CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-807

MEDICAL REVIEW

AND

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Division Director Summary Review of NDA 21-807

NDA: 21-807
Drug: Soltamox™ (tamoxifen citrate) Oral Solution
Applicant: Savient Pharmaceuticals, Inc.
Date: October 29, 2005

This is a 505(b)(2) application for Soltamox™ (tamoxifen citrate) Oral Solution for all of the approved indications of the reference drug, Nolvadex (tamoxifen citrate) Tablets. However, the information in the Nolvadex package insert regarding treatment of McCune-Albright syndrome has been deleted from the package insert because of pediatric exclusivity.

Medical and Clinical Pharmacology and Biopharmaceutics Review

A joint Medical and Clinical Pharmacology and Biopharmaceutics Review was completed by Roshni Ramchandani, Ph.D., Brian Booth, Ph.D. and Ramzi Dagher, M.D. An amended final review was completed on September 29, 2005. The following summary of the application is provided in the review:

> Tamoxifen citrate was first approved as an oral tablet in 1977 (NOLVADEX ®) . Nolvadex is indicated in the treatment of metastatic breast cancer. It reduces the occurrence of contralateral breast cancer in patients receiving adjuvant therapy for breast cancer. It is also indicated for reduction in the incidence of breast cancer in women at high risk for breast cancer. Additionally, it reduces the risk of invasive breast cancer in women with Ductal Carcinoma in situ, following breast surgery and radiation. The current application was submitted as a 505(b)(2) NDA, based on one bioavailability/bioequivalence study comparing Soltamox to the US reference product Nolvadex oral tablets and also includes an additional arm to evaluate the effect of food.
>
> The study (# C0501) was a 1- period, parallel bioequivalence study, in healthy perimenopausal and postmenopausal female subjects under fasting conditions, randomized to either Soltamox oral solution 10 mg/5 ml, administered as 2 x 5ml (20 mg) solution, or Nolvadex 20 mg tablets, administered as 1 x 20 mg tablet. An additional group of female subjects were given Soltamox oral solution following a standard meal to examine the effect of food on tamoxifen pharmacokinetics (PK) following Soltamox. There were no significant differences in PK parameters between the tablet and solution formulations under fasting conditions. The 90% confidence intervals for the Cmax, AUCt and AUCinf were within the 80%-125% limits required for bioequivalence. Comparison of Soltamox PK under fasted and fed conditions showed an 11-15% increase in AUC for tamoxifen following food intake compared to the fasted state. The Cmax, Tmax and half-life were not affected by food intake. This increase was not considered to be clinically significant.

> Following a DSI audit, data from 14 subjects in the group that received Soltamox following food intake were excluded due to inability to confirm the time of dosing relative to food intake. Re-analysis of the data showed a 5% decrease in AUCinf following food intake, with no effect on Cmax, AUCt, Tmax or half- life. Thus, food does not appear to have a significant effect on Soltamox exposure.

The recommendation was that "The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the current submission to be acceptable. The labeling changes proposed by the applicant are acceptable, with minor revisions."

Audit by the Division of Scientific Investigations

The clinical and analytical sites were audited and the report was completed on June 15, 2005. The audit report conclusions are provided below:

> Following the above inspections, DSI concludes that there is no assurance that the following subjects in the fed group were dosed within 10 minutes of breakfast completion:
>
> - all subjects in the fed group at the [redacted] site (item 2 above).
> - subjects 023 and 024 at the [redacted] site (item 3 above).
>
> DSI recommends that the above subjects be excluded from the food effect evaluation.

As noted above in the Medical and Clinical Pharmacology and Biopharmaceutics Review, "data from 14 subjects in the group that received Soltamox following food intake were excluded due to inability to confirm the time of dosing relative to food intake. Re-analysis of the data showed a 5% decrease in AUCinf following food intake, with no effect on Cmax, AUCt, Tmax or half- life."

Chemistry Review

The Chemistry Review by Ruth E. Wager, Ph.D. and Chengyi Liang, Ph.D. was completed on September 12, 2005. The review stated that "NDA 21-807 is recommended for approval from the standpoint of chemistry, manufacture and controls. The applicant has satisfactorily responded to the deficiencies and the Office of Compliance has provided an overall acceptable recommendation." The claim for categorical exclusion from the requirement of filing an environmental assessment was found to be acceptable.

DMETS Consultation

The DMETS consultation dated June 29, 2005 made the following recommendations:

1. DMETS has no objections to the use of the proprietary name, Soltamox™ . This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document

2. DMETS recommends implementation of the label and labeling revisions as outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Soltamox™, acceptable from a promotional perspective.

The labeling recommendations were considered during the review.

DDMAC Consult

The DDMAC consult by Joseph Grillo had no comments on the draft labeling.

Conclusion

I concur that the application should be approved.

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

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/s/

Robert Justice
10/29/2005 04:33:21 PM
MEDICAL OFFICER

MEDICAL AND CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-807
AMENDMENT

Drug name:	SOLTAMOX™
Generic name:	Tamoxifen citrate
Formulation:	Solution for oral administration (10 mg/5 ml)
Indication:	Treatment of breast cancer
Applicant:	Savient Pharmaceuticals One Town Center Boulevard, 14th floor East Brunswick, NJ 08816
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	23-Dec-2004, 21-July-2005
OCPB Reviewer:	Roshni Ramchandani, Ph.D.
Medical Reviewer:	Ramzi Dagher, M.D.
OCPB Team Leader:	Brian Booth, Ph.D.
Type of Submission:	505 (b) (2)

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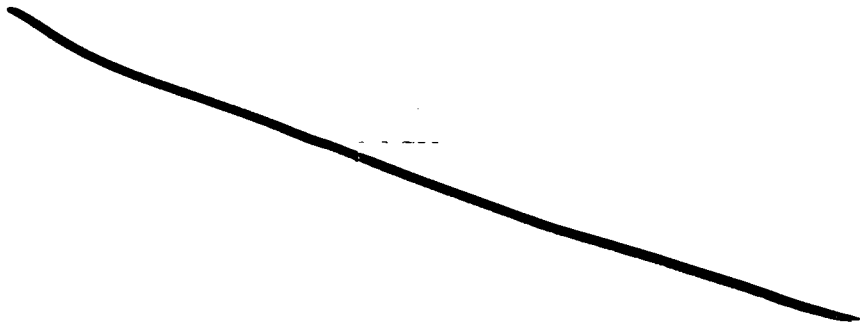
I. Executive Summary

SOLTAMOX™ is an oral solution of tamoxifen citrate, which is a non-steroidal antiestrogen. Tamoxifen citrate was first approved as an oral tablet in 1977 (NOLVADEX®). Nolvadex is indicated in the treatment of metastatic breast cancer. It reduces the occurrence of contralateral breast cancer in patients receiving adjuvant therapy for breast cancer. It is also indicated for reduction in the incidence of breast cancer in women at high risk for breast cancer. Additionally, it reduces the risk of invasive breast cancer in women with Ductal Carcinoma in situ, following breast surgery and radiation. The current application was submitted as a 505(b)(2) NDA, based on one bioavailability/bioequivalence study comparing Soltamox to the US reference product Nolvadex oral tablets and also includes an additional arm to evaluate the effect of food.

The study (# C0501) was a 1-period, parallel bioequivalence study , in healthy perimenopausal and postmenopausal female subjects under fasting conditions, randomized to either Soltamox oral solution 10 mg/5 ml, administered as 2 x 5ml (20 mg) solution, or Nolvadex 20 mg tablets, administered as 1 x 20 mg tablet. An additional group of female subjects were given Soltamox oral solution following a standard meal to examine the effect of food on tamoxifen pharmacokinetics (PK) following Soltamox. There were no significant differences in PK parameters between the tablet and solution formulations under fasting conditions. The 90% confidence intervals for the Cmax, AUCt and AUCinf were within the 80%-125% limits required for bioequivalence. Comparison of Soltamox PK under fasted and fed conditions showed an 11-15% increase in AUC for tamoxifen following food intake compared to the fasted state. The Cmax, Tmax and half-life were not affected by food intake. This increase was not considered to be clinically significant.
Following a DSI audit, data from 14 subjects in the group that received Soltamox following food intake were excluded due to inability to confirm the time of dosing relative to food intake. Re-analysis of the data showed a 5% decrease in AUCinf following food intake, with no effect on Cmax, AUCt, Tmax or half-life. Thus, food does not appear to have a significant effect on Soltamox exposure.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the current submission to be acceptable.
The labeling changes proposed by the applicant are acceptable, with minor revisions.



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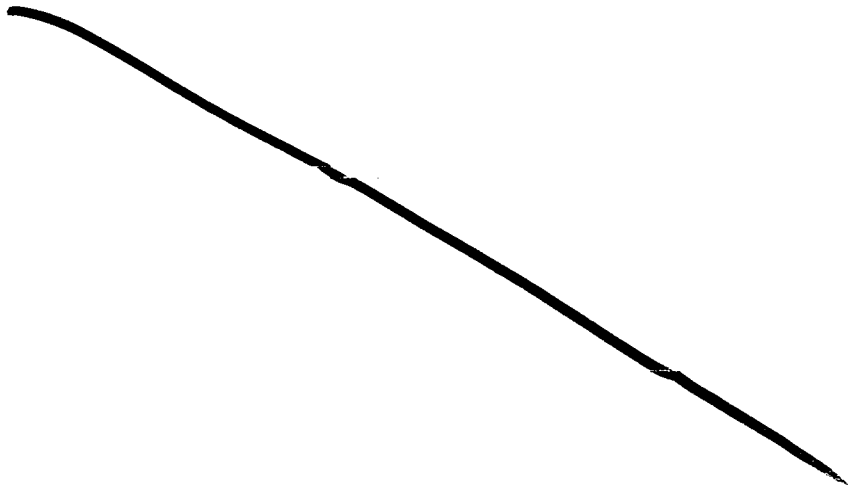
✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- Medical and 1



B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A single study was conducted to evaluate the bioavailability/bioequivalence of the proposed Soltamox oral solution formulation compared to the Nolvadex oral tablet formulation and to examine the effect of food on the pharmacokinetics of tamoxifen. The study (# C0501) was a 1-period, parallel bioequivalence study in healthy perimenopausal and postmenopausal female subjects under fasting conditions, randomized to either Soltamox oral solution 10 mg/5 ml, administered as 2 x 5ml (20 mg) solution, or Nolvadex 20 mg tablets, administered as 1 x 20 mg tablet. An additional group of female subjects were given Soltamox oral solution following a standard meal to examine the effect of food on tamoxifen PK following Soltamox.
As the following table indicates, there were no significant differences in PK parameters between the tablet and solution formulations under fasting conditions. The 90% confidence intervals for the Cmax and AUCinf (and AUCt) were within the 80%-125% limits required for bioequivalence.

