018554_S021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-554/S-021

APPROVAL LETTER

NDA 18-554/S-021

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products
Support and Training, Worldwide Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

23 MAR 2001

Dear Ms. Nehring:

Please refer to your supplemental new drug application dated March 5, 2001, received March6, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eulexin® (flutamide) Capsules, USP.

This "Changes Being Effected" supplemental new drug application provides for the following revision of the **WARNINGS – Use in Women** section of the package insert to strengthen and further clarify the existing information contained in this section.

WARNINGS
Use in Women

> "EULEXIN Capsules are for use **only** in men. This product has no indication for women and should not be used in this population, particularly for nonserious or nonlife-threatening conditions."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 5, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-554/S-021." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-554/S-021

FINAL PRINTED LABELING

EULEXIN•
brand of flutamide
CAPSULES

WARNINGS

Hepatic Injury

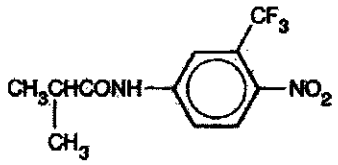
There have been post-marketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported oases occurred within the initial 3 months of treatment with flutamide.

Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, 'flu-like" symptoms. hyper bilirubinuria, jaundice or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

DESCRIPTION

EULEXIN Capsules contain flutamide, an acetanilid, nonsteroidal, orally active antiandrogen having the chemical name, 2-methyl- *N* -[4-nitro-3-(trifluoromethyl)phenyl] propanamide.

Each capsule contains 125 mg flutamide. The compound is a buff to yellow powder with a molecular weight of 276.2 and the following structural formula:



The inactive ingredients for EULEXIN Capsules include: corn starch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may contain methylparaben, propylparaben, butylparaben, and the following dye systems: FD&C Blue 1, FD&C Yellow 6, and either FD&C Red 3 or FD&C Red 40 plus D&C Yellow 10, with titanium dioxide and other inactive ingredients.

CLINICAL PHARMACOLOGY

General: In animal studies, flutamide demonstrates potent antiandrogenic effects. It exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues or both. Prostatic carcinoma is known to be androgen-sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen, eg, castration. Elevations of plasma testosterone and estradiol levels have been noted following flutamide administration.

Pharmacokinetics

Absorption: Analysis of plasma, urine, and feces following a single oral 200 mg dose of tritium-labeled flutamide to human volunteers showed that the drug is rapidly and completely absorbed. Following a single 250 mg oral dose to normal adult volunteers, the biologically active alpha-hydroxylated metabolite reaches maximum plasma concentrations in about 2 hours, indicating that it is rapidly formed from flutamide.

Distribution: In male rats neither flutamide nor any of its metabolites is preferentially accumulated in any tissue except the prostate after an oral 5 mg/kg dose of ^{14}C-flutamide. Total drug levels were highest 6 hours after drug administration in all tissues. Levels declined at roughly similar rates to low levels at 18 hours. The major metabolite was present at higher concentrations than flutamide in all tissues studied. Following a single 250 mg oral dose to normal adult volunteers, low plasma levels of flutamide were detected. The plasma half-life for the alpha-hydroxylated metabolite of flutamide is about 6 hours. Flutamide, *in vivo,* at steady-state plasma concentrations of 24 to 78 ng/mL, is 94% to 96% bound to plasma proteins. The active metabolite of flutamide, *in vivo,* at steady-state plasma concentrations of 1556 to 2284 ng/mL, is 92% to 94% bound to plasma proteins.

Metabolism: The composition of plasma radioactivity, following a single 200 mg oral dose of tritium-labeled flutamide to normal adult volunteers, showed that flutamide is rapidly and extensively metabolized, with flutamide comprising only 2.5% of plasma radioactivity 1 hour after administration. At least 6 metabolites have been identified in plasma. The major plasma metabolite is a biologically active alpha-hydroxylated derivative which accounts for 23% of the plasma tritium 1 hour after drug administration. The major urinary metabolite is 2-amino-5-nitro-4-(trifluoro-methyl)phenol.

Excretion: Flutamide and its metabolites are excreted mainly in the urine with only 4.2% of the dose excreted in the feces over 72 hours.

Plasma Pharmacokinetics of Flutamide and Hydroxyflutamide in Geriatric Volunteers (mean SD)

	Single Dose		Steady State	
	Flutamide	Hydroxyflutamide	Flutamide	Hydroxyflutamide
C_{max} (ng/mL)	25.2 • 34.2	894 • 406	113 • 213	1629 • 586
Elimination half-life (hr)	--	8.1 • 1.3	7.8	9.6 • 2.5
T_{max} (hr)	1.9 • 0.7	2.7 • 1.0	1.3 • 0.7	1.9• 0.6
C_{min} (ng/mL)	--	--	--	673 • 316

Special Populations:

Geriatric: Following multiple oral dosing of 250 mg t.i.d. in normal geriatric volunteers, flutamide and its active meta bolite approached steady-state plasma levels (based on pharmacokinetic simulations) after the fourth flutamide dose. The half-life of the active metabolite in geriatric volunteers after a single flutamide dose is about 8.1 hours and at steady state in 9.6 hours.

