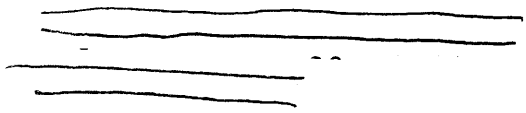
DRUG: Tamoxifen Citrate

CGMP STATEMENT/EIR UPDATED STATUS:
An EER was issued 5/95 for the listed firms. EER was found acceptable as per OC on 10/10/96.

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:

Pharmachemie BV
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

The Tamoxifen Citrate nds is ——————— by:



The ——————————— #——— was most recently updated on 31-Oct-1996. The DMF Amendment was reviewed by this reviewer on 18-November-1996, and was found satisfactory at that time. The COMIS system was checked on 4-Mar-1997, and no updates to the DMF have been received since the last review.

BIOEQUIVALENCY STATUS: Satisfactory. Office level Bioequivalence signoff occurred on 1/7/97.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Method validation by the District Laboratory is not required for the approval of the application. Pharmachemie's methods for drug product release (as indicated in the COA) are those described in the USP for the drug product.

Pharmachemie has submitted validation information for the ——— method submitted for the drug product (refer to pp. 1152 - 1168) which included reproducibility, linearity, accuracy precision and limit of quantitation determinations.

The stability indicating nature of the [redacted] Method #2 for the determination of impurities was assessed by stress testing of the drug product, and subsequent analysis. Detection and quantitation of [redacted] testing was performed. Included in the validation studies were evaluations of linearity, precision, accuracy, reproducibility, resolution and stability.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? The product will be marketed in [redacted] bottles of 60 and 250 tablets as well as [redacted]

Container/closure for 60s: [redacted] white, [redacted] bottle [redacted] #93200332) manufactured using [redacted] Closure [redacted] is a white, [redacted] (#93201264) using [redacted]

Container/closure for 250s [redacted] white, [redacted] bottle [redacted] #93200332) manufactured using [redacted] Closure [redacted] is a white, [redacted] (#93201264) using [redacted]

[redacted] A [redacted] #93215025) inside a [redacted], #93400230). Pharmachemie uses the [redacted]

LABELING: Satisfactory as per C. Holquist/J. Grace on 2/28/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Pharmachemie has submitted a translation of the original Batch Manufacturing Record for Tamoxifen Citrate Tablets Exhibit Batch; Lot #92Z0702. The batch is a [redacted] tablet) batch size. The batch size meets the requirements of OGD. Pharmachemie has also submitted a blank Manufacturing Batch Record for a [redacted] tablet batch, which is identified as the production batch size. The exhibit batch was manufactured 8/4/92 and was used for the bio study and stability studies.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
The bioequivalence batches manufactured in support of these ANDA's were as described above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The production batch sizes for the 10 mg tablet will be [redacted] tablets.

Manufacturing process for intended production size batch is same as for the exhibit batch.

cc: ANDA #74-539
HFD-600/Reading Fil
HFD-625/KFurnkranz

/S/ 3/4/97

x:\new\firmsnz\pharmach\ltrs&rev\74539app.sum

/S/ 3/6/97

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

DATE: December 11, 1996

FROM: **Supervisory Chemist, Drug Chemistry Branch**
Northeast Regional Laboratory, HFR-NE560

SUBJECT: **ANDA 74-539: Tamoxifen Citrate Tablets**
Pharmachemie, Haarlem, Netherlands
Astra, Westborough, MA 01581

TO: Kenneth Furnkranz, Review Chemist
Office of Generic Drugs, CDER, HFD-625

The analysis of Tamoxifen Citrate Tablets was performed by the Northeast Regional Laboratory using the firm's method and the sample provided. The results of that analysis are listed below.

	Results	Limits
Assay:	[redacted]	[redacted]
Dissolution:	[redacted]	Q = [redacted]
Content Uniformity:	90.4 - 101.8% ave = 97.2% , RSD = 4.0%	85.0 - 115.0% RSD = or < 6.0%
Identification: [redacted]	Complies	[redacted]
[redacted]	Complies	
Retention time [redacted]	Complies	
[redacted]	Complies	

No analytical problems were encountered in performing the analysis of this product using the firm's method. All analytical results were within the specifications. The method appears to be suitable for regulatory analysis of this product.

/S/

Ella S. Walker

MINUTES OF PHONE CALL

DATE: March 19, 1997

SUBJECT: ANDA 74-539, Tamoxifen Citrate Tabs

ORGANIZATION: Pharmachemie USA

PARTICIPANTS: Allen Rudman
Helen Dekloet

I contacted the firm and asked for David Hayden, but instead was put in contact with Helen Dekloet. She informed me that David Hayden was no longer the representative and that all further correspondence should be sent to her at the following address: 323 Davis Street, North Boro MA 01532. She was informed that the parent company would have to inform the FDA of this new information.

She was also asked to clarify how the expiry date was going to be applied to the product, given that there was a [redacted]. Would the expiry date be based on the date of manufacturer or the date that the product was [redacted] container listed on the label. Ms. Dekloet said that she would contact the parent company and let me know. She was informed that the information could be sent in as a fax amendment along with the change of US agent to expedite the approval. For other application a correspondence letter of the US agent change would be satisfactory.

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-539** Date of Submission: **February 19, 1997**

Applicant's Name: **Pharmachemie B.V.**

Established Name: **Tamoxifen Citrate Tablets USP, 10 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: September 18, 1996 (60s and 250s).

Carton Labeling: September 18, 1996 (1 x 60s and 1 x 250s).

Professional Package Insert Labeling:
February 19, 1997 (Rev. January 1997).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Nolvadex®

NDA Number: 17-970

NDA Drug Name: Nolvadex®

NDA Firm: Zeneca Pharmaceuticals

Date of Approval of NDA Insert and supplement #:
November 15, 1996/S-035, 034, 033, 032
Has this been verified by the MIS system for the NDA?
Yes
Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Nolvadex® labels in file folder.

Basis of Approval for the Carton Labeling: Nolvadex® labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the labeling of Nolvadex (Approved November 15, 1996; Revised 3/96 - S-035). The CLINICAL PHARMACOLOGY section was revised to delete the last paragraph prior to Clinical Studies because it compared 20 mg tablet to 10 mg tablet and this firm is only marketing the 10 mg tablet.

2. There is one patent remaining on Nolvadex which expires 8/20/02. No exclusivities remain. Pharmachemie

intends to market upon expiration of the patent.

3. Storage/Dispensing

   ANDA - Store at controlled room temperature: 15°-30°C (59°-86°F). Dispense in a well-closed, light-resistant container.

