DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

AUG - 7 2000

William R. Woolever
Director, Post-Marketing Regulatory Affairs
Shire Laboratories, Inc.
1550 East Gude Drive
Rockville, MD 20850

RE: NDA 20-497
Fareston® (toremifene citrate)
MACMIS ID# 8823

Dear Mr. Woolever:

As part of our routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware that Shire Laboratories, Inc. (Shire) is promoting its product, Fareston, in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and its implementing regulations. Reference is made to a sales aid (F01019935K) that was submitted under cover of Form FDA 2253.

We request that you cease distribution and use of false or misleading messages in all promotional materials as outlined below.

Misleading Efficacy Claims

Shire claims that Fareston is "First-line therapy for advanced breast cancer," which implies that Fareston is useful for treating advanced breast cancer in women regardless of tumor type or menopausal status. This claim is overly broad and does not adequately communicate the limitations to the indication from the approved product labeling (APL):

> *Fareston is indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.*

Therefore, your claim is misleading because it implies usefulness in a broader population than has been demonstrated by substantial evidence.

In addition, Shire claims that Fareston demonstrated "First-line efficacy equal to tamoxifen in three randomized, well-controlled clinical trials with 1157 patients." Following this statement are graphs of response rates, median times to progression, and median survival for Fareston versus tamoxifen patients. This presentation is misleading because only data from one of the trials (i.e., the North American trial) are presented. This selective presentation of information misleadingly suggests that all three clinical trials demonstrated equal efficacy responses for Fareston as compared to tamoxifen. However, only two of the three studies showed similar results for all effectiveness endpoints, none of these results were statistically significant, and the third study showed more favorable results for tamoxifen (i.e., longer time to progression).

Overstatement of Safety Regarding Carcinogenic Potential

Shire minimizes the risks associated with Fareston treatment by presenting statements that imply that Fareston has no or minimal carcinogenic potential. For example:

> *Designed for safety/minimal carcinogenic potential*
>
> *No endometrial cancers attributable to Fareston in over 17 years of clinical experience*
>
> *No endometrial cancers attributable to Fareston in 11 years of market experience*

However, these statements are not supported by substantial evidence. The tumorigenicity information in the Warnings section of the APL states:

> *Since most toremifene trials have been conducted in patients with metastatic disease, adequate data on the potential endometrial tumorigenicity of long-term treatment with Fareston are not available. Endometrial hyperplasia has been reported. Some patients treated with Fareston have developed endometrial cancer, but circumstances (short duration of treatment or prior antiestrogen treatment or premalignant conditions) make it difficult to establish the role of Fareston.*

Your claims misleadingly suggest that Fareston is safer in the intended population than has been demonstrated by substantial evidence. Furthermore, marketing experience does not provide substantial evidence for safety claims.

Misleading Comparative Safety Claims

Moreover, Shire presents information from nonclinical studies to suggest clinical significance, including superior safety over tamoxifen, when no such relevance or superiority has been demonstrated by substantial evidence. The following are examples of claims that imply superior safety of Fareston over tamoxifen:

> *No DNA adducts have been reported with Fareston. In contrast, adducts were detected in the endometria of 6 of 13 patients treated with tamoxifen, compared to none in untreated controls. Another study found adducts in the endometria of 5 of 7 breast cancer patients treated with tamoxifen.*
>
> *If efficacy is equal, wouldn't a safer, less expensive first-line drug be preferable?*

In addition to these claims, Shire presents the chemical structures of tamoxifen and toremifene and labels them "problem" and "solution," respectively, based on the potential ability to form DNA adducts. The clinical relevance of DNA adducts has not been established. This overall presentation is misleading because it suggests that Fareston is safer than tamoxifen based on chemical or mechanism of action properties when this has not been demonstrated by substantial evidence. Likewise, your claims that Fareston is "The next generation of selective estrogen-receptor modulators (SERMs)" and that Fareston offers "The next generation of first-line clinical benefits" are unsubstantiated and imply superiority over other SERMs.

Lack of Fair Balance

Promotional materials are lacking in fair balance if they fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as the typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. These pieces lack fair balance with respect to the presentation of risk information. Shire uses graphs, pictures, bullets, and enlarged fonts to prominently display efficacy information but does not display risk information with reasonably comparable prominence.