Mean (SD) Pharmacokinetic Parameters Following Single Oral Administration of 20mg of Soltamox™ Oral Solution and Tamoxifen Citrate Tablet

Parameter	Test (treatment B) Soltamox™ Oral Solution (n=30) Mean (SD)	Reference (treatment A) Tamoxifen Citrate Tablet (n=33) Mean (SD)
AUC (ng•hr/mL)	4131.57 (1499.45)	4105.61 (1431.90)
AUC_T (ng•hr/mL)	3108.82 (847.38)	3229.47 (900.86)
C_{max} (ng/mL)	53.38 (14.03)	55.94 (13.63)
T_{max} (hour)[a]	4.5 (2.13-8.00)	4.5 (3.0-8.0)
t½ (hour)	255.70 (69.58)	227.43 (58.88)

a: Median (Range)

Comparison of Soltamox PK under fasted and fed conditions showed an 11-15% increase in AUC for tamoxifen following food intake compared to the fasted state. The Cmax, Tmax and half-life were not affected by food intake. This increase was not considered to be clinically significant.

Following a DSI audit, data from 14 subjects in the group that received Soltamox following food intake were excluded due to inability to confirm the time of dosing relative to food intake. Re-analysis of the data showed a 5% decrease in AUCinf following food intake, with no effect on Cmax, AUCt, Tmax or half-life. Thus, food does not appear to have a significant effect on Soltamox exposure.

OCPB Briefing held on 6-Jun-2005:
Attendees: Mehul Mehta, Brian Booth, Arzu Selen, June Komura, Roshni Ramchandani

II. Question Based Review

A. General Attributes of the Drug

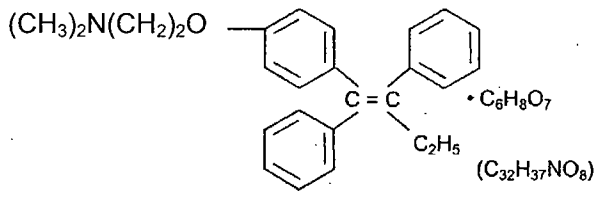
A1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

SOLTAMOX is an oral solution of tamoxifen. Tamoxifen citrate was first approved as an oral tablet in 1977 (NOLVADEX®), and represented a significant advance in the treatment of breast cancer. SOLTAMOX has been approved in the UK since 1999, and was recently approved in Ireland and Germany. The same formulation and manufacturing process that was approved in the UK will be used in the US.

This application was submitted as a 505 (b) (2) NDA, based on one bioavailability/bioequivalence study comparing SOLTAMOX to the US reference product NOLVADEX® oral tablets.

A2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Tamoxifen citrate is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-l-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1). The structural formula:



Tamoxifen citrate has a molecular weight of 563.62, the pKa is 8.85, the equilibrium solubility in water at 37^0C is 0.5 mg/mL and in 0.02 N HCl at 37^0C, it is 0.2 mg/mL.

SOLTAMOX™ solution is for oral administration. Each 5mL solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen. Table I gives the composition of the formulation.

Table 1: Composition of SOLTAMOX formulation

Ingredient	Quantity (per 5 ml)
Tamoxifen citrate	15.2 mg
Ethanol	
Glycerol	
Propylene glycol	
Sorbitol solution	
Licorice flavor	
Aniseed flavor	
Purified Water	

A3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Tamoxifen citrate 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 binds to estrogen receptors and inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

Tamoxifen has been approved as adjuvant therapy and chemotherapy of breast cancer. It has been approved for the following indications:

- metastatic breast cancer in women and men;
- adjuvant treatment of node-positive breast cancer in postmenopausal women and node-negative breast cancer following total mastectomy or segmental mastectomy, axiallary dissection and breast irradiation;
- treatment of women with ductal carcinoma in situ following breast surgery and radiation;
- reduction in breast cancer incidence in high risk women. In premenopausal women with metastatic breast cancer, tamoxifen is an alternative to oophorectomy or ovarian irradiation.

Tamoxifen tablets (Nolvadex) have also been approved for McCune-Albright syndrome in pediatric patients. Since this indication is still covered by exclusivity, it will not be included in the SOLTAMOX labeling.

A4. What are the proposed dosage(s) and route(s) of administration?

For patients with breast cancer: the recommended daily tamoxifen dose is 20-40 mg.
For patients with ductal carcinoma in situ (DCIS), the recommended dose is tamoxifen citrate 20 mg daily for 5 years.
For reduction in breast cancer incidence in high risk women, the recommended dose is tamoxifen citrate 20 mg daily for 5 years.

A 20 mg dose of Soltamox™ is administered as 2 x 5mL (equivalent to 2 teaspoons) of the oral solution.

B: Clinical Pharmacology

General attributes

B1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant has conducted one study in support of the 505(b)(2) application for SOLTAMOX oral solution for the treatment of breast cancer. The study (# C0501) was a 1-period, parallel bioequivalence study in healthy perimenopausal and postmenopausal female subjects under fasting conditions, randomized to either SOLTAMOX oral solution 10 mg/5 ml, administered as 2 x 5ml (20 mg) solution, or NOLVADEX® 20 mg tablets, administered as 1 x 20 mg tablet. An additional group of female subjects were given SOLTAMOX oral solution following a standard meal to examine the effect of food on tamoxifen PK following SOLTAMOX.

B2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how were they measured in clinical pharmacology and clinical studies?

No PD measures of effectiveness were assessed during the studies included in the current application.
No exposure-response analysis is included in the current application.

B3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The plasma samples obtained in the submitted study were analyzed for concentrations of tamoxifen using LC/MS/MS. This was considered to be appropriate for assessment of the PK of tamoxifen and comparison of exposures for bioavailability and bioequivalence comparisons.

Pharmacokinetics

B4. What are the PK characteristics of the drug?

The following summary of the PK characteristics of tamoxifen was derived from the product label.

Single Dose Pharmacokinetics

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 mg/mL (range 35 to 45 mg/mL) occurred approximately 5 hours after dosing. The Tmax of 5 hours suggests that tamoxifen absorption occurs primarily in the small intestine, and the similar Tmax values obtained following tablet and solution formulations indicates that the absorption is determined by the permeability characteristics of the drug and that solubility would not be expected to be a rate-limiting factor in the absorption of tamoxifen. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of the active metabolite, N-desmethyl tamoxifen, is 15 mg/mL (range 10 to 20 mg/mL).

Multiple Dose Pharmacokinetics:

Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 mg/mL (range 67-183 mg/mL) for tamoxifen and 336 mg/mL (range 148-654 mg/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 mg/mL (range 71-183 mg/mL) and 353 mg/mL (range 152-706 mg/mL), respectively.

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 steady-state, crossover study of 10 mg tamoxifen tablets given twice a day vs. a 20 mg tamoxifen tablet given once daily, the 20 mg tamoxifen tablet was bioequivalent to the 10 mg tamoxifen tablets.

Metabolism:

Tamoxifen is extensively metabolized after oral administration. It is a substrate for multiple CYP isozymes including 3A, 2C9, 2C19, 2B6 and 2D6 (Rochat, 2005). N-desmethyl tamoxifen is the major metabolite found in patients' plasma. CYP3A4 and CYP2C9 are thought to be involved in this process, although other CYP isozymes have also shown formation of this metabolite in in vitro studies. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have also been identified as metabolites in plasma. Several CYPs have been implicated in this pathway, including 2D6, 2C9, 2C19, 3A4. Tamoxifen is not a substrate of P-glycoprotein but it does inhibit P-glycoprotein-mediated transport in vitro (Bekaii-Saab et al., 2004)

Excretion:

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 is excreted mainly as polar conjugates (mainly as glucuronide), with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

Special Populations:

The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

Drug Interactions:
In vitro studies showed that erythromycin, cyclosporine, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent Ki of 20, 1, 45 and 30 μM, respectively. The clinical significance of these in vitro studies is unknown. Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were co-administered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and Cmax by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and Ndesmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not of tamoxifen.

C. Intrinsic Factors

No specific intrinsic factors were evaluated in this submission. Please refer to the label for additional information on intrinsic factors previously evaluated for tamoxifen.

C1. What is the influence of gender on the PK of tamoxifen?

The CO-501 study submitted by the applicant was conducted only in women. The sponsor has included data from another study, called TAMOX1, comparing the oral solution formulation (SOLTAMOX) to the Nolvadex-D oral tablet formulation used in Great Britain.
The TAMOX1 study was a 2-period crossover study comparing the tablet and oral solution formulations in healthy males, 18-45 years of age. The PK parameters for tamoxifen in the oral solution arm of the study, particularly the Cmax and AUC, were about half the estimates obtained in the study submitted in the current application (CO-501), as indicated in the following table.

Table 2: Comparison of PK parameters for tamoxifen following SOLTAMOX in healthy males (TAMOX1 study) and healthy females (C0501 study).

	TAMOX1 study	**C0501 study**
Study sample (subjects)	24 healthy males (all subjects received both SOLTAMOX and NOLVADEX-D®)*	30 healthy females (additional 30 females received SOLTAMOX fed and 34 females received NOLVADEX®)
Study design	2-period crossover	Parallel
Age	18-45 years	44-64 years
Weight	65-99.5	48.6-88.6
PK Parameters [Mean (SD)]		
Dose	20 mg (SOLTAMOX)	20 mg (SOLTAMOX)
Cmax (ng/ml)	25.7 (4.5)	53.4 (14.0)
Tmax (hr)	4.2 (1.1)	4.3 (1.0)
AUCinf (ng.hr/ml)	2266.9 (540.4)	4131.6 (1499.5)
T1/2 (hr)	205.5 (65.2)	255.7 (69.6)

*: Nolvadex-D is the UK tablet formulation

At this time, the reasons for the apparent differences in PK parameters are unclear. However, there are several possible experimental factors that might have played a role in the apparent gender difference:

1. Differences in study procedures. The studies were conducted in different locations USA).
2. Demographic differences: There were marked differences between the subjects enrolled in the 2 studies, with regard to their weight and age, as indicated in table 2. Additionally, most subjects in the Tamox1 study were Caucasian, while most subjects in the C0501 study were Hispanic.
3. Differences in analytical methodology: The TAMOX1 study used HPLC with fluorescence detection, while the C0501 study used LC-MS-MS. However, a review of the analytical method validation did not reveal any major differences/problems. Both assays had adequate precision and accuracy and comparable LLOQs.
4. Concomitant medications: Concomitant medications that could potentially interact with tamoxifen were not allowed starting 14 days prior to dosing in both studies.