   NDA - Store at room temperature; avoid excessive heat (over 104°F, 40°C).

   USP - Preserve in well-closed, light-resistant containers.

4. Both Pharmachemie's and Zeneca's tablets are unscored.

5. Both the NDA and the ANDA have container sizes of 60s (CRC) and 250s.

6. All inactives are listed in the DESCRIPTION section of the package insert. See page 32 in Chem 4 of the January 26, 1996 submission.

7. The tablet description in the HOW SUPPLIED section of the insert is correct. See page 94 in section XI of the January 26, 1996 submission.

8. Bio acceptable on January 15, 1997.

Date of Review: February 26, 1997

Date of Submission: February 19, 1997

Primary Reviewer: /S/ **Date:** 2/28/97

Secondary Reviewer: /S/ **Date:** 2/28/97

Team Leader: /S/ **Date:** 2/28/97

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cc:

ANDA 74-539
DUP/DIVISION FILE
HFD-613/CHolquist/AVezza/JGrace (no cc)
njg/2/28/97/X:\NEW\FIRMSNZ\PHARMACH\LTRS&REV\74539AP.L
Review

RECORD OF TELEPHONE CONVERSATION

I telephoned J. David Hayden to inform him of the labeling deficiencies for this application. He was unavailable. I explained to his secretary that I was faxing the deficiencies and if he had any questions to call me. I also included instructions to submit the revisions as a telephone amendment.

APPEARS THIS WAY ON ORIGINAL

DATE
1/13/97

ANDA NUMBER
74-539

IND NUMBER

TELECON

INITIATED BY APPLICANT/SPONSOR

MADE X BY TELE.

X FDA

_ IN PERSON

PRODUCT NAME
Tamoxifen Citrate

FIRM NAME
Pharmachemie B.V.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
J. David Hayden

TELEPHONE NUMBER
201-265-1942

SIGNATURE
/S/

RECORD OF TELEPHONE CONVERSATION

I was requested to call the firm with the labeling deficiencies because the chemist had only one deficiency and was going to call the firm. I spoke with Mr. Hayden. I explained we had sent a labeling only letter to him in September with the same deficiencies I put in my review. He said he didn't remember getting the letter. He requested I fax him a copy of the deficiencies again. I did. The following day he called back and explained he did forward that letter to the company and they were working on FPL. He explained they are slow in printing and would send as soon as it was available.

APPEARS THIS WAY
ON ORIGINAL

DATE
10/10/96

ANDA NUMBER
74-539

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X

MADE BY TELE. _

X **FDA**

_ **IN PERSON**

PRODUCT NAME
Tamoxifen Citrate

FIRM NAME
Pharmachemie

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
J. David Hayden
US Agent

TELEPHONE NUMBER
(202) 265-1942

SIGNATURE
/S/

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: September 25, 1996

Date of Submission: September 18, 1996

Primary Reviewer: Carol Holquist

Secondary Reviewer: John Grace

ANDA Number: 74-539

Review Cycle: 3 - FPL Container labels, Carton labeling and Draft insert labeling

Applicant's Name [as seen on 356(h)]: Pharmachemie B.V.

Manufacturer's Name (If different than applicant): Same

Established Name: Tamoxifen Citrate Tablets USP, 10 mg

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

B. LABELING DEFICIENCIES

1. CONTAINER (60s and 250s)

Satisfactory in final print.

2. CARTON (1 x 60s and 1 x 250s)

Satisfactory in final print.

3. INSERT

Due to changes in the labeling of the listed drug (Nolvadex; Zeneca Pharmaceuticals; Approved March 26, 1996, Revised January 1996), revise your insert as follows:

a. DESCRIPTION

Revise the chemical name as follows:

...[*p*...phenoxy)-*N*, N...

[Note: *Italics*]

b. CLINICAL PHARMACOLOGY

Clinical Studies

i. Revise the section heading to read "Clinical Studies".

[Note: Decrease in prominence.]

ii. Revise paragraph seven to read as follows:

NSABP B-14, a prospective, double-blind, randomized study, women with axillary node-negative, estrogen-receptor positive(≥ 10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

With four years of follow-up after this re-randomization, 92% of the women that received five years of tamoxifen alive and disease-free, compared to 86% of the women scheduled to receive 10 years of tamoxifen. This difference was not statistically significant. One additional...

c. WARNINGS

i. Paragraph 4 - Delete from the fourth sentence.

ii. Add the following text as the seventh paragraph:

[redacted]

d. PRECAUTIONS

i. General - Revise paragraph one to read as follows:

Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe.

ii. Drug Interactions - Insert the following text as the second paragraph:

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen.

e. ADVERSE REACTIONS

i. Revise paragraph five as follows:

...hair loss and vaginal dryness.

ii. Revise paragraph seven as follows:

[redacted]

iii. Delete '[redacted]' from the first sentence of paragraph nine.

f. DOSAGE AND ADMINISTRATION

i. Revise paragraph one to read as follows:

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

ii. Revise paragraph two to read as follows:

...or three (Toronto) times a day for two years.

[redacted] Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit(see CLINICAL PHARMACOLOGY).

[redacted]

Please revise your labels and labeling, as instructed above, and submit final printed container labels, carton and insert labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Nolvadex

NDA Number: 17-970

NDA Drug Name: Nolvadex

NDA Firm: Zeneca Pharmaceuticals

Date of Approval of NDA Insert and supplement #: March 26, 1996/S-034

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Nolvadex labels in file folder.

Basis of Approval for the Carton Labeling: Nolvadex labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23 and Supplement #3.	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	

Is this package size inadequate? Prevention Act may require a CRC			
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate. Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the labeling of Nolvadex (Approved January 23, 1996; Revised 3/95) with the changes noted in S-034 approved March 26, 1996.

2. There is one patent remaining on Nolvadex which expires 8/20/02. No exclusivities remain. Pharmachemie intends to market upon expiration of the patent.

3. Storage/Dispensing

   ANDA - Store at controlled room temperature: 15°-30°C(59°-86°F). Dispense in a well-closed, light-resistant container.

NDA - Store at room temperature; avoid excessive heat (over 104°F, 40°C).

USP - Preserve in well-closed, light resistant containers.

4. Both Pharmachemie's and Zeneca's tablets are unscored.

5. Bottles of 60s have CRC.

7. All inactives are listed in the DESCRIPTION section of the package insert. See page 32 in Chem 4 of this submission.

8. The tablet description in the HOW SUPPLIED section of the insert is correct. See page 94 in section XI of this submission.

9. We sent a labeling letter out to inform them of the labeling changes but they did not amend with the revised labeling. Therefore, I chose to reiterate the revisions. After discussion with John Grace - We will not put these comments in the letter again.