Race: There are no known alterations in flutamide absorption, distribution, metabolism, or excretion due to race.

Renal Impairment: Following a single 250 mg dose of flutamide administered to subjects with chronic renal insufficiency, there appeared to be no correlation between creatinine clearance and either C_{max} or AUC of flutamide. Renal impairment did not have an effect on the C_{max} or AUC of the biologically active alpha-hydroxylated metabolite of flutamide. In subjects with creatinine clearance of <29 mL/min, the half-life of the active metabolite was slightly prolonged. Flutamide and its active metabolite were not well dialyzed. Dose adjustment in patients with chronic renal insufficiency is not warranted.

Hepatic Impairment: No information on the pharmacokinetics of flutamide in hepatic impairment is available (see WARNINGS , Hepatic Injury).

Women, Pediatrics: Flutamide has not been studied in women or pediatric patients.

Drug-Drug Interactions: Interactions between EULEXIN Capsules and LHRH-agonists have not occurred. Increases in prothrombin have been noted in patients receiving warfarin therapy (see PRECAUTIONS).

Clinical Studies: Flutamide has been demonstrated to interfere with testosterone at the cellular level. This can complement medical castration achieved with LHRH agonists which suppresses testicular androgen production by inhibiting luteinizing hormone secretion.

The effects of combination therapy have been evaluated in two studies. One study evaluated the effects of flutamide and an LHRH agonist as neoadjuvant therapy to radiation in stage B_2-C prostatic carcinoma and the other study evaluated flutamide and an LHRH agonist as the sole therapy in stage D_2 metastatic carcinoma.

Stage B_2-C Prostatic Carcinoma: The effects of hormonal treatment combined with radiation were studied in 466 patients (231 EULEXIN Capsules + goserelin acetate implant + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B_2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of EULEXIN Capsules (250 mg t.i.d.) and goserelin acetate (3.6 mg depot) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years, $P<0.001$). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, $P=0.058$). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, $P<0.001$). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, $P<0.001$).

Stage D $_2$ Metastatic Carcinoma: To study the effects of combination therapy in metastatic disease, 617 patients (311 leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostatic carcinoma were enrolled in a large multicentered, controlled clinical trial.

Three and one-half years after the study was initiated, median survival had been reached. The median actuarial survival time was 34.9 months for patients treated with leuprolide and flutamide versus 27.9 months for patients treated with leuprolide alone. This 7-month increment represents a 25% improvement in overall survival time with the flutamide therapy. Analysis of progression-free survival showed a 2.6 month improvement in patients who received leuprolide plus flutamide, a 19% increment over leuprolide and placebo.

INDICATIONS AND USAGE

EULEXIN Capsules are indicated for use in combination with LHRH agonists for the management of locally confined Stage B $_2$-C and Stage D $_2$ metastatic carcinoma of the prostate.

Stage B $_2$-C Prostatic Carcinoma: Treatment with EULEXIN Capsules and the goserelin acetate implant should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Stage D $_2$ Metastatic Carcinoma: To achieve benefit from treatment, EULEXIN Capsules should be initiated with the LHRH agonist and continued until progression.

CONTRAINDICATIONS

EULEXIN Capsules are contraindicated in patients who are hypersensitive to flutamide or any component of this preparation.

EULEXIN capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment).

WARNINGS

Hepatic-Injury: SEE BOXED WARNING

Use in Women: EULEXIN Capsules are for use **only** in men. This product has no indication for women and should not be used in this population, particularly for nonserious or nonlife-threatening conditions."

Fetal toxicity: Flutamide may cause fetal harm when administered to a pregnant woman (see Pregnancy).

Aniline toxicity: One metabolite of flutamide is 4-nitro-3-flouro-methylaniline. Several toxicities consistent with aniline exposure, including methmoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (e.g. persons with glucose-6 -phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methomoglobin levels should be considered.

PRECAUTIONS

General: In clinical trials, gynecomastia occurred in 9% of patients receiving flutamide together with medical castration.

Information for Patients: Patients should be informed that EULEXIN Capsules and the drug used for medical castration should be administered concomitantly, and that they

should not interrupt their dosing or stop taking these medications without consulting their physician.

Laboratory Tests: Regular assessment of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise significantly and consistently during EULEXIN therapy the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen while continuing the LHRH analogue may be considered.