The male subjects in the TAMOX1 study did show a shorter half-life compared to the females in the C0501 study (205.5 hrs vs. 255.7 hrs), however it is unlikely that this difference would account for a 50% difference in the Cmax and AUC between the genders.

There have been no published studies specifically examining gender differences in tamoxifen pharmacokinetics. The following table summarizes studies have evaluated tamoxifen PK in separate groups of males and females. Data from the submitted studies (C0501 and TAMOX1) are also included for comparison.

Reference	**Dose**	**Mean Cmax (ng/ml)**	**Cmax normalized to dose (Cmax/Dose) (ng/ml/kg)**	**SD**	**CV%**	**Analytical Method**
Guelen et al, 1987 (n=10)	40 mg tablets in healthy males	71	1.8	21	30%	HPLC with fluorescence detection
Fuchs et al, 1996 (n=24)	30 mg tablets in post menopausal females	63.6	2.1	11.1	17.3%	HPLC with fluorescence detection
D. de Vos et al, 1989 (n=12)	40 mg tablets in healthy males	73	1.8	20	27%	HPLC with fluorescence detection
CO501 (n=30)	20 mg Soltamox in post	55.94	2.7	13.63	24%	LC/MS/MS

	menopausal females					
TAMOX1 (n=24)	20 mg Soltamox in healthy males	25.7	1.28	4.5	17%	HPLC with fluorescence detection

On average, the Cmax values compared across the literature and in the two studies in the current submission (CO501 and TAMOX1) do appear to be lower than in males. However given the variability seen across the studies and the two groups, it is unclear at this time if there is a gender difference for Tamoxifen. So the reasons for the differences in exposure in the two studies, CO501 and TAMOX1, may be due to other factors.

D. Extrinsic Factors

No extrinsic factors were examined in the studies included in this submission. Please refer to the label for additional information on extrinsic factors previously evaluated for tamoxifen.

E. General Biopharmaceutics

E1. What is the relative bioavailability of the proposed to-be-marketed oral solution formulation relative to the currently marketed tablet formulation?

The applicant has conducted a study to assess the bioavailability of the proposed oral solution formulation of tamoxifen, SOLTAMOX, relative to the currently marketed Nolvadex oral tablet formulation. The study (#C0501) was a randomized, 1-period, parallel, bioequivalence study of SOLTAMOX (tamoxifen) oral solution 10 mg/5 ml administered as 2 x 5 ml (20 mg) solution and Nolvadex (tamoxifen) 20 mg oral tablet administered as 1 x 20 mg tablet, in healthy perimenopausal and postmenopausal female subjects. The pharmacokinetics of Soltamox and Nolvadex were evaluated under fasting conditions. An additional arm of the study evaluated the PK of Soltamox following a standard meal to assess the effect of food.

A total of 34 females were randomized to receive Nolvadex tablets (treatment A) and 31 females to Soltamox solution under fasted conditions (treatment B). An additional 31 females were randomized to receive Soltamox following a meal (treatment C). A single dose of Nolvadex or Soltamox was administered on day 1 and serial blood samples were collected for measurement of plasma tamoxifen levels through day 21 of the study. Blood samples for PK assessments were obtained on Day 1(pre-dose and at 1, 2, 3, 3.5, 4.5, 6, 8, 12 hours post dose), day 2 (24 and 36 hours post-dose), day 3 (48 hours post-dose), day 4 (72 hours post-dose), day 5 (96 hours post-dose), day 6 (120 hours post-dose), day 8 (168 hours post-dose), day 11 (240 hours post-dose), day 16 (360 hours post-dose), day 18 (408 hours post-dose), and day 22 (504 hours post-dose).

The plasma levels of tamoxifen were measured using LC/MS/MS. For each treatment, the following PK parameters were estimated: Cmax, Tmax, AUCt (area under the curve from time 0

to the last measurable time point), AUCinf (area under the curve from time 0 to infinity), λz (terminal rate constant) and t1/2 (terminal half-life). Treatments A and B were compared using t-tests. The ratio of the geometric least squares means of the test treatment (treatment B) to the reference treatment (treatment A) was calculated, along with its 90% confidence interval. Bioequivalence was defined as a 90% confidence interval that fell within the range: 80% and 125%.

Figure 1 shows the concentration-time profiles for all subjects in the study, and figure 2 shows the mean concentration-time profiles by treatment. Tamoxifen plasma concentrations for 1 subject (002/008) who received the tablet were a fraction (~$1/10^{th}$) of the levels measured in other subjects, regardless of treatment, across all time points (see figure 1). Drug administration for the subject was confirmed and no evidence of any analytical laboratory errors was found. Product failure was suspected, and the data for that subject was excluded from the analysis.

Figure 1: Tamoxifen concentration vs. time profiles for treatment A: Nolvadex (upper panel) and treatment B: Soltamox (lower panel), across subjects. The plot illustrates the markedly lower levels achieved by the outlier subject 002/008 who received the oral tablet formulation.

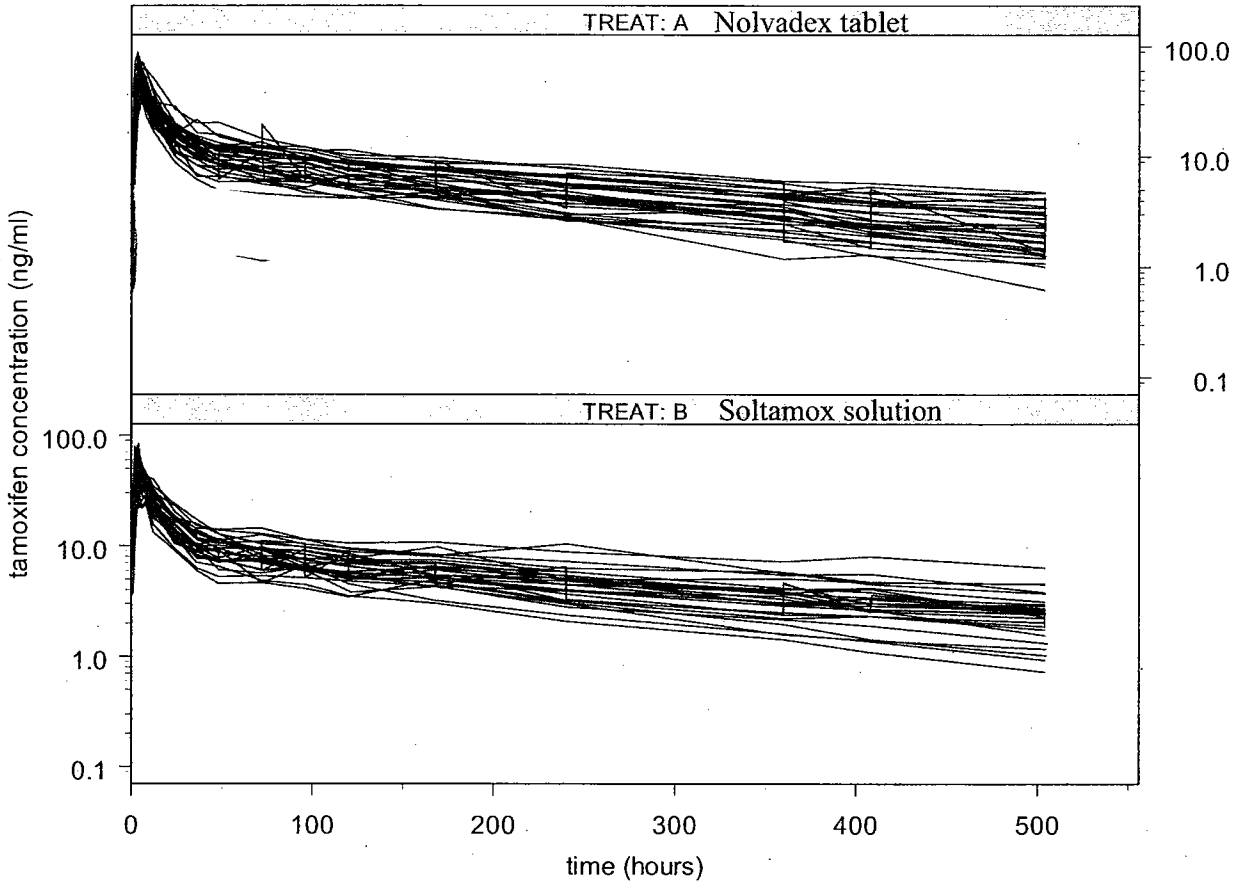


Figure 2: Mean tamoxifen concentration vs. time profiles by treatment (excluding outlier subject 002/008).

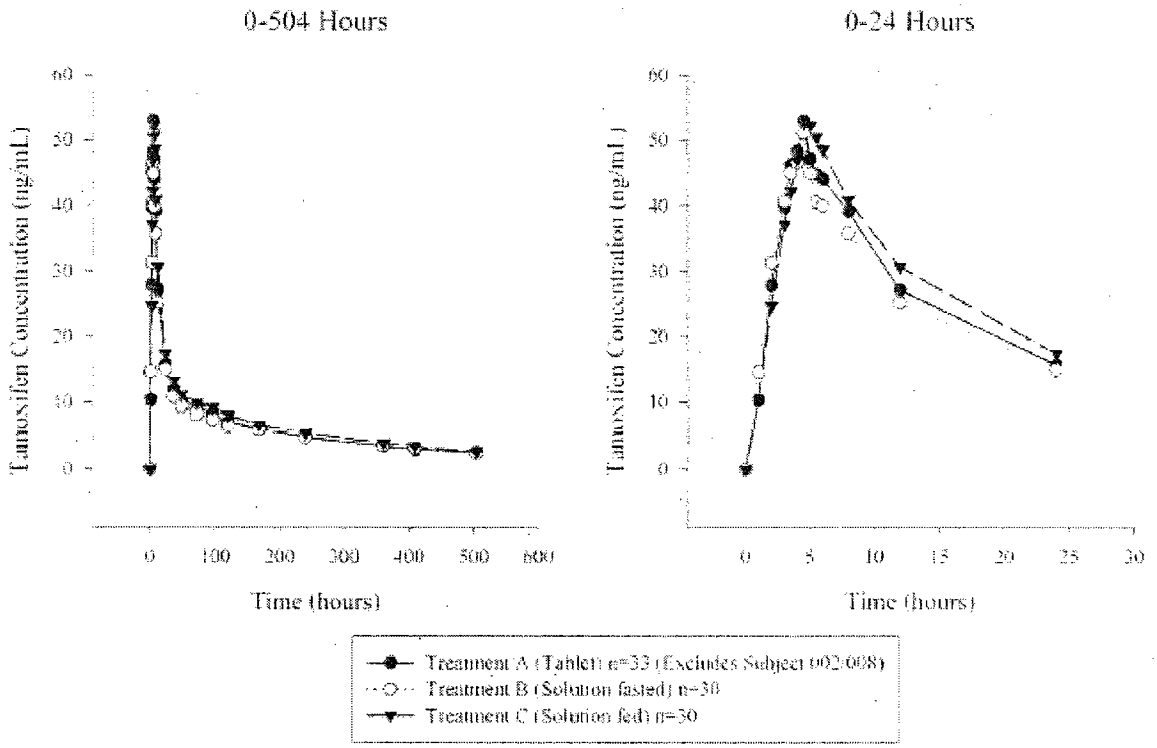


Table 3 shows the PK results from the study (excluding the outlier subject). There were no significant differences in PK parameters between treatments. Table 4a shows the Cmax and AUC ratios and 90% confidence intervals (excluding the outlier subject). The 90% CI were within the 0.80-1.25 limits required for bioequivalence. Table 4b shows the shows the Cmax and AUC ratios and 90% confidence intervals when all subjects were included. When the data for the outlier subject were included, the 90% C.I. for Cmax and AUCt were within the 0.80-1.25 range, however, the 90% C.I. for AUCinf exceeded the upper limit for bioequivalence (0.9037-1.2516).