/S/

Primary Reviewer

Date

/S/

Team Leader
Labeling Review Branch

Date 10/2/96

cc: /S/ 10/30/96

ANDA 74-539
HFD-613/CHolquist/AVezza/JGrace (no cc)
9/25/96/firmsnz/pharmach/ltrs&rev/74539NA3.L
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-539

CORRESPONDENCE

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

April 27, 2000

NEW CORRESP
NC

Gary Buehler, Acting Director
Office of Generic drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 74-539
TAMOXIFEN CITRATE TABLETS USP, 10 mg
NEW CORRESPONDENCE - REVISED EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

In accord with a telephone request by Theresa Watkins earlier today, we submit herewith a revised exclusivity statement for the above referenced tentatively approved ANDA. This revised statement addresses the exclusivity I-244 which covers the indication to _____. The labeling included in our ANDA does not include reference to this indication and will not until such time as the exclusivity is expired; October 29, 2001.

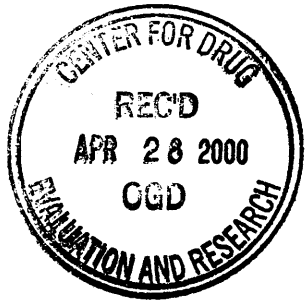
This information is submitted for your review and final approval of ANDA 74-539. Please feel free to telephone me should you have additional questions at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

Deborah Jaskot
Authorized U.S. Agent for
Pharmachemie B.V.

Enclosure
cc: Pharmachemie B.V.



TEVA

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
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Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

April 18, 2000

NDA ORIG AMENDMENT
N/A M

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ANDA #74-539
TAMOXIFEN CITRATE TABLETS USP, 10 mg
MINOR AMENDMENT - RESPONSE TO 4/13/00 REQUEST FOR 90 DAY AMENDMENT

Dear Mr. Buehler:

In accord with a telephone request by Pat BeersBlock and Michelle Dillahunt of the Office of Generic Drugs on April 13, 2000, we submit herewith a minor amendment to the above-referenced tentatively-approved ANDA. As requested, this amendment constitutes a 90-day amendment for this file. Please note that at this time, there are no updates to be made to this pending ANDA.

This information is submitted for your review and approval of ANDA #74-539. Please feel free to contact me should you have any questions at (215) 256-8400 extension 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/jbp
Enclosures

cc: Pharmachemie B.V.

CENTER FOR DRUG
REC'D
APR 19 2000
OGD
EVALUATION AND RESEARCH

/S/ 4-21-00

PCH

PCH NEDERLAND

Pharmachemie bv
Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 (0)23 5 147 147
Fax +31 (0)23 5 312 879

ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank No. 18 89 85

NEW CORRESP

NC

Office of Generic Drugs
Centre for Drug Evaluation and Research Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2775

DATE November 1, 1999
REFERENCE B.99.469
BEHANDELD DOOR Dr. J.G.C. Omtzigt
TELEPHONE +31 23 5 147 271
SUBJECT Change in responsible agent
ENCLOSURES

Dear Sir, Madam,

This is to inform the FDA that Pharmachemie BV, Haarlem, The Netherlands, authorizes:

Ms. Deborah A. Jaskot
TEVA U.S.A. Inc.
1510 Delp Drive
Kulpsville, PA 19443
telephone number: : 215 256 8400
fax number : 215 256 8105

to act as responsible agent in connection with all matters relating to Pharmachemie BV.

Ms. Deborah A. Jaskot will replace our former agent:
Ms. Hellen de Kloet
Pharmachemie U.S.A. Inc.
1510 Delp Drive (Teva Building)
Kulpsville, PA 19443

PCH

We officially authorize Ms. Deborah A. Jaskot, TEVA U.S.A. Inc. to act as agent for Pharmachemie B.V., Haarlem, The Netherlands. In this function as representative for Pharmachemie BV she is authorized to perform all correspondence with the Food and Drug Administration relating to the following files:

Tamoxifen Citrate Tablets USP, 10 mg	ANDA No: 74-539
Tamoxifen Citrate Tablets USP, 20 mg	ANDA No: 74-858

Sincerely Yours,
PHARMACHEMIE B.V.

Biense Th. Visser
President

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-539

MAR 9

Pharmachemie USA, Inc.
Attention: Hellen de Kloet
U.S. Agent for: Pharmachemie B.V.
323 Davis Street
Northborough, MA 01532

Dear Madam:

This is in reference to your abbreviated new drug application dated August 26, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tamoxifen Citrate Tablets USP, 10 mg (base).

Reference is also made to our Tentative Approval letter for this application dated April 3, 1997, and to your amendments dated August 18, and September 4, 1998. You have stated in your August 18, 1998 amendment that the 30-month period provided for under 21 CFR 314.107(b)(3) was not extended by the court and that the 30-month period has expired. Based upon that finding, you have requested that this application be approved.

We have completed the review of this abbreviated application as amended, and have concluded that based upon the information you have presented to date, the drug product continues to be regarded as safe and effective for use as recommended in the submitted labeling. However, the application remains **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is therefore subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application, Nolvadex Tablets of Zeneca Pharmaceuticals, is subject to a period of patent protection which expires on August 20, 2002 (U.S. Patent 4,536,516 [the '516 patent]). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the '516 patent is invalid or unenforceable. Section 505 (j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action for patent infringement is brought before the expiration of forty-five days from the date the notice provided

under paragraph (2)(B)(I) is received by both the new drug application (NDA) and patent holders. You have notified the Agency that Pharmachemie B.V. (Pharmachemie) has complied with the requirements of Section 505(j)(2)(B) of the Act, and that an action for patent infringement was initiated against Pharmachemie within 45-days of receipt of the notice in the United States District Court for the District of Maryland (Zeneca Limited v. Pharmachemie B.V., Civil Action No. S96-884). You have also notified the Agency that the litigation was subsequently moved from the District of Maryland to the District of Massachusetts (Civil Action No. 96-12413-RCL). Your August 18, 1998, amendment requests the agency to approve the application based upon the expiration of the 30-month period provided for in 21 CFR 314.107(b)(3).

However, the Act also provides that approval of an abbreviated application that contains a certification described in Section 505(j)(2(A)(vii)(IV) (a "Paragraph IV Certification"), and that is for a drug product for which a previous abbreviated application has been submitted which also contains a Paragraph IV Certification, shall be made effective not earlier than one hundred and eighty (180) days after:

a. the date the Secretary receives notice of the first commercial marketing of the drug under the previous application, or

b. the date of a final decision of a court holding the '516 patent which is the subject of the certification to be invalid or not infringed, whichever event occurs first (Section 505(j)(5)(B)(iv).