In addition, you failed to include serious adverse effects associated with Fareston in clinical trials, specifically, elevated liver function tests. Omission of this important safety information minimizes the risks associated with Fareston.

Promotion of Unapproved Uses

Shire promotes Fareston for unapproved uses by making the following statements:

> *An antiatherogenic effect on lipids*
>
> *Fareston lowers total cholesterol, LDL, and in one report, raised HDL, thereby exerting a positive effect that is important in a postmenopausal population at risk of atherosclerosis*
>
> *Fareston prevents the age-associated decrease in bone density that contributes to osteoporosis*

The sales aid includes bar graphs showing the beneficial effect of Fareston on cholesterol levels. These claims and representations promote the use of Fareston for lowering lipids and cholesterol and maintaining bone density. Therefore, this presentation constitutes promotion of unapproved uses for Fareston, in violation of the Act and its implementing regulations.

Shire should immediately cease dissemination of these and similar claims and presentations in all promotional materials for Fareston. Shire should submit in writing, on or before August 21, 2000, a description of the steps that will be taken to comply with the above request. In your response, you should include a list of all materials that were discontinued and the date of discontinuation.

Shire should direct its response to me by facsimile at (301) 594-6771, or by written communication at the Food and Drug Administration; Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID# 8823 and NDA 20-497.

Sincerely,

/S/

Jean-Ah Choi, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

First-line therapy for advanced breast cancer

The next generation of selective estrogen-receptor modulators

FARESTON®

(toremifene citrate)

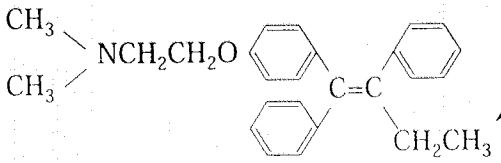
Designed for safety

FARESTON®
(toremifene citrate)
60mg Tablets

Once-a-day

Designed for minimal carcinogenic potential

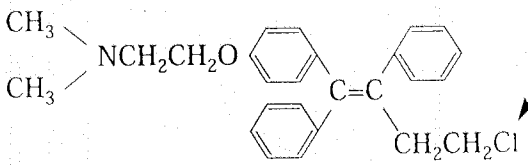
tamoxifen



Problem

This ethyl group binds to DNA to form mutagenic adducts that may initiate neoplasias.

toremifene



Solution

The single chlorine atom prevents DNA binding and adduct formation.

Fareston is not an alkylator

Carcinogenic Properties	Fareston	tamoxifen
Alkylation[1]	No	Yes
Initiation[2]	No	Yes
Promotion[3]	Weak	Strong

■ No DNA adducts have been reported with Fareston

In contrast, adducts were detected in the endometria of 6 of 13 patients treated with tamoxifen, compared to none in untreated controls.[4] Another study found adducts in the endometria of 5 of 7 breast cancer patients treated with tamoxifen.[5]

1. Williams GM. *Prim Care Can* 1999;19(suppl 2):29-31
2. Williams GM *et al. Carcinogenesis* 1997;18:2247-53
3. Dragan Y *et al. Carcinogenesis* 1995;16:2733-38
4. Shibutani S *et al. Chem Res Toxicol* 1999;12:646-53
5. Hemminki *et al. Cancer Res* 1996;56:437-7

FARESTON®
(toremifene citrate)
60mg Tablets

Once-a-day

Designed for safety in practice

No endometrial cancers attributable to Fareston in over 17 years of clinical trial experience[6,7]

In clinical trials, endometrial cancer developed in 2 of 565 tamoxifen patients, but not in any of the 592 Fareston patients.[8]

No endometrial cancers attributable to Fareston in 11 years of market experience[6,7]

Fareston has been prescribed for up to 11 years around the globe, including all of Western Europe, Russia, Japan, Australia, New Zealand, South Korea, Taiwan, Argentina, Peru, and South Africa.[6]

Please see enclosed full Prescribing Information.

6. Data on file, Roberts Pharmaceutical Corporation.
7. Maenpaa J *et al. J Nat Can Inst* 1999;91:972.
8. Gams R *Oncology* 1997;11(suppl 4):25-28.