Reviewer Analysis: The rewiewer re-analyzed the bioequivalence data to verify the 90% confidence intervals for the Cmax, AUCt and AUCinf across the treatments, using SAS v.8.02. The results of the analysis are identical to the results reported by the applicant (for details of analysis, please see Appendix C).

Additionally, a power analysis was done to verify that the study had adequate statistical power to detect a difference between treatments, if there was any. Given the inter-individual variability of 35%, a sample size of 60 (30 per arm) would have a power estimate of 0.8737 to detect a 20% difference at α=0.05. This indicates that the lack of difference between the 2 formulations is statistically robust, and the 2 formulations are bioequivalent.

Table 3: Mean (SD) Pharmacokinetic Parameters following Single Oral Administration of 20mg of SOLTAMOX™ Oral Solution and Tamoxifen Citrate Tablet.

Parameter	Test (treatment B) Soltamox™ Oral Solution (n=30) Mean (SD)	Reference (treatment A) Tamoxifen Citrate Tablet (n=33) Mean (SD)
AUC (ng•hr/mL)	4131.57 (1499.45)	4105.61 (1431.90)
AUC_T (ng•hr/mL)	3108.82 (847.38)	3229.47 (900.86)
C_{max} (ng/mL)	53.38 (14.03)	55.94 (13.63)
T_{max} (hour)[a]	4.5 (2.13-8.00)	4.5 (3.0-8.0)
t½ (hour)	255.70 (69.58)	227.43 (58.88)

a: Median (Range)

Table 4A: Bioequivalence of Soltamox oral solution and Nolvadex tablets.

Parameter	Geometric Means Test (treatment B: soltamox) (n=30)	Geometric Means Reference (treatment A: Nolvadex) (n=33)	Ratio[a]	90% C.I.[b]
AUCinf (ng.hr/ml)	3899.62	3876.49	1.0060	0.8721-1.1604
AUCt (ng.hr/ml)	3000.03	3111.76	0.9641	0.8624-1.0778
Cmax (ng/ml)	51.53	54.39	0.9473	0.8515-1.0539

a: ratio of the geometric LS means of the test to reference formulations.
b: the confidence interval (C.I.) is calculated based on the least squares means difference (natural logarithm scale) back transformed to the original measurement scale.

Table 4B: Bioequivalence of Soltamox oral solution and Nolvadex tablets ***(including the outlier subject 002/008).***

Parameter	Geometric Means Test (treatment B: soltamox) (n=30)	Geometric Means Reference (treatment A: Nolvadex) (n=34)	Ratio[a]	90% C.I.[b]
AUCinf (ng.hr/ml)	**3899.62**	**3666.68**	1.0635	**0.9037-1.2516**
AUCt (ng.hr/ml)	3000.03	2931.68	1.0233	0.8893-1.1775
Cmax (ng/ml)	51.53	50.88	1.0127	0.8773-1.1691

a: ratio of the geometric LS means of the test to reference formulations.
b: the confidence interval (C.I.) is calculated based on the least squares means difference (natural logarithm scale) back transformed to the original measurement scale.

Subject with anomalous tamoxifen levels (#002/008):
As described previously, tamoxifen plasma concentrations for one subject, 002/008, who received the Nolvadex tamoxifen tablet in study C0501, were a fraction of the concentrations achieved in the remaining subjects in the study. All study procedures including tablet administration were verified and no deviations that could have explained this anomalous PK profile were noted.

Study CO501-2
A follow-up study, C0501-2, was designed to re-evaluate the PK of the Nolvadex tamoxifen tablet in subject 002/008 (re-numbered as 002/908) as well as 5 other subjects who also received the Nolvadex tablet from the same lot (lot# 3246J, expiration: January 2005) at the same study site in [redacted]. The design and procedures of the retest study were identical to those in the original study.

On re-testing in a sub group (CO501-2), the outlier subject's plasma levels increased dramatically relative to the initial dose administered in CO501, and were consistent with the levels seen across other subjects (figure 2). The other 5 subjects showed comparable plasma tamoxifen levels across both sessions.

Figure 2: Plasma tamoxifen concentration-time profile following Nolvadex for the outlier subject obtained during the original study (C0501) and on repeat administration (C0501-2). The mean tamoxifen concentration-time profile following Nolvadex is also plotted for comparison.

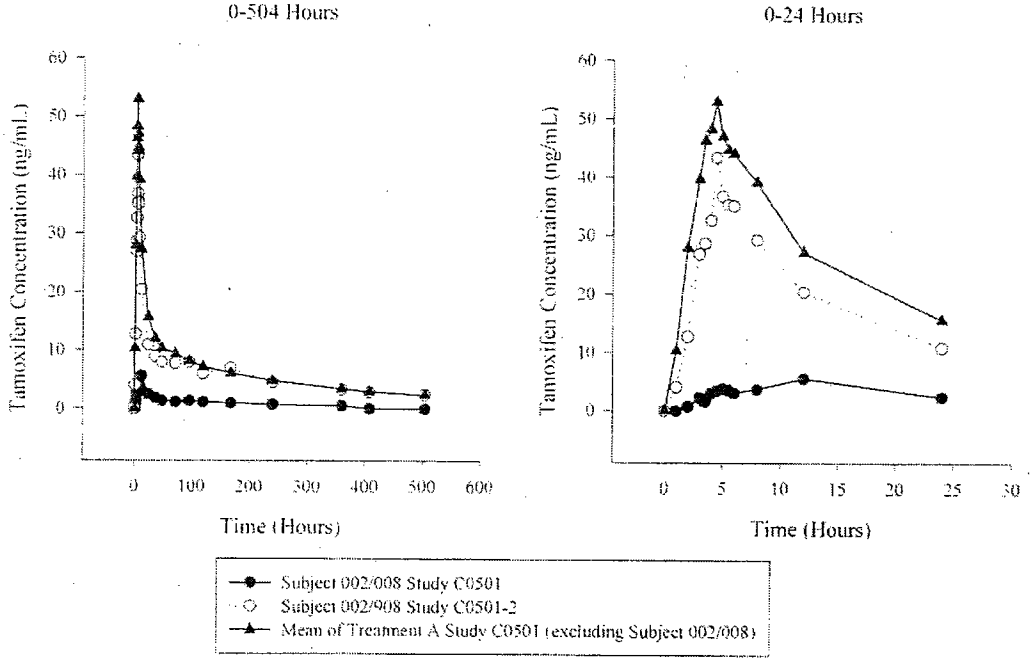


Table 5 shows the exposure measures for the subjects across studies C0501 and C0501-2, and highlights the within-subject variability in exposure for tamoxifen. For the other 5 subjects in

study C0501-2, the within-subject variability was low (CV%: 1%-15%, see table 5) relative to the between-subject variability seen across the subjects in the original study (CV% for AUC: 35% and for Cmax: 25%, see table 3).

Table 5: PK parameters for subjects in re-evaluation study C0501-2, and comparison with parameters from original study (C0501). Subject 002/908 was identified as an outlier with very low Cmax and AUCs during the original study.

Subject	AUC (ng.hr/ml)			Cmax (ng/ml)		
	C0501	C0501-2	%Diff*	C0501	C0501-2	%Diff*
002/901	7240.8	7140.6	-1%	81.2	68.7	-15%
002/903	7112.6	6172.6	-13%	72.3	63.5	-12%
002/908	584.5	3720.8	537%	5.6	43.4	673%
002/927	6178.0	6774.0	10%	73.9	75.2	2%
002/933	5418.5	4631.4	-15%	57.5	67.0	17%
002/937	3487.3	3728.6	7%	48.3	60.3	25%

*: %Diff = (C0501-2 – C0501)/C0501 x 100

Table 6 shows the results of the analysis performed in two ways: 1) by substituting the retest values for all six subjects for the original values 2) by substituting the retest values for subject #002/008 for her original values (i.e. instead of her initial anomalous results). The results of the analysis indicate that the 90% C.I. for Cmax, AUCT and AUC fall within the bioequivalence limits of 80-125%.

Table 6: Bioequivalence of SoltamoxTM oral solution and Nolvadex tablets substituting results from study CO501-2.

Parameter	LS Means Test (treatment B: soltamox) (n=30)	LS Means Reference (treatment A: Nolvadex) (n=34)	Ratio[a]	90% C.I.[b]
6 subjects replaced				
AUCinf (ng.hr/ml)	3899.62	**3666.68**	1.0635	**0.9037-1.2516**
AUCt (ng.hr/ml)	3000.03	2931.68	1.0233	0.8893-1.1775
Cmax (ng/ml)	51.53	50.88	1.0127	0.8773-1.1691
Only Subject 002/008 replaced				
AUCinf	3899.62	3871.82	1.0072	0.8747-1.1598

(ng.hr/ml)				
AUCt (ng.hr/ml)	3000.03	3104.25	0.9664	0.8656-1.0789
Cmax (ng/ml)	51.53	54.03	54.03	0.8580-1.0599

a: ratio of the geometric LS means of the test to reference formulations, where test is tamoxifen oral solution (treatment B) and reference is tamoxifen tablet formulation (treatment A).
b: the confidence interval (C.I.) is calculated based on the least squares means difference (natural logarithm scale) back transformed to the original measurement scale.