Please note that an abbreviated application for Tamoxifen Citrate Tablets, USP containing a Paragraph IV Certification was accepted for filing by this office prior to the filing of your application. Accordingly, your application will be eligible for final approval beginning on the date that is one hundred and eighty (180) days after the first commercial marketing of the drug product under the previous application, or the date of a final court decision described under Section 505(j)(5)(B)(iv), whichever is earlier. We refer you to the Agency's recently published guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

In confirmation of the above, we refer you to the agency's response dated March 2, 1999, to a Citizens Petition (Docket No. 98P-0493/PSA1&RC1) in which the agency has agreed with the petitioner to stay the effective date of approval of any ANDA for Tamoxifen Citrate Tablets, USP other than the one submitted by Barr Laboratories, Inc., until 180 days after the date of the first commercial marketing of the drug product under Barr's ANDA, or the date of a final decision of a court holding the tamoxifen patent to be invalid or not infringed.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60-days but not more than 90-days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product received this second tentative approval, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Alternatively and if applicable, this amendment should also be submitted to state that no changes were made to the terms of the application since the date of this second tentative approval. This amendment should be designated clearly in your cover letter as a MINOR amendment. In addition to, or instead of this amendment, the Agency may request at any time prior to the date of final approval of this application that you submit an amendment containing the information described above. Failure to submit either or, if requested, both amendments, may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list, commonly referred to as the "Orange Book".

Prior to submitting the amendment(s), please contact Denise Huie, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

/S/

2/9/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

323 Davis Street
Northborough
Massachusetts 01532
Telephone: (508) 393-0973
Fax: (508) 393-0974
email: pchusa@gis.net

PHARMACHEMIE U.S.A., INC.

telefax message

To	: Office of Generic drugs
Attn	: Mr. Ken Furnkranz
Faxnumber	: 1 301 594 0180
From	: Hellen de Kloet
Date	: September 04, 1998
Subject	: **Telefax Amendment #12** **Response on Telephone Request: additional statement** **Tamoxifen Citrate Tablets 10 mg, ANDA 74-539**
Cc	:
Number of pages	: 4 (including this page)

Dear Mr. Furnkranz,

Attached to this message is Pharmachemie B.V.'s Telefax Amendment #12 in response to your September 03, 1998 Telephone Request. The signed form 356h as well as the requested statement is included in this amendment.

The hard copy will be sent to you by mail today.

Please contact me if I can be of service to you.

Sincerely,

Ms. Hellen de Kloet
Vice President
Medical & Regulatory Affairs

323 Davis Street
Northborough
Massachusetts 01532
Telephone: (508) 393-0973
Fax: (508) 393-0974
email: pchusa@gis.net

PHARMACHEMIE U.S.A., INC.

September 04, 1998

NDA ORIG AMENDMENT
N / AM

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: Telefax Amendment #12
ANDA 74-539 Tamoxifen Citrate Tablets 10 mg.

This message was sent to you by telefax on September 04, 1998.

Dear Sir/Madam,
Enclosed in duplicate is Pharmachemie B.V.'s Telefax Amendment #12 in response to your September 03, 1998 telephone call.

A third copy - Field Copy - is also enclosed and is certified to be a "true' copy of the submission.

Please contact me if I can be of service to you.

Sincerely,

Ms. Hellen de Kloet
Vice President
Medical & Regulatory Affairs

RECEIVED
SEP 08 1998
GENERIC DRUGS

NB: could you please confirm receipt

Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 879
Telex 41879 phchm nl
ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 18 89 85

PHARMACHEMIE BV

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Date: March 21st, 1997
Ref.: avk/465.97

SUBJECT: Tamoxifen Citrate Tablets USP, 10 mg
ANDA 74-539 - Telefax amendment #10

Dear Sir, Madam,

Please refer to our ANDA 74-539 for Tamoxifen Citrate Tablets USP, 10 mg, submitted on August 26th, 1994, and accepted for filing on December 6th, 1994, and to our amendments dated November 16th, 1995; January 19th, 1996; February 8th, 1996; April 26th, 1996; September 10th, 1996; October 15th, 1996, October 22nd, 1996; November 6th, 1996; December 20th, 1996, February 17th, 1997 and to your telefone request of March 19th, 1997.

Enclosed herewith is an telefax amendment to the application containing our response to your telefone request of March, 19th, 1997.

Thank you for your kind attention to this matter.

Sincerely yours,
PHARMACHEMIE B.V.

Dr. J.B.M.M. van Bree
Director Regulatory Affairs

04

Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 879
Telex 41879 phchm nl
ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 18 89 85

PHARMACHEMIE BV

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Date : March 14th, 1997
Ref. : mw.0422.97

Subject: CHANGE IN RESPONSIBLE AGENT
Product: ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

Dear Sir, dear Madam,

This is to inform the FDA that Pharmachemie B.V., Haarlem, The Netherlands, authorizes:

Ms. Hellen de Kloet, Vice President
Pharmachemie U.S.A. Inc.
323 Davis Street
Northborough, MA 01532
telephone number: 508 393 0973
fax number: 508 393 0974

to act as responsible agent in connection with all matters relating to Pharmachemie B.V.

Ms. De Kloet will replace our former agent:

Mr. J.D. Hayden, President
Pharmachemie U.S.A. Inc.
338 Country Club Drive
Oradell, New Jersey 07649

Ms. De Kloet has been authorized to act on behalf of Pharmachemie B.V. in communications with the U.S. Food and Drug Administration (FDA).

We officially authorize Ms. De Kloet, Pharmachemie U.S.A., Inc. to act as agent for Pharmachemie B.V., Haarlem, The Netherlands. In this function as representative for Pharmachemie B.V. she will correspond with the FDA concerning ANDA 74-539 for Tamoxifen Citrate Tablets USP, 10 mg and may receive all correspondence from the Food and Drug Administration relating to this file.

Sincerely yours,
PHARMACHEMIE B.V.

RECEIVED
MAR 17 1997
GENERIC DRUGS

A.J. Nykerk
Senior Vice President, Product Development

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

February 19, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Division of Labeling and Program Support
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Mr. Jerry Phillips

Dear Mr. Phillips:

SUBJECT: Telephone Amendment #9
ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Telephone Amendment #9 in response to your fax of January 13, 1997.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. van Bree

ANDA 74-539

JAN 15

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
U.S. Agent for: Pharmachemie BV
338 Country Club Drive
Oradell NJ 07649

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Tamoxifen Citrate Tablets USP, 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

NDA ORIG AMENDMENT

AF

December 30, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

SUBJECT: Amendment #8
ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Amendment #8 in response to your September 13 and October 10, 1996 letters.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. van Bree

RECEIVED
DEC 31 1996
GENERIC DRUGS

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

ORIGINAL

PHARMACHEMIE U.S.A., INC.