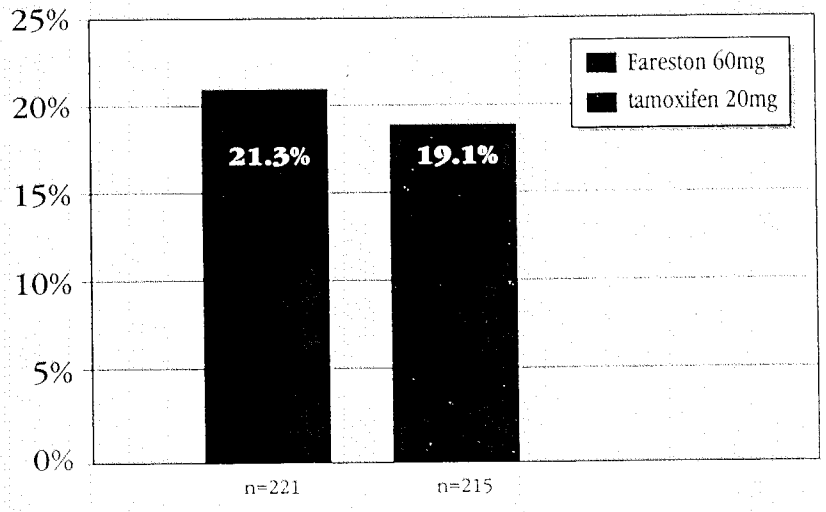
FARESTON®
(toremifene citrate)
60mg Tablets

Once-a-day

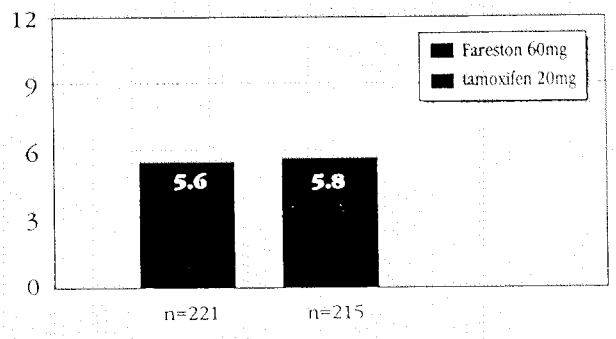
Designed for effectiveness

- First-line efficacy equal to tamoxifen in three randomized, well-controlled clinical trials with 1157 patients [8]
- Proven effective in hundreds of thousands of patient-years of treatment worldwide [6]

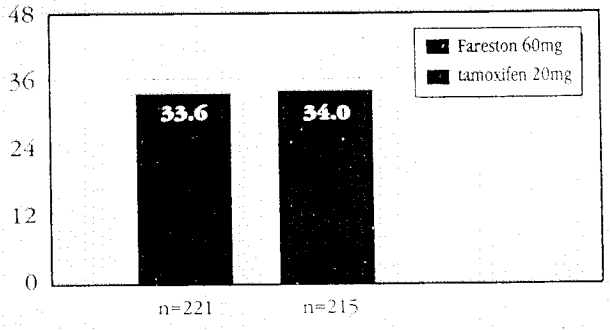
Response rate in North American trials [9] *



Median time to progression [9] * *(months)*



Median survival [9] * *(months)*



6. Data on file, Roberts Pharmaceutical Corporation
7. Maenpaa J *et al. J Nat Can Inst* 1999;91:972
8. Gams R *Oncology* 1997;11(suppl 4):23-28
9. Hayes DF *et al. J Clin Oncol* 1995;13:255-66
* Not statistically significant