This confirms the findings of Study CO501 and supports the bioequivalence of Soltamox™ oral solution and Nolvadex® tablets.

E3. What is the effect of food on the PK of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the pharmacokinetics of tamoxifen tablets have not been reported in the published literature. Nevertheless, because Soltamox is a new oral formulation of tamoxifen, the Agency requested that the effect of food on drug absorption and PK be evaluated. This was accomplished by extending the proposed study to include an additional arm in study C0501. In addition to the tablet formulation (treatment A) and Soltamox under fasted conditions (treatment B), a third arm of the study administered Soltamox under fed conditions. A group of healthy females were given Soltamox oral solution (tamoxifen dose=20 mg) following ingestion of a standard high-fat breakfast (1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 serving of hash-brown potatoes, 6 fl. oz. orange juice and 8 fl. oz. whole milk). Serial plasma samples were obtained for tamoxifen levels at the same time points as the other groups. PK parameters were compared between the fasted (treatment B) and fed (treatment C) conditions.

Figure 3 shows the plasma tamoxifen concentrations following soltamox administered under fasted and fed conditions. Table 7 shows the PK results for the food effect part of the study. The AUCinf and AUCt under the fed condition were 11% and 15% higher than the fasting condition (see table 7). The upper limit of the 90% C.I. for AUCinf and AUCt were higher than the pre-set limit of 1.25 for bioequivalence, indicating that there is a food effect on the tamoxifen exposure. Given the relatively high between-subject variability (CV% for AUC: 35%), it appears that the observed food effect (increase of 11-15% in AUC) was small and is not likely to be clinically relevant.

Table 7: Mean (SD) Pharmacokinetic Parameters Following Single Oral Administration of 20mg of SOLTAMOX™ Oral Solution under fasted and fed conditions.

	Treatment B Soltamox™ - fasted (n=30) Mean (SD)	**Treatment C Soltamox™-fed (n=30) Mean (SD)**	**%difference (fed-fasted) /fasted**

Parameter			
AUC (ng•hr/mL)	4131.57 (1499.45)	4601.56 (1749.31)	11%
AUC_T (ng•hr/mL)	3108.82 (847.38)	3571.77 (917.71)	15%
C_{max} (ng/mL)	53.38 (14.03)	56.09 (14.34)	5%
T_{max} (hour) [a]	4.5 (2.13-8.00)	5.0 (4.0-8.0)	-
t½ (hour)	255.70 (69.58)	232.87 (75.48)	9%

a Median (Range)

Table 8: Bioequivalence of Soltamox oral solution under fasted and fed conditions.

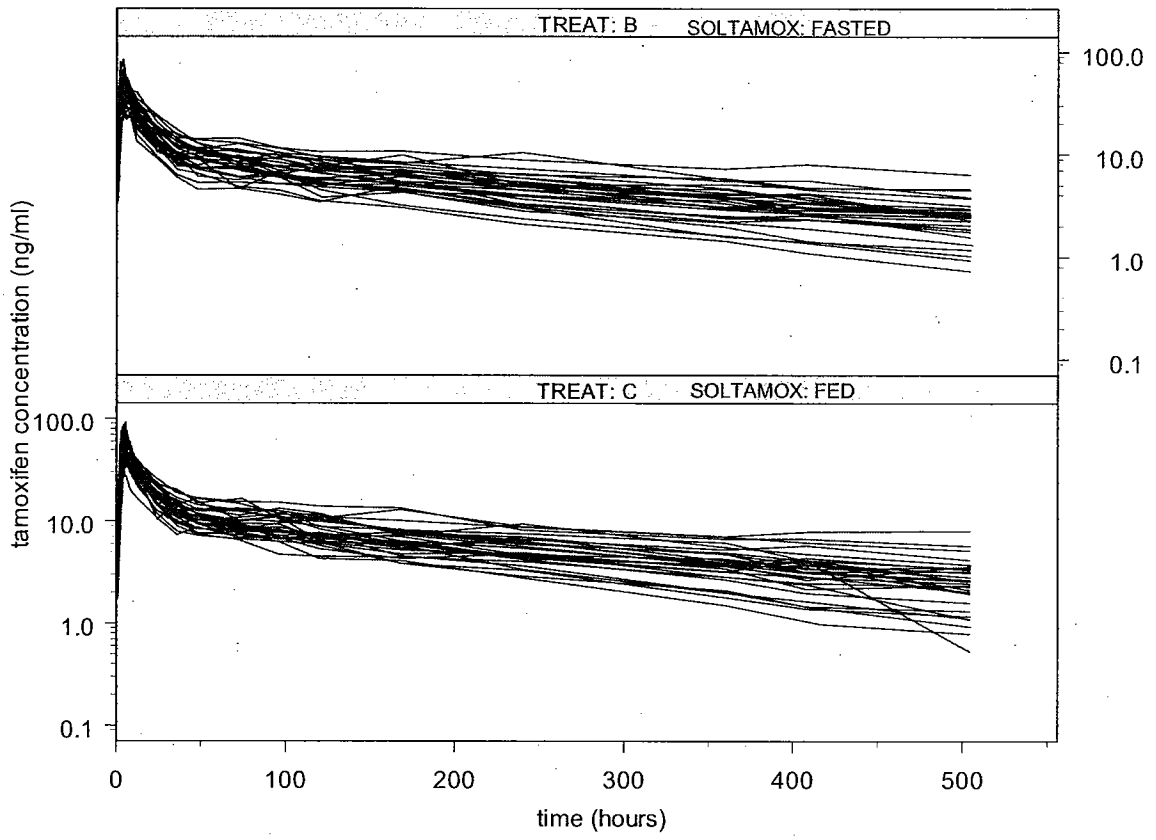
Parameter	Geometric Means Reference Treatment B: Soltamox - Fasted (n=30)	Geometric Means Test Treatment C: Soltamox - Fed (n=30)	Ratio[a]	90% C.I.[b]
AUCinf (ng.hr/ml)	3899.62	4341.98	1.1134	0.9620-1.2887
AUCt (ng.hr/ml)	3000.03	3466.02	1.1553	1.0307-1.2950
Cmax (ng/ml)	51.53	54.44	1.0565	0.9473-1.1783

a: ratio of the geometric LS means of the test to reference formulations.
b: the confidence interval (C.I.) is calculated based on the least squares means difference (natural logarithm scale) back transformed to the original measurement scale.

The Division of Scientific Investigation conducted an audit of the bioequivalence studies conducted by the applicant. The DSI report is included in Appendix E. The DSI concluded that there was no assurance that 14 of the 30 subjects in the Fed group (Soltamox oral solution following standard breakfast) were dosed within 10 min of completion of the breakfast, and recommended that the subjects be excluded from the food effect evaluation

Section G includes a re-analysis of the data showing a 5% decrease in AUCinf following food intake, with no effect on Cmax, AUCt, Tmax or half-life (tables 10 and 11). Thus, food does not appear to have a significant effect on Soltamox exposure.

Figure 2: Tamoxifen concentration vs. time profiles for:
treatment B: Soltamox under fasted conditions (upper panel) and
treatment C: Soltamox under fed conditions (lower panel), across subjects.



F: Analytical Section

F1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma and urine samples were analyzed for tamoxifen concentrations using a validated LC-MS-MS method.

F2. Which metabolites have been selected for analysis and why?

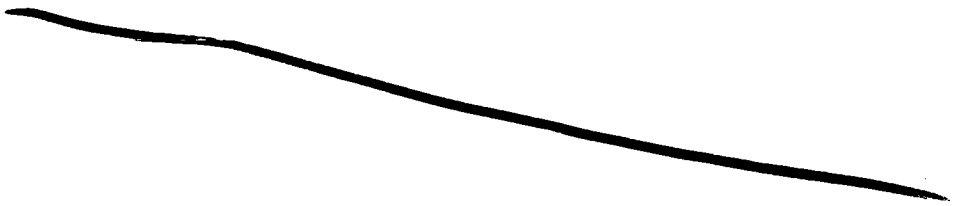
No metabolites were included in the analysis.

F3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentrations of tamoxifen were measured.

F4. What is the bioanalytical method that is used to assess concentrations of the drug?

Method:



Validation:
The assay was validated to determine the precision and accuracy of the calibration standards as well as for controls (quality control samples at 3 different concentrations).
Studies were performed to evaluate freeze-thaw stability, bench-top stability, storage at -20°C in unextracted QC samples, and reinjection and refrigeration stability of extracted QC samples.
Recovery studies were conducted for tamoxifen and the internal standard.
Specificity was determined using six lots of blank plasma. None of the samples showed peaks corresponding to m/z ratios for tamoxifen or internal standard, indicating that there was no endogenous interferences, and that the method had adequate specificity.
Linearity was demonstrated over the calibration range from 0.5 to 100 ng/ml using standards at 0.5, 1, 3, 10, 20, 40, 80 and 100 ng/ml.

Appendix B3 includes a comprehensive summary of the validation results.

F5. What are the figures of merit and performance characteristics for the methods used to assess concentrations of drug?

Linear Range for Calibration Curve	0.5 – 100 ng/ml
LLOQ	0.5 ng/ml
Recovery mean %A: CV% (precision)	 87.5% 0.89-13.35%
Standards Precision – CV% Accuracy - %deviation	 0.99 – 5.38% -3.61 – 3.14%

Precision and Accuracy at LLOQ	
Precision – CV%	4.17%
Accuracy - %deviation	-6.90%
QC samples (1.5, 30, 75 ng/ml)	
Precision – CV%	2.90 – 4.94%
Accuracy - %deviation	-0.08 – 3.97%
Stability of Extracted QC samples	
Reinjection stability: mean %A	99.59%
Refrigeration stability mean %A	99.94%
Stability of Unextracted QC samples	
Bench-top stability: mean %A	97.98%
Freeze/thaw stability: mean %A	
4 cycles	103.52%
1 cycle	97.46%
Long-term storage stability: mean %A	
6 months and 2 days	94.15%
Stability of solutions	
Long-term (6 mo) storage stability: mean %A	
Standard stock solution	100.25%
Working standard solution	100.35%
Working internal standard solution	102.05%

Mean %A: (mean of extracted standard peak area ratio)/(mean of unextracted standard peak area ratio)x100.