November 13, 1996

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Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Mr. Furnkranz

Dear Mr. Furnkranz:

SUBJECT: Minor Amendment #7
ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Minor Amendment #7 in response to your November 1, 1996 telephone request.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. van Bree

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

CP
NEW CORRESP
NC/B

November 1, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
NOV 0 4 1996
GENERIC DRUGS

Dear Sir/Madam:

SUBJECT: Amendment #6
ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Amendment #6 in response to the April 23, 1996 letter from the FDA.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. van Bree

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

October 23, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Mr. Furnkranz/Mr. Cmela

Dear Messrs. Furnkranz and Cmela:

SUBJECT: Telephone Amendment to Amendment #5
ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Telephone Amendment to Amendment #5 in response to your October 11, 1996 request.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. van Bree

ANDA 74-539

Pharmachemie USA, Inc.
Attention: J. David Hayden
P.O. Box 145
Oradell, NJ 07649

SEP 13 1996

Dear sir:

This is in reference to your abbreviated new drug application dated August 26, 1994 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tamoxifen Citrate Tablets USP, 10 mg.

Reference is made to our not approvable letter of June 18, 1996.

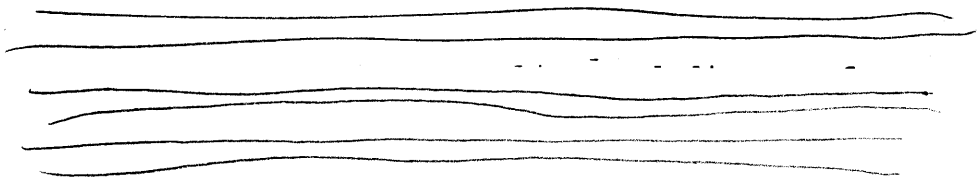
The following comments pertain to labeling deficiencies only.

In addition to the comments regarding your insert labeling in our letter of June 18, 1996, revise your insert labeling to be in accord with changes in the labeling of the listed drug (Nolvadex; Zeneca Pharmaceuticals; Approved March 26, 1996, Revised January 1996), as follows:

1. CLINICAL PHARMACOLOGY

Clinical Studies - Revise paragraph seven to read as follows:

NSABP B-14, a prospective, double-blind, randomized study, [redacted] women with axillary node-negative, estrogen-receptor positive(≥ 10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, a significant improvement in disease-free survival was demonstrated in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50. [redacted]



2. WARNINGS

Paragraph 4 - Delete [redacted] ' from the fourth sentence.

3. PRECAUTIONS

a. General - Revise paragraph one to read as follows:

Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe.

b. Drug Interactions - Insert the following text as the second paragraph:

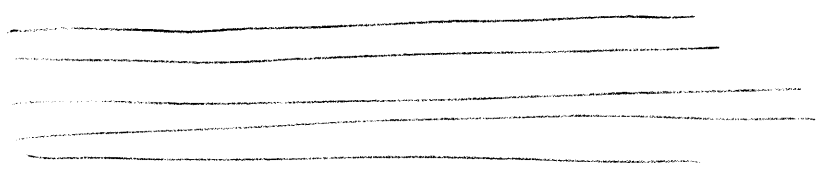
There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen.

4. ADVERSE REACTIONS

a. Revise paragraph five as follows:

...hair loss and vaginal dryness.

b. Revise paragraph seven as follows:



c. Delete " [redacted] from the first sentence of paragraph nine.

5. DOSAGE AND ADMINISTRATION

a. Revise paragraph one to read as follows:

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

b. Revise paragraph two to read as follows:

...or three (Toronto) times a day for two years.

Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see CLINICAL PHARMACOLOGY).

Please revise your package insert labeling, and submit in final print with your amendment to our June 18, 1996, letter. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with the differences annotated and explained.

This letter addressed unique issues involving only labeling. Again, we refer you to our letter of June 18, 1996, for the requirements to reopen the file on this application.

Sincerely yours,

9/13/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 879
Telex 41879 phchm nl
ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 18 89 85

PHARMACHEMIE BV

AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Date: September 10th, 1996
Ref.: mw.250.96

SUBJECT: Tamoxifen Citrate Tablets USP, 10 mg
ANDA 74-539 - Minor Amendment

Dear Sir, Madam,

Please refer to our ANDA 74-539 for Tamoxifen Citrate Tablets USP, 10 mg, submitted on August 26th, 1994, and accepted for filing on December 6, 1994, and to our amendments dated November 16th, 1995, January 19th, 1996, February 8th, 1996 and April 26th, 1996 and to your letter of June 18th, 1996 outlining deficiencies in the application.

Enclosed herewith is an amendment to the application containing our response to your June 18th, 1996 letter. We have attempted to respond to each question and request in your letter completely and clearly, but please do not hesitate to call if there are any remaining issues.

Lastly, please note that the Paragraph IV Patent Certification and Exclusivity Statement submitted as part of Amendment No. 3 on February 8, 1996 with respect to this abbreviated new drug application contained an incorrect date for the prior Paragraph III Certification that was being amended. As the file reflects, the correct date of the prior certification is October 10th, 1994.

Thank you for your kind attention to this matter.

Sincerely yours,
PHARMACHEMIE B.V.

A.J. Nykerk
Senior Vice President
Product Development

isi 96-678

Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 879
Telex 41879 phchm nl
ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 18 89 85

PHARMACHEMIE BV

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Date: September 10th, 1996
Ref.: mw.251.96

SUBJECT: LETTER OF AUTHORIZATION FOR RESPONSIBLE AGENT

Dear Sir, Madam,

We officially authorize Mr. J. David Hayden, President, PHARMACHEMIE U.S.A., INC. to act as agent for PHARMACHEMIE B.V., Haarlem, The Netherlands. In this function as representative for Pharmachemie B.V. he will file the amendment to ANDA 74-539 for Tamoxifen Citrate Tablets USP, 10 mg, and may receive all correspondence from the Food and Drug Administration relating to this file.

Thank you for your attention to this matter.

Sincerely yours,
PHARMACHEMIE B.V.

A.J. Nykerk
Senior Vice President
Product Development

ANDA 74-539

Pharmachemie USA, Inc.
Attention: J. David Hayden
P.O. Box 145
Oradell, NJ 07649

JUN 18 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated August 26, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tamoxifen Citrate Tablets USP, 10 mg.