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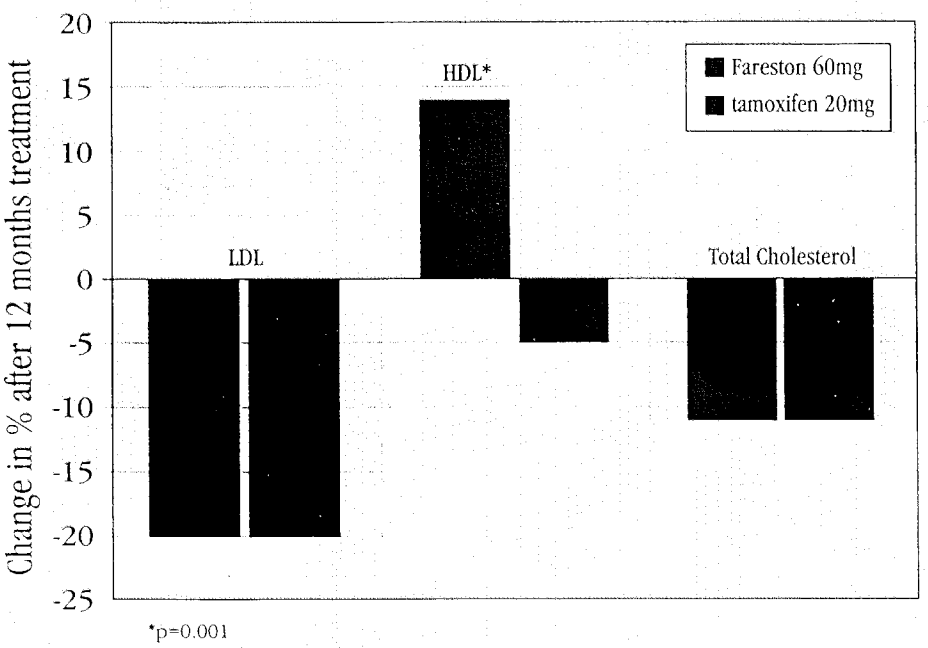
60mg Tablets

Once-a-day

An antiatherogenic effect on lipids

- Fareston lowers total cholesterol,[10,11] LDL[10,11] and in one report, raised HDL,[10] thereby exerting a positive effect that is important in a postmenopausal population at risk of atherosclerosis.

Effect of antiestrogens on cholesterol levels [10]



*p=0.001

Maintains bone density

- Fareston prevents the age-associated decrease in bone density that contributes to osteoporosis [12]

Please see enclosed full Prescribing Information.

10. Saarto T *et al. J Clin Oncol* 1996;14:429-33
11. Gylling, H. *et al. J Clin Oncol* 1995;13:2900-5
12. Marttunen MB *et al. J Clin Endocrinol Metab* 1998;83:1158-61

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Once-a-day

Proven tolerability

As well-tolerated as tamoxifen at all doses studied[8]

In North American clinical trials vs tamoxifen, the most commonly observed side effects were hot flashes (35% vs 30%), sweating (20% vs 17%), nausea (14% vs 15%), and vaginal discharge (13% vs 16%); these side effects occurred at similar grades and frequency in each treatment group.[9]

Proven safety

A low risk of serious side effects[8]

During clinical trials involving 1157 patients treated with Fareston or tamoxifen, there was a low incidence of serious side effects, including cardiac events (2.2% vs 2.5%) and thromboembolic events (3.5% vs 3.5%), respectively.[8]

There was a higher incidence of ocular events (10.3% vs 9.6%) in both arms, but these, like some of the cardiovascular events, may be age-associated.[8]

As with other antiestrogens, tumor flare, hypercalcemia, and vaginal bleeding have been reported in some breast cancer patients being treated with Fareston. Patients with a history of thromboembolic disease should generally not be treated with Fareston.

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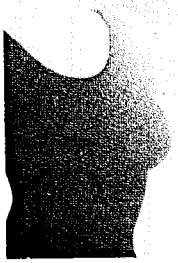
8. Gams R *Oncology* 1997;11(suppl 1):23-28
9. Hayes DF *et al. J Clin Oncol* 1995;13:255-66

The next generation of first-line clinical benefits

- Antitumor effectiveness
- Low carcinogenic potential
- Antiatherosclerotic lipid profile
- Maintains bone density
- Well-tolerated
- Once-a-day dosage
- Favorably priced



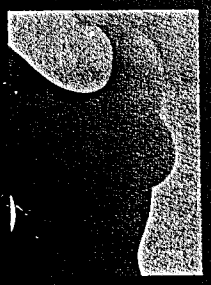
FARESTON®
(toremifene citrate)
60mg Tablets

Once-a-day

Designed for safety

Designed to improve the benefit/risk ratio

If efficacy is equal,
wouldn't a safer, less expensive first-line drug be preferable?



FARESTON®
(toremifene citrate)
60mg Tablets

Once-a-day

The next generation
of selective estrogen-receptor modulators

ROBERTS®
PHARMACEUTICALS

FARESTON® (toremifene citrate): Manufactured by ORION CORPORATION, Espoo, 02200 Finland. Distributed by Roberts Laboratories Inc., a subsidiary of **ROBERTS PHARMACEUTICAL CORPORATION,** Eatontown, NJ 07724, USA

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