G. Addendum – DSI Report

The Division of Scientific Investigation conducted an audit of the bioequivalence studies conducted by the applicant. The DSI report is included in Appendix E. The DSI concluded that there was no assurance that 14 of the 30 subjects in the Fed group (Soltamox oral solution following standard breakfast) were dosed within 10 min of completion of the breakfast, and recommended that the subjects be excluded from the food effect evaluation.

Based on the DSI recommendation, the data from the food effects part of the study were re-evaluated. Tables 10 and 11 show the PK results for the fasted and fed groups with the reduced number of subjects in the fed group (16 instead of the original 30).

Table 10: Mean (SD) Pharmacokinetic Parameters Following Single Oral Administration of 20mg of SOLTAMOX™ Oral Solution under fasted and fed conditions-excluding subjects with unconfirmed dosing as described in text above.

Parameter	Treatment B Soltamox™ - fasted (n=30) Mean (SD)	Treatment C Soltamox™-fed (n=16) Mean (SD)	%difference (fed-fasted) /fasted
AUC (ng•hr/mL)	4131.57 (1499.45)	3908.39 (994.39)	5%
AUC_T (ng•hr/mL)	3108.82 (847.38)	3145.61 (561.83)	1%
C_{max} (ng/mL)	53.38 (14.03)	53.89 (15.73)	1%
T_{max} (hour) [a]	4.5 (2.13-8.00)	5.0 (4.0-8.0)	-
t½ (hour)	255.70 (69.58)	222.15 (66.33)	13%

a Median (Range)

Table 11: Bioequivalence of Soltamox oral solution under fasted and fed conditions-excluding subjects with unconfirmed dosing as described in text above.

Parameter	Geometric Means Reference Treatment B: Soltamox - Fasted (n=30)	Geometric Means Test Treatment C: Soltamox - Fed (n=16)	Ratio[a]	90% C.I.[b]
AUCinf (ng.hr/ml)	3899.62	3787.82	0.9713	0.8200-1.1506
AUCt (ng.hr/ml)	3000.03	3097.13	1.0324	0.9032-1.1799
Cmax (ng/ml)	51.53	51.93	1.0079	0.8806-1.1535

a: ratio of the geometric LS means of the test to reference formulations.
b: the confidence interval (C.I.) is calculated based on the least squares means difference (natural logarithm scale) back transformed to the original measurement scale.

The AUCinf under the fed condition was 5% higher than the fasting condition (see table 10). The upper limit of the 90% C.I. for AUCinf and AUCt were within the pre-set limit of 1.25 for bioequivalence, indicating that there is no effect of food on tamoxifen exposure following Soltamox (see table 11). Given the relatively high between-subject variability (CV% for AUC: 35%), it appears that the observed food effect (increase of 5% in AUC) was small and is not likely to be clinically relevant.

To verify that the sample size of the fed and fasted groups had adequate power for observing a significant difference if there was one, the power was estimated for detecting a 20% difference between groups, given an estimate of variability (CV%) of 25%, at an alpha (α) level of 0.05. For the original sample, with 30 subjects per group, the estimate of power was 0.86.
With the reduced sample size of 16 subjects in the fed group and 30 subjects in the fasted group, the estimate of power reduced to 0.72. This is lower than the desired power level of 0.80,

however, given the close similarity between estimates of Cmax and AUC for the 2 groups, it is unlikely that increasing the sample size of the fed group (an increase to 22 subjects would provide power ~ 0.80).

References:

Bekaii-Saab TS, Perloff MD, Weemhoff JL, Greenblatt DJ, von Moltke LL. Interactions of tamoxifen, N-desmethyltamoxifen and 4-hydroxytamoxifen with P-glycoprotein and CYP3A. Biopharm Drug Dispos 25:283-289, 2004.

de Vos D, Guelen PJ, Stevenson D. The bioavailability of Tamoplex (tamoxifen). Part 4. A parallel study comparing Tamoplex and four batches of Nolvadex in healthy male volunteers. Methods Find Exp Clin Pharmacol 11:647-655, 1989.

Fuchs WS, Leary WP, van der Meer MJ, Gay S, Witschital K, von Nieciecki A. Pharmacokinetics and bioavailability of tamoxifen in postmenopausal healthy women. Arzneimittelforschung 46:418-422, 1996.

Guelen PJ, Stevenson D, Briggs RJ, de Vos D. The bioavailability of Tamoplex (tamoxifen). Part 2. A single dose cross-over study in healthy male volunteers. Methods Find Exp Clin Pharmacol 9:685-690, 1987.

Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. Clin Pharmacokinet 44:349-366, 2005.

III. Detailed Labeling Recommendations

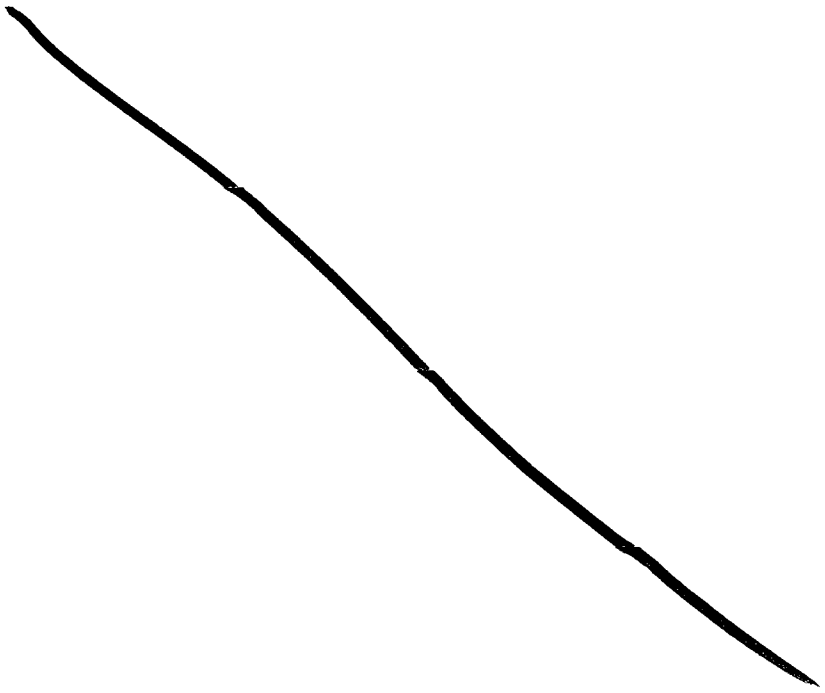
The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the current submission to be acceptable.

The applicant's labeling changes are acceptable, [with the following minor revisions…]

1. Labeling revision #1

Current Applicant Label

CLINICAL PHARMACOLOGY



2 Page(s) Withheld

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IV. Appendices

A. Proposed Package Insert (Annotated)

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B. Individual Study Synopses

1. Study #: C0501

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Name of Company: Savient Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: Soltamox™ Oral Solution		
Name of Active Ingredient: tamoxifen citrate		

Title of Studies: (C0501) Randomized, 1-period, Parallel, Bioequivalence Study of Soltamox™ (tamoxifen) Oral Solution 10 mg/5mL Administered as 2 x 5 mL (20 mg) Oral Solution and Nolvadex® (tamoxifen) 20 mg Tablets Administered as a 1 X 20 mg Tablet in Healthy Perimenopausal and Postmenopausal Female Subjects Under Fed and Fasting Conditions

(C0501-2) Open-Label, Single-Dose Re-challenge Study of Nolvadex® (tamoxifen citrate) 20 mg Tablets Administered as a 1 X 20 mg Tablet in Healthy Perimenopausal and Postmenopausal Female Subjects Under Fasting Conditions

Investigators: [redacted]

Study Centers: [redacted]

Publication (reference): None

Study Period: January 8, 2004 to July 6, 2004	**Phase of Development:** 1

Objectives: The primary objective of Study C0501 was to compare the rate and extent of absorption of Soltamox™ Oral Solution (tamoxifen) 10 mg/5 mL oral solution (test) administered as 2 x 5 mL (20mg) oral solution versus Nolvadex® (tamoxifen) 20 mg tablets (reference) administered as 1 x 20 mg tablet under fasting conditions. The secondary objective was to determine the drug absorption from the Soltamox™ Oral Solution under fed conditions.

Study C0501-2 was conducted to re-evaluate the pharmacokinetics of the Nolvadex® tablet for one subject (002/008) with discordant pharmacokinetic results in Study C0501 along with five other subjects who also received a Nolvadex® tablet in the previous study (C0501). [redacted]

Methodology: Study C0501 was a multi-center (two sites), open-label, randomized, 1-period, parallel group bioequivalence study. Potential study participants visited the clinical research facility as needed for screening evaluations. Eligible subjects then reported to the clinic on the day prior to dose administration (Day –1). Each subject was randomized to receive a single dose of study medication (either Treatment A, B, or C) on the morning of Day 1 and remained in the clinic until released by the Investigator on Day 3. Treatments A (Nolvadex® 20 mg tablets) and B (Soltamox™ Oral Solution) were administered in the fasted state, while Treatment C (Soltamox™ Oral Solution) was administered 10 minutes after a standard high-fat breakfast. Subjects returned to the clinic for pharmacokinetic and safety assessments on Days 4, 5, 6, 8, 11, 16, 18, and 22.

The design and procedures of Study C0501-2 were identical to those of the original study (C0501) with the exception that only six subjects were treated and all subjects received the Nolvadex® tablet (reference).

Number of Subjects Planned and Analyzed: Up to 96 subjects were planned; 95 were treated and analyzed for safety; 94 were analyzed for pharmacokinetics in Study C0501. Six subjects were treated and analyzed for safety and pharmacokinetics in Study C0501-2.

Diagnosis and Main Criteria for Inclusion: Healthy, non-pregnant perimenopausal or postmenopausal females

Duration of Treatment: Single dose administered on Day 1. Follow-up asssessments conducted through Day 22.

Test Product, Dose and Mode of Administration, Batch Number: Soltamox™ Oral Solution (tamoxifen) 20 mg (2 x 5 mL of a 10 mg/5 mL solution) administered under fasting and fed conditions, Lot Number 005380

Reference Therapy, Dose and Mode of Administration, Batch Number: Nolvadex® (tamoxifen) 20 mg tablets administered as 1 x 20 mg tablet under fasting conditions, Lot Number 3246J

Criteria for Evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters were estimated for each of the three treatments:

maximum plasma concentration (C_{max}), time that C_{max} was observed after dosing (T_{max}), area under the concentration versus time curve from time 0 to the last measured concentration (AUC_T), area under the concentration versus time curve from time 0 to infinity (AUC), terminal or elimination rate constant (λ_z [Ke]), and terminal or elimination half-life ($t_{½}$).