Reference is also made to your amendments dated December 28, 1994, December 6, 1995 and January 26, February 12, and May 13, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. [redacted]

B. Labeling Deficiencies:

1. GENERAL COMMENT

We note that you have listed "Pharmachemie USA Inc." on all labels and labeling without any of the qualifying statements defined in 21 CFR 201.1. Based on previous discussions with J. David Hayden of "Pharmachemie USA, Inc,", we are aware that Pharmachemie USA, Inc. is not a distributor for your product. We are also aware that the final printed model labels and labeling for your products include a Pharmachemie BV logo, and the inclusion of Pharmachemie USA is an attempt to meet our former requirements to include a US address. We have reconsidered our position on this and we no longer require a US address. On this basis please delete "Pharmachemie USA" from all labels and labeling.

2. CONTAINER (60s and 250s)

See GENERAL COMMENT.

3. CARTON (1 x 60s and 1 x 250s)

a. See GENERAL COMMENT.

b. Increase the prominence of the strength and relocate it so it appears in conjunction with the established name.

c. Correct the spelling of "from" in the temperature storage recommendations on the 250 count carton.

4. INSERT

a. DESCRIPTION

i. Inactive Ingredients

A) Alphabetize the listing of the inactive ingredients.

B) Revise to read "lactose, monohydrate" rather than '[illegible]'

ii. Replace [illegible]" with "molecular" and include the molecular formula.

iii. To be in accord with USP 23, revise the molecular weight to read '[illegible]' rather than "563.62".

iv. Revise the chemical name to read the same as the second name listed in USP 23.

b. ACTIONS/CLINICAL PHARMACOLOGY

i. Revise the section heading to read:

CLINICAL PHARMACOLOGY

ii. Revise paragraph five to read as follows:

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration for N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic...tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for three months are 122 ng/mL (range 71-183 ng/mL) and 353 ng/mL (range 152-706 ng/mL) respectively. After initiation of therapy steady state

concentrations for tamoxifen are achieved in about 4 weeks and steady state concentrations...

iii. Clinical Studies

A) Decrease the prominence of this subsection heading to be consistent with the other subsection headings throughout the insert.

B) Paragraph one, line 9 - Revise to read "trials" rather than "[redacted] .

C) Paragraph three, line 7 - Revise to read "poor" rather than "[redacted]

c. INDICATIONS AND USAGE

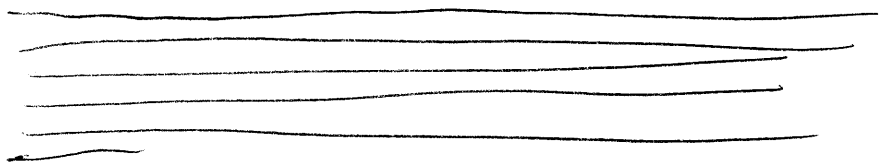
Revise to read "[redacted]," rather than "tamoxifen".

d. CONTRAINDICATIONS

Tamoxifen [redacted] is...

e. WARNINGS

i. Revise paragraph four to read:



ii. Begin a new paragraph with the following sentence:

Tamoxifen has been associated with changes...

iii. Pregnancy Category D - Italicize "*in utero*" throughout this subsection. [4 places]

f. PRECAUTIONS

i. Relocate "Drug Interactions" subsection to appear after "Laboratory Tests" subsection.

ii. Mutagenesis - Italicize "*in vitro*" throughout this subsection. [3 places]

iii. Impairment of Fertility, penultimate sentence ...another study where significance...

g. ADVERSE REACTIONS

i. Fifth paragraph - ...seen infrequently... [Note: "infrequently" rather than " [redacted].

ii. Replace [redacted] with "women" in the following places:

Ninth paragraph - first sentence and the eleventh paragraph - first and last sentences.

iii. Tenth paragraph, last sentence - ...was not significantly different...

iv. Revise the last paragraph to read as follows:

.. [redacted]

h. DOSAGE AND ADMINISTRATION

First paragraph - .. [redacted]

i. HOW SUPPLIED

i. Indicate that your tablets are unscored.

ii. Revise to read:

Tamoxifen Citrate Tablets (equivalent to 10 mg of tamoxifen) are round, biconvex...on the other side and are supplied in bottles of 60s and 250s.

iii. Revise to read "Tam 10" rather than [redacted].

iv. We encourage the inclusion of your NDC numbers.

v. Include the temperature storage recommendations as seen on your container labels.

j. Include the "manufactured by" statement.

k. Include the date of the latest revision of the insert.

Please revise your labels and labeling, as instructed above, and submit final printed container labels, carton and draft insert labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

C. In addition to responding to these deficiencies, please note and acknowledge the following in your response:

> Satisfactory evaluation of the CGMP compliance of the facilities listed in your application is required prior to the approval of your ANDA.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 6/19/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

May 13, 1996

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

SUBJECT: Amendment #4
ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Amendment #4 which contains a statement certifying that a notice of non-infringement of a patent has been received by Zeneca Limited and Zeneca Inc.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk

ANDA 74-539

APR 23 1996

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
U.S. Agent for: Pharmachemie BV
P.O. Box 145
Oradell, NJ 07649

Dear Sir:

Reference is made to the bioequivalence amendment submitted on December 6, 1995, for Tamoxifen Citrate Tablets USP, 10 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

> Data should be submitted to support the long term stability of tamoxifen and N-desmethyltamoxifen, i.e., the stability in frozen study samples for the period equal to the time from the day the plasma samples were collected to the day the last sample was analyzed (3 months).

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

P.O. Box 145.
Cradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

NEW CORRESP
NC Noted WAI 2/22/96
/S/

RECEIVED

FEB 13 1996

GENERIC DRUGS

February 12, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

SUBJECT: **AMENDMENT #3**
ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Amendment #3 regarding revised patent certification.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden nap

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

January 26, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

SUBJECT: **AMENDMENT #2**
ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is Pharmachemie B.V.'s Major Amendment #2 in response to the June 6, 1995 letter from the FDA.

Pharmachemie B.V.'s Letter of Authorization for me to act as their Responsible Agent is found on page 5.

A third copy - Field Copy - is also enclosed and is certified to be a "true" copy of this submission.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

December 6, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

SUBJECT: **AMENDMENT #1**
ANDA 74-539
Tamoxifen Citrate Tablets USP, 10 mg

Enclosed in duplicate is our submission for this amendment which is comprised of four binders. A "Diskette With All Pharmacokinetic Data" is inserted in Volume 4 of 4, Question 5 - page 1435.

A field copy is also enclosed which is certified to be a "true" copy of this submission.

The Letter of Authorization for me to act as Pharmachemie B.V.'s agent is on page 5.

Please contact me if I can be of service to you.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk

RECEIVED
DEC 07 1995
GENERIC DRUGS

Tamoxifen Citrate Tablets USP, 10 mg
ANDA 74-539

JUL 27 1995

Pharmachemie U.S.A., Inc.
U.S. Agent for Biochemie, BV
Attention: J. David Hayden
Post Office Box 145
Oradell, NJ 07649

Dear Mr. Hayden:

Reference is made to the bioequivalence study and waiver request submitted on August 26, 1994, for Tamoxifen Citrate Tablets USP.

The Office of Generic Drugs has reviewed the data comparing the test product with the reference listed drug, Nolvadex® Tablets (Zeneca), and the data is incomplete for the following reasons:

1. The area under the plasma concentration-time curve (AUC_{0-t}) has been calculated for up to 216 hours for tamoxifen and for up to 576 hours for N-desmethyltamoxifen. AUC_{0-t} should be calculated, for both N-desmethyltamoxifen and for tamoxifen, up to time the last measurable (quantifiable) time point for each subject.

2. The arithmetic means of the plasma concentrations for each sampling time point both for N-desmethyltamoxifen and for tamoxifen should be included in the statistical summary.

3. [redacted] of the analysis of the unknown samples for tamoxifen and N-desmethyltamoxifen, including all associated standard curves and [redacted] were not submitted for at least one-fifth (20%) of the subjects, chosen at random.

4. The complete analytical raw data was not submitted for all subjects for both tamoxifen and N-desmethyltamoxifen.

5. To help the review of this application please submit 3.5" Diskettes, in ASCII code, which contain all pharmacokinetic data for both N-desmethyltamoxifen, and tamoxifen, for each subject.

6. There were six groups in the study design, the following model is recommended for use in the statistical analysis of the study:

Y = Group Trt Group*Trt.

7. No data was submitted which demonstrated the long term stability of both tamoxifen and N-desmethyltamoxifen (i.e., their stability in frozen study samples for the period equivalent to the time from the day the plasma samples were collected to the day the last sample was analyzed).

8. The expiration date or the date of manufacture as well as the content uniformity for both the test and the reference products were not submitted. A modification of the dissolution test report to include this information might be appropriate, to avoid this issue in future submissions.

9. Dissolution was not conducted in accordance with USP specifications. Comparative dissolution testing using the USP recommendation of 1000 mL of 0.02N HCl (instead of 900 mL), is required. The dissolution profiles should be determined at 15, 30, 45 and 60 minutes.

Please note items 1-5 and 7-9 and ensure that such data is included in subsequent submissions, since this data is relevant to all submissions.

As described under 21 CFR 314.96 an action which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, ~~Ph.~~D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-539

Pharmachemie USA, Inc.
Attention: J. David Hayden
U.S. Agent for Pharmachemie B.V.
P.O. Box 145
Oradell, NJ 07649

JUN 6 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated August 26, 1994, and accepted for filing on December 6, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tamoxifen Citrate Tablets USP, 10 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. [redacted]

2. [redacted]

a. [redacted]

b. [redacted]

Redacted 2

pages of trade secret and/or confidential commercial information

[redacted]

B. Labeling Deficiencies:

CONTAINER (60s and 250s):

1. Store at controlled room temperature...

2. Delete [redacted] in the "Keep out of reach of children" statement.

3. Add the following -

   Dispense in well-closed, light-resistant container.

4. You have referred the user to an "attached" insert. Will your insert actually be attached to the outside of the container?

INSERT:

GENERAL COMMENTS

1. Revise your package insert labeling to be in accord with the most recently approved labeling for the listed drug Nolvadex (Zeneca; Approved July 20, 1994; Revised April 1994).

Please revise your container labels and package insert labeling as described above, then prepare and submit final printed container labels and draft package insert labeling.

C. In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Satisfactory evaluation of the CGMP compliance of the facilities listed in your application is required prior to the approval of your ANDA. We defer our request for this evaluation at the present time as the manufacturing facility for the drug substance cited in your ANDA differs from that stated in the supporting DMF.

2. Please be advised that process validation is the responsibility of the FDA investigator. The in-process control tests performed on the exhibit batches should be conducted on future production batches until such time as the process is fully validated and reductions from in-process testing can be justified. Please note that deletion of in-process tests requires approval of a supplemental application per 21 CFR 314.70(b)

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 6/5/97

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-539

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
U.S. Agent for: Pharmachemie BV
P.O. Box 145
Oradell, NJ 07649

JAN [illegible]

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letters dated September 22, 1994, and November 10, 1994, and your amendments dated October 14, 1994; December 5, 1994.

NAME OF DRUG: Tamoxifen Citrate Tablets USP, 10 mg

DATE OF APPLICATION: August 26, 1994

DATE OF RECEIPT: August 30, 1994

DATE ACCEPTABLE FOR FILING: December 6, 1994

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

David Konigstein
Consumer Safety Officer
(301) 594-0370

Sincerely yours, 1/11/95

/S/
Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-539
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief, /S/ date 1/9/95
HFD-615/WRussell, CSO /S/ 1/9/95 date
HFD-625/MSmela, Sup Chemist /S/ date 1/9/95
HFD-610/JPhillips, Chief LRB date
WP File\russell\74\74-539
F/T bcw/1-5-95
ANDA Acknowledgement Letter!

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

December 28, 1994

International Programs and
Technical Support Branch
HFC-134, R12-23
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir or Madam:

SUBJECT: ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Enclosed is a copy of our letter to the FDA - Division of Labeling and Program Support - regarding the revised Certification Statement dated December 22, 1994 on the above ANDA.

This field copy has been certified to be a true copy of this submission.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

COPY
ATTENTION:
FDA - IPTSB

December 28, 1994

Mr. Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Johnston:

SUBJECT: ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

In response to your letter of November 10, 1994 (copy attached), we forwarded to you on December 5, 1994 a revised Certification Statement (copy attached).

Following this I received a call from your office requesting that we send a revised Certification Statement that would certify that none of our personnel have been convicted of a felony as described in Section 306(a).

The latest revision, dated December 22, 1994, is enclosed in duplicate. We trust that this is satisfactory and that this application can be released from "Refuse to File".

A field copy has been submitted to the Office of Generic Drugs, International Programs and Technical Support Branch, and is certified to be a true copy of this submission.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk
FDA - IPTSB

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

505(b)(2) 1/4/95 /S/

December 28, 1994

NEW CORRESP

NC

Mr. Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Johnston:

SUBJECT: ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

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Following this I received a call from your office requesting that we send a revised Certification Statement that would certify that none of our personnel have been convicted of a felony as described in Section 306(a).