Treatments A and B were analyzed for bioequivalence, and Treatments B and C were analyzed to determine the effect of food on the pharmacokinetics of Soltamox™Oral Solution.

For Study C0501-2, in addition to the analyses decribed above, the within subject variability for the pharmacokinetic parameters was assessed by comparing the results obtained in the original study (C0501) to the results from the retest study (C0501-2).

Safety: Safety was evaluated through the recording and monitoring of adverse events (AEs), physical examination results, and the assessment of clinical laboratory values, vital signs, and electrocardiogram (ECG) measurements.

Statistical Methods:

Efficacy:

Therapeutic efficacy was not assessed in this study.

Pharmacokinetics:
All pharmacokinetic results were summarized using appropriate descriptive statistics. Following log-transformation (natural log), AUC, AUC_T, and C_{max} results were compared between treatment groups using the two one-sided t-test procedure. The primary analysis was a comparison of the rate and extent of absorption of Soltamox™ Oral Solution 10 mg/5 mL administered as 2 x 5 mL (20 mg tamoxifen, test) versus Nolvadex® (tamoxifen) 20 mg tablets (reference) administered under fasting conditions. The ratio of the geometric least squares means (antilog of the least squares means) of the test treatment to the reference treatment was calculated, along with its 90% confidence interval. Bioequivalence was defined as a 90% confidence interval that fell within the interval 80 to 125%. The Wilcoxon signed rank test was applied to the comparison of T_{max} values. A secondary comparison of the pharmacokinetics of Soltamox™ Oral Solution under fed and fasting conditions was conducted.

Safety: Safety parameters were summarized using descriptive statistics. No statistical analyses of the safety parameters were planned.

SUMMARY – CONCLUSIONS:

Efficacy Results:

Therapeutic efficacy was not assessed in this study.

Pharmacokinetic Results:

A total of 96 subjects were enrolled and randomized in the study, 34 to Nolvadex® tablets, 31 to Soltamox™ solution (fasted), and 31 to Soltamox™ solution (fed). Of the 96 subjects randomized, 34, 31, and 30 subjects, respectively, were treated, and 34, 30, and 30 completed the study. One subject in the Soltamox™ fed treatment group (Subject 001/025) discontinued for an AE prior to treatment, and one subject in the Soltamox™ fasted group (Subject 002/022) was lost to follow-up after the 48-hour post-dose timepoint. This subject was not included in the PK summary or analyses.

Results of the study showed that tamoxifen plasma concentrations for one subject (Subject 002/008) who received a tamoxifen tablet were a small fraction of those measured in other subjects, regardless of group, at all time points to end of study (Day 22). As dosing for the subject was confirmed and no evidence of analytical laboratory error was found, product failure was suspected. When the results for this subject were included in the analysis of bioequivalence, the 90% confidence intervals around the C_{max} and AUC_T ratios met the bioequivalence criteria; however, the 90% CI around the AUC ratio of Soltamox™ Oral Solution and Nolvadex® tablets was 90.37% - 125.16%. When results for this subject were excluded, the two formulations were found to be bioequivalent.

To gain some understanding of this anomaly, a retest study (Study C0501-2) of the outlier subject along with five others from the same previous dosing cohort (i.e., Nolvadex® tablet) was conducted under a protocol that was essentially identical to the original C0501 protocol. On retest, the outlier subject's AUC values for tamoxifen increased by approximately 7 fold relative to her initial dosing; the AUCs for the other five subjects were comparable to their values from the original study. When the statistical analysis on the pharmacokinetic data set was performed using the outlier subject's retest results (instead of her initial anomalous results) or when the analysis was performed substituting the data from all six retest subjects (replacing their initial results), the 90% CIs for C_{max}, AUC_T and AUC fell within the FDA's guideline for bioequivalence.

Additional statistical analyses were performed to assess the within subject variability for C_{max}, AUC, and AUC$_T$ between the result obtained in the original study and the retest study. The results of these analyses demonstrated clearly that the coefficients of variation (%CVs) for the 5 cohort subjects were low (~10% or less), while CVs for the outlier subject were ~100%, suggesting that her first result was an anomaly, and providing justification for the exclusion of this subject's data from the bioequivalence analysis conducted in the original study. Although the reason for the first outcome cannot be conclusively explained, the results of the retest suggest that the likely cause for the anomalous result on first dosing was product failure of the tablet.

Pharmacokinetic Results (continued):

Administration of Soltamox™ Oral Solution after a high-fat meal resulted in slower absorption and 11 to 15% greater AUC of tamoxifen compared to that observed after administration in the fasted state. Because the effect was slight and C_{max} was unaffected, the difference in AUC is not likely clinically meaningful.

Safety Results:

Of the 96 subjects randomized in the study, 95 received a single 20 mg dose of tamoxifen. Of these, 34 subjects received one 20 mg Nolvadex® tablet after an overnight fast, 31 subjects received 2 x 5 mL of the Soltamox™ Oral Solution after an overnight fast, and 30 subjects received 2 x 5 mL of the Soltamox™ Oral Solution following a high-fat breakfast. In addition, six subjects from the original study received a second 20 mg Nolvadex® tablet in the retest study, C0501-2. Three of these subjects (002/001, 002/003, and 002/008) received the second dose after an 81-day washout period, while three other subjects (002/027, 002/033, and 002/037) received the second dose after a 71-day washout.

Treatment was well tolerated by all subjects, and the incidence of AEs was comparable across treatment groups, with 8 (23.5%), 9 (29.0%), and 6 (20.0%) subjects in Treatment Groups A, B, and C, respectively, reporting at least one treatment-emergent AE. As would be expected in a single-dose study in healthy perimenopausal or postmenopausal females, the incidence of treatment-related AEs was low; only six subjects experienced AEs considered to be possibly or probably related to study drug : throat irritation (two subjects in Group B and one subject in Group C); headache (one subject in Group A and one subject in Group B); vomiting (one subject in Group B); and flushing (one subject in Group A). All reported events were mild or moderate in intensity, with the exception of one event of severe arthritis (unrelated) in the Nolvadex® tablet group. Among the few AEs considered related to treatment, three of 61 subjects (4.9%) treated with Soltamox™ Oral Solution reported throat irritation on the day of dosing, while none of the subjects in the Nolvadex® tablet group reported this event. The events were all mild; two of the events resolved within 2 hours and the other resolved within 24 hours of onset. No other apparent treatment-related trends were observed in the incidence of AEs. No AEs were reported among the six subjects in the retest study. Across both studies, no clinically meaningful changes were observed in clinical laboratory assessments, physical examination findings, vital signs measurements, or ECG results.

Conclusions:

Soltamox™ Oral Solution and Nolvadex® tamoxifen tablets were well tolerated and were found to be bioequivalent in this study with similar safety profiles. The effect of food on drug absorption and pharmacokinetics of the oral solution was minimal.

Date of Report: November 1, 2004

2. Study #: TAMOX1

SYNOPSIS

Investigators

Study year

December 1997– January 1998

Objective

The aim of the study was to investigate the oral bioavailability of a new generic solution of Tamoxifen manufactured by Rosemont Pharmaceuticals Ltd compared to the currently marketed tablet formulation Nolvadex™ manufactured by Zeneca Ltd in a single dose administration.

Number of subjects

24

Inclusion criteria

To participate all subjects must be determined healthy on the basis of physical, examination and results of blood, urine, ECG and laboratory tests. All other medication was prohibited for 14 days prior to and during the study. Caffeine beverages were prohibited during the blood sampling period in the clinic. All volunteers gave written informed consent. The polish version of the informed consent and volunteer information appears on page 2 of the CRF. The original English language version in contained in appendix A of the protocol.

Test products

Test product A: Tamoxifen solution containing 10mg/5ml
Manufactured by Rosemont Pharmaceuticals Ltd, BN TAG100S
Reference product B: Nolvadex D™ tablets 20mg. Manufactured by Zeneca, BN PN 292. All products were administered orally.

Duration of treatment

One single dose given on 2 consecutive periods. Each period separated by 28 days wash-out.

Criteria for Evaluation

Based on HPLC analysis of extracted blood samples the following parameters were evaluated: Cmax, Tmax AUC_∞, AUC_t, T 0.5. Blood samples were taken at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 4, 5, 6, 8, 12, 24, 48, 96, 168, 336, 504, and 672 hours.

Analytical Methods

Two different sample preparation methods were used to prepare the plasma sample for HPLC detection of the Tamoxifen levels in plasma. The first method was used for samples up to 168 hours and plasma concentrations above 2.5ng/ml, the second at longer sampling times and concentrations below this level. Two methods were used for analysis since the sample preparation time in method 1 was shorter and less expensive but method 2 was more sensitive giving a limit of detection of 0.25ng/ml.

Statistical Methods

Comparison of the values of Cmax, Tmax, AUCt, and AUC_∞ between the reference and test products using: Mean, standard deviation, ANOVA, t-tests ($p=0.05$). Comparison of the 90% confidence interval ratios (CI) using log transform data of Cmax, Tmax, T0.5, AUCt, and AUC_∞. Statistical calculations were performed by an independent statistician using the SAS system.