The latest revision, dated December 22, 1994, is enclosed in duplicate. We trust that this is satisfactory and that this application can be released from "Refuse to File".

A field copy has been submitted to the Office of Generic Drugs, International Programs and Technical Support Branch, and is certified to be a true copy of this submission.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk
FDA - IPTSB

RECEIVED

DEC 29 1994

GENERIC DRUGS

ORIGINAL

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

COPY
ATTENTION:
IPTSB

December 5, 1994

Mr. Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Johnston:

SUBJECT: ANDA 74-539 Tamoxifen Citrate Tablets USP, 10 mg

Reference is made to your letter of November 10, 1994 (copy attached).

Enclosed, in duplicate, is our revised Certification Statement. We believe that this conforms to your request.

A field copy has been submitted to the Office of Generic Drugs, International Programs and Technical Support Branch, and is certified to be a true copy of this submission.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. A.J. Nykerk
FDA - IPTSB

ANDA 74-539

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
U.S. Agent for: Pharmachemie BV
P.O. Box 145
Oradell, NJ 07649

NOV 10 1994

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 26, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Tamoxifen Citrate Tablets USP, 10 mg.

Reference is also made to our "Refuse to File" letter dated September 22, 1994, and your amendment dated October 14, 1994.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to include a list of convictions with your debarment certification. As mentioned in our earlier letter, firms with no convictions to list should submit a statement to that effect.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

Gordon R Johnston 11/10/94
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-539
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Acting Chief /S/ 11/4/94 date
HFD-615/WRussell, CSO /S/ 10/24/94 date
HFD-625/MSmela, Sup. Chem. /S/ 11/8/94 dated date
WP File B:\rtfanda\74-539
F/T File hrw 10-24-94
ANDA Refuse to File!

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

October 14, 1994

Dr. Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Johnston:

SUBJECT: Tamoxifen Citrate Tablets USP, 10 mg
ANDA 74-539

With reference to your letter dated September 22, 1994 (copy attached), please find attached in duplicate Pharmachemie B.V.'s completion of its Abbreviated New Drug Application for Tamoxifen Citrate Tablets USP, 10 mg, ANDA 74-539.

We are enclosing the following information and commitments:

- original exclusivity statement
- original patent certification
- original debarment certification
- side-by-side comparison of our proposed labeling with the approved labeling of the reference listed drug
- comparative in vitro dissolution data between our proposed drug product and the reference listed drug

At your request, an additional copy of the file has been submitted to the Office of Generic Drugs. A signed certification that the submitted field copy is a true copy of the application has been included.

Please contact me if additional information is requested.

Sincerely,

J. David Hayden
President

JDH/nap
Enclosures

RECEIVED
OCT 1 8
GENERIC DRUGS

cc: Dr. A.J. Nykerk
FDA - International Programs & Technical Support Branch

ANDA 74-539

SEP 22 1994

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
U.S. Agent for: Pharmachemie BV
P.O. Box 145
Oradell, NJ 07649

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 26, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Tamoxifen Citrate Tablets USP, 10 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to properly address exclusivity for the proposed product. You must provide a statement as to whether, according to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations, 13th Edition, the **reference listed drug** is entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Act [refer to 21 CFR 314.94(a)(3)(iii)].

Please clarify your patent certification. The certification you have provided is a combination of Paragraph III (refrain from marketing your drug product until the patent expiration date) and Paragraph IV (the patent is invalid or will not be infringed by the manufacture, use, or sale of the proposed drug product) [Food Drug and Cosmetic Act (FD&C Act), Section 505(j)(2)(A)(vii)(III)&(IV)]. If you choose to submit a Paragraph IV certification, notification of the patent holder is required [FD&C Act, Section 505(j)(B)(i)&(ii)].

You have failed to provide a debarment certification with an original signature, which includes a list of convictions, as required by Section 306(k)(1) and (k)(2) of the Generic Drug Enforcement Act (GDEA) of 1992. Relevant convictions are those for which a person can be debarred as described in Sections 306(a) and (b) of the Regulations. Firms with no convictions to list should submit a statement to that effect. Please provide a revised certification.

The regulations require submission of a side-by-side comparison of your proposed labeling with the approved labeling of the reference listed drug [21 CFR 314.94(a)(8)(iv)]. Labeling is clarified in the regulations to include both container labels and package insert labeling. Please include a side-by-side comparison of the package insert and container labels for the proposed and reference listed drug products. All differences should be annotated and explained.

You must submit a third (field) copy of the technical section of the application. A foreign applicant shall send the field copy to:

Office of Generic Drugs, CDER, FDA,
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

In addition, a signed certification with an original signature stating that the submitted field copy is a "true" copy of the technical section of the application is required to be submitted in the archival copy of the abbreviated application. Please refer to Sections 21 CFR 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352.

You have failed to provide comparative in vitro dissolution data between your proposed drug product and the reference listed drug. Comparative dissolution data profiles should include **individual tablet data** as well as the mean, range, and standard deviation at each time point for twelve tablets.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

Gordon R. Johnston 9/21/94
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-539
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/GJohnston, Chief /S/ date 9/16/94
HFD-615/PRickman, CSO /S/ date 9/16/94
HFD-615/WRussellCSO /S/ date 9/19/94
HFD-625/MSmela, Sup. Chem. /S/ date 9/19/94
WP File\B:\rtfanda\74-539
F/T File hrw 9-14-94
ANDA Refuse to File!

/S/ 9/19/94

P.O. Box 145.
Oradell, New Jersey 07649.
Telephone: (201) 265-1942.
Fax (201) 265-1525

PHARMACHEMIE U.S.A., INC.

Return to file
WP
8/31/94

IS 9/9/94

August 26, 1994

Dr. Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Sporn:

SUBJECT: Submission Abbreviated New Drug Application
Tamoxifen Citrate Tablets USP

Pursuant to the authorization letter executed by Pharmachemie B.V., Holland, page 11 of this application, J. David Hayden, President, Pharmachemie U.S.A. is filing this Abbreviated New Drug Application for Tamoxifen Citrate Tablets USP.

Enclosed are the following:

1. ARCHIVAL COPY (2 volumes) plus
PHARMACOKINETIC SECTION (2 volumes)

2. CHEMISTRY SECTION (2 volumes) plus
PHARMACOKINETIC SECTION (2 volumes)

This product will be manufactured at the plant of Pharmachemie B.V. in Haarlem, The Netherlands.

Sincerely,

J. David Hayden

J. David Hayden
President

JDH/nap
Enclosures

cc: Dr. Nykerk, V.P. Product Development

RECEIVED
AUG 30 1994
OFFICE OF GENERIC DRUGS