Summary

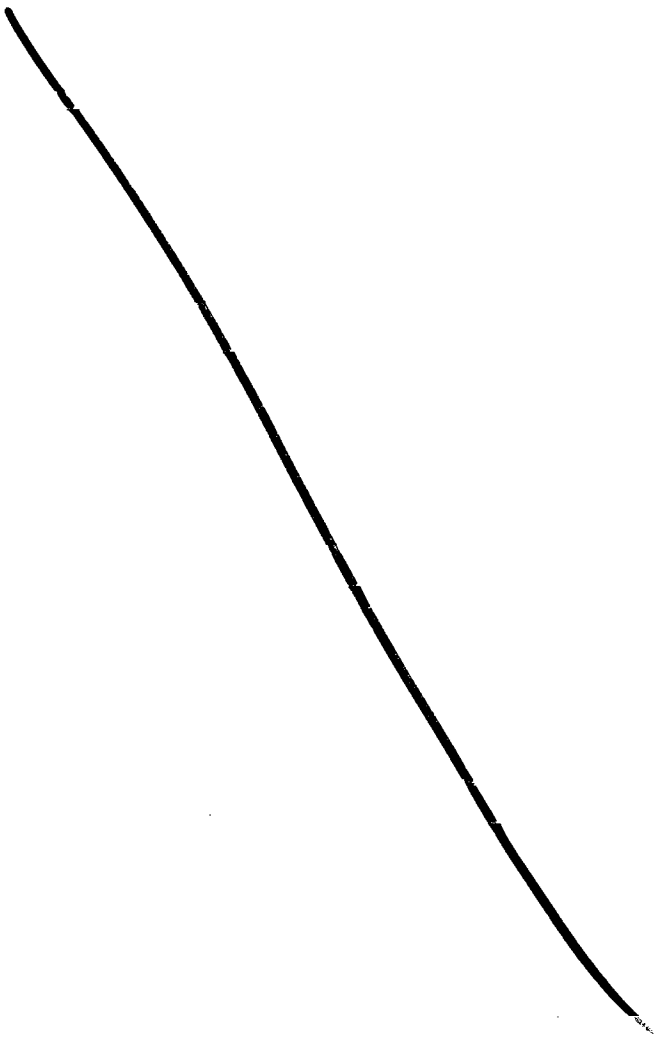
Bioequivalence Parameter	Units	Reference	Test	Point Estimate	LogR	LogT	90% CI	Test outcome
Cmax	ng/ml	27.04	25.69	0.95	3.28	3.23	0.91-1.00	Equivalent
Tmax	hrs	4.54	4.21	0.94	1.47	1.41	0.84-1.05	Equivalent
T0.5	hrs	183.8	205.5	1.10	5.17	5.27	1.03-1.19	Equivalent
AUCt	ng/ml.hr	1661.7	1733.5	1.04	7.39	7.43	0.97-1.12	Equivalent
AUC_∞	ng/ml.hr	2146.7	2266.9	1.06	7.64	7.70	1.00-1.14	Equivalent

Recovery was ca. 104% for method 1 and 102.6% for method 2. Precision data showed a maximum CV of 8.5% (5ng/ml intra-day) for method 1 and 8.9% (0.5ng/0.5ml inter-day) for method 2 (limit 10%). The mean plasma concentration time curves are presented on pages 12 and 13 of this report.

Conclusions

No statistically significant differences in terms of t-test were found (at the p=0.05 level) for any of the studied parameters. The products were within the 90% confidence interval ratio limits (0.8 - 1.25) for all the studied parameters. The products can therefore be regarded as fully bioequivalent.

Fig 1. Individual plasma concentration time curves following a single dose of 20 mg tamoxifen oral solution or 20mg Nolvadex D



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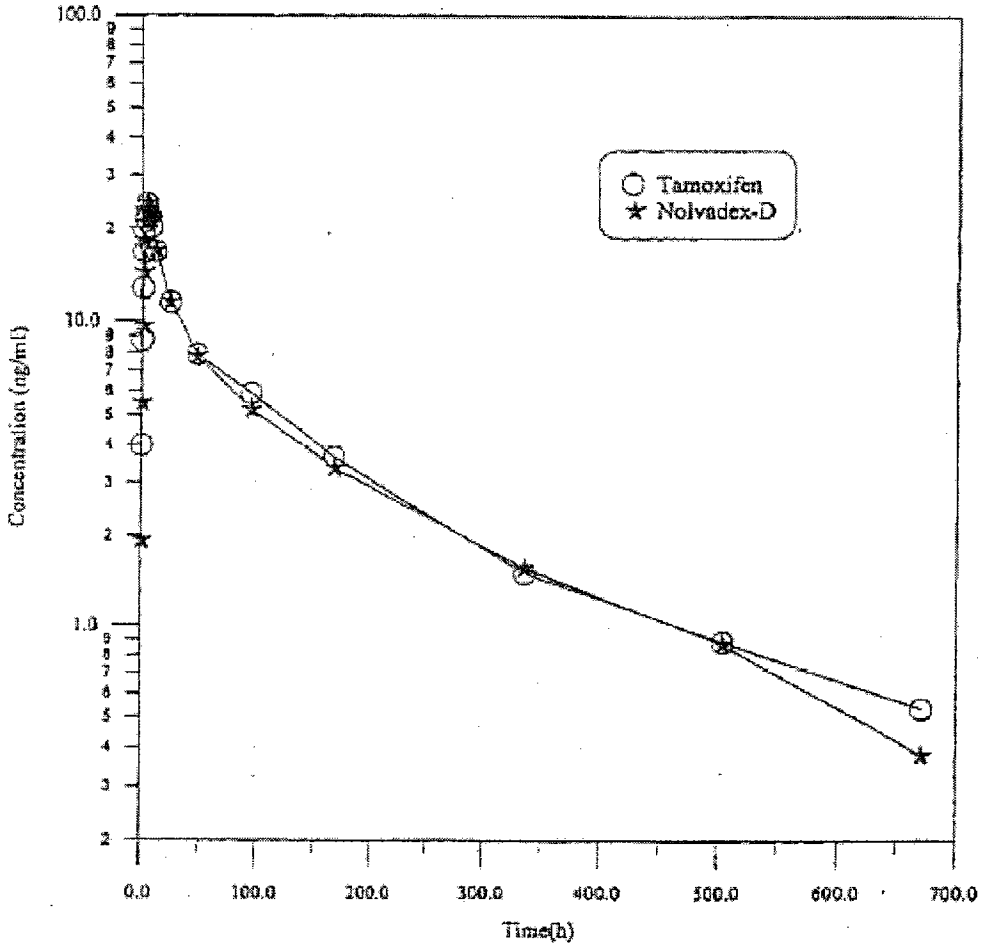
Withheld Track Number: Clin Pharm/Bio- 4

Fig 6. Mean of plasma tamoxifen concentration/time curve following a single 20 mg oral dose of Tamoxifen oral solution or 20 mg oral dose of Nolvadex-D.



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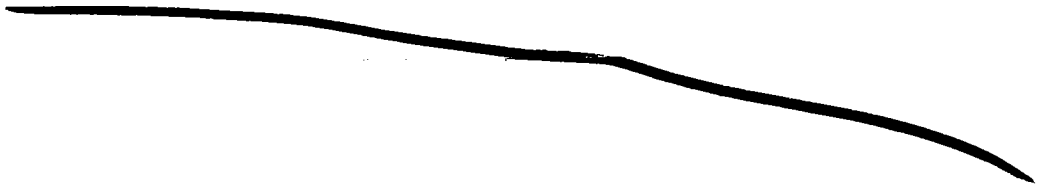
3. Bioanalytical Validation Report



Validation:

The following studies were conducted to validate the analytical method for tamoxifen.

- precision and accuracy of the calibration standards
- precision and accuracy of the quality control (QC) samples at 3 different concentrations
- recovery study for tamoxifen and internal standard
- specificity of method
- linearity over the calibration range
- stability studies:
    - freeze-thaw, bench-top and storage at -20°C in unextracted QC samples
    - reinjection and refrigeration stability of extracted QC samples.

The following table summarizes the results of the validation studies. Individual study results follow.

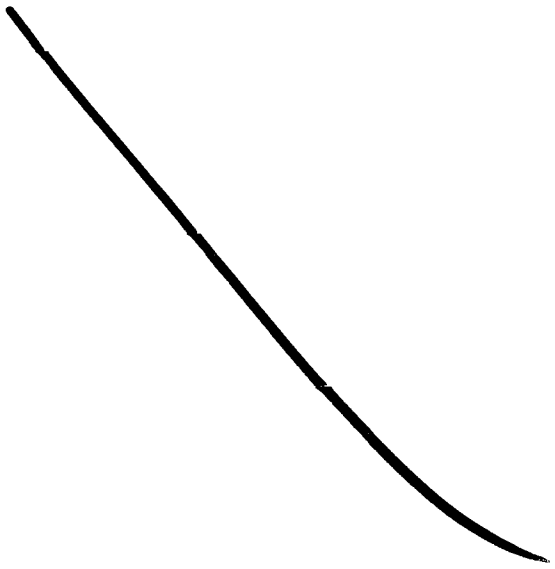
Linear Range for Calibration Curve	0.5 – 100 ng/ml
LLOQ	0.5 ng/ml
Recovery mean %A: CV% (precision)	 87.5% 0.89-13.35%
Standards Precision – CV% Accuracy - %deviation	 0.99 – 5.38% -3.61 – 3.14%
Precision and Accuracy at LLOQ Precision – CV% Accuracy - %deviation	 4.17% -6.90%
QC samples (1.5, 30, 75 ng/ml) Precision – CV% Accuracy - %deviation	 2.90 – 4.94% -0.08 – 3.97%
Stability of Extracted QC samples Reinjection stability: mean %A Refrigeration stability mean %A	 99.59% 99.94%
Stability of Unextracted QC samples	

Bench-top stability: mean %A	97.98%
Freeze/thaw stability: mean %A	
4 cycles	103.52%
1 cycle	97.46%
Long-term storage stability: mean %A	
6 months and 2 days	94.15%
Stability of solutions	
Long-term (6 mo) storage stability: mean %A	
Standard stock solution	100.25%
Working standard solution	100.35%
Working internal standard solution	102.05%

Mean %A: (mean of extracted standard peak area ratio)/(mean of unextracted standard peak area ratio)x100.

Calibration Curve and Linearity

Linearity of the method was demonstrated over the calibration range from 0.5 to 100 ng/ml. The calibration standard solutions were at 0.5, 1, 3, 10, 20, 40, 80 and 100 ng/ml. The following figure shows the concentration vs. peak area ratios. The lower limit of quantitation was determined to be 0.5 ng/ml.



28 Page(s) Withheld

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Withheld Track Number: Clin Pharm/Bio- 5

D. CPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-807	**Brand Name**	SOLTAMOX™ Oral Solution
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Tamoxifen citrate
Medical Division	HFD-150	**Drug Class**	Anti-cancer – anti-estrogen
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	Treatment and prevention of breast cancer
OCPB Team Leader	Brian Booth	**Dosage Form**	Oral solution (10mg/5ml)
		Dosing Regimen	20-40 mg/day
Date of Submission	12/29/2004	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	6/01/05	**Sponsor**	Savient Pharmaceuticals Inc.
PDUFA Due Date	10/28/05	**Priority Classification**	S
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
A. Healthy Volunteers-				
single dose:				
multiple dose:				
B. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
Pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Oral bioavailability of test formulation (solution) compared to currently marketed tablet formulation
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			Parallel arm of above study included evaluation of food effect.
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• Bioavailability of oral solution (test formulation) compared to marketed tablet (reference) formulation. • Effect of food on bioavailability of oral solution.	
Other comments or information not included above		
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-807, HFD-850 (Electronic Entry), HFD-150 (Cottrell),
HFD-860 (Mehta, Rahman, Booth, Ramchandani), CDR (Biopharm).

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

/s/

Roshni Ramchandani
9/29/2005 10:58:00 AM
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MEDICAL OFFICER

Brian Booth
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Atiqur Rahman
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