Drug Interactions: Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide was initiated. Therefore close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when EULEXIN Capsules are administered concomitantly with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 1-year dietary study in male rats, interstitial cell adenomas of the testes were present in 49% to 75% of all treated rats (daily oral doses of 10, 30, and 50 mg/kg/day were administered). These produce plasma C_{max} values that are 1, 2-3, and 4-fold, respectively, those associated with therapeutic doses in humans. In male rats similarly dosed for 1 year, tumors were still present after 1 year of a drug-free period, but the incidences were 43% to 47%. In a 2-year carcinogenicity study in male rats, daily administration of flutamide at these same doses produced testicular interstitial cell adenomas in 91% to 95% of all treated rats as opposed to 11% of untreated control rats. Mammary adenomas, adenocarcinomas, and fibroadenomas were increased in treated male rats at exposure levels that were 1- to 4-fold those observed during therapeutic dosing in humans. There are likewise reports of malignant breast neoplasms in men treated with EULEXIN Capsules (see ADVERSE REACTIONS section).

Flutamide did not demonstrate DNA modifying activity in the Ames *Salmonella/* microsome Mutagenesis Assay. Dominant lethal tests in rats were negative.

Reduced sperm counts were observed during a 6-week study of flutamide monotherapy in normal human volunteers.

Flutamide did not affect estrous cycles or interfere with the mating behavior of male and female rats when the drug was administered at 25 and 75 mg/kg/day prior to mating. Males treated with 150 mg/kg/day (30 times the minimum effective antiandrogenic dose) failed to mate; mating behavior returned to normal after dosing was stopped. Conception rates were decreased in all dosing groups. Suppression of spermatogenesis was observed in rats dosed for 52 weeks at approximately 3, 8, or 17 times the human dose and in dogs dosed for 78 weeks at 1.4, 2.3, and 3.7 times the human dose.

Animal Toxicology

Serious cardiac lesions were observed in 2/10 beagle dogs receiving 25 mg/kg/day for 78 weeks and 3/16 receiving 40 mglkglday for 2-4 years. These lesions, indicative of chronic injury and repair processes, included chronic myxomatous degeneration. intra-artrial fribrosis, myocardial acidophilic degeneration, vasculitis and perivasculitis. The doses at which these lesions occurred were associated with 2-hydroxyflutamide levels that were 1 to 12-fold greater than those observed in humans at therapeutic levels.

Pregnancy: Pregnancy Category D. There was decreased 24-hour survival in the offspring of pregnant rats treated with flutamide at doses of 30, 100 or 200 mg/kg/day (approximately 3, 9 and 19 times the human dose). A slight increase in minor variations in the development of the sternabrae and vertabrae was seen in fetuses of cats treated with two higher doses. Feminization of the male cats also occurred at the two higher dose levels. There was a decreased survival rate in the offspring of rabbits receiving the highest dose (15 mg/kglday, equal 1.4 times the human dose).

ADVERSE REACTIONS

Stage B $_2$-C Prostatic Carcinoma: Treatment with EULEXIN Capsules and the goserelin acetate implant did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing EULEXIN Capsules + goserelin acetate implant + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below:

	Adverse Events During Acute Radiation Therapy (within first 90 days of radiation therapy)	
	(n=231) Goserelin acetate implant + EULEXIN Capsules + Radiation	(n=235) Radiation Only
	% All	% All
Rectum/Large Bowel	80	76
Bladder	58	60
Skin	37	37

	Adverse Events During Late Radiation Phase (after 90 days of radiation therapy)	
	(n=231) LHRH-A + EULEXIN Capsules + Radiation	(n=235) Radiation Only
	% All	% All
Diarrhea	36	40
Cystitis	16	16
Rectal Bleeding	14	20
Proctitis	8	8
Hematuria	7	12

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

Stage D $_2$ Metastatic Carcinoma: The following adverse experiences were reported during a multicenter clinical trial comparing EULEXIN Capsules + LHRH agonist versus placebo + LHRH agonist.

The most frequently reported (greater than 5%) adverse experiences during treatment with EULEXIN Capsules in combination with an LHRH agonist are listed in the table below. For comparison, adverse experiences seen with an LHRH agonist and placebo are also listed in the following table.

	(n=294) Flutamide + LHRH agonist % All	(n=285) Placebo + LHRH agonist % All
Hot Flashes	61	57
Loss of Libido	36	31
Impotence	33	29
Diarrhea	12	4
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other GI	6	4

As shown in the table, for both treatment groups, the most frequently occurring adverse experiences (hot flashes, impotence, loss of libido) were those known to be associated with low serum androgen levels and known to occur with LHRH agonists alone.

The only notable difference was the higher incidence of diarrhea in the flutamide + LHRH agonist group (12%), which was severe in 5% as opposed to the placebo + LHRH agonist (4%), which was severe in less than 1%.

In addition, the following adverse reactions were reported during treatment with flutamide + LHRH agonist.

Cardiovascular System: hypertension in 1% of patients.

Central Nervous System: CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients.

Gastrointestinal System: anorexia 4%, and other GI disorders occurred in 6% of patients.

Hematopoietic System: anemia occurred in 6%, leukopenia in 3%, and thrombocytopenia in 1% of patients.

Liver and Biliary System: hepatitis and jaundice in less than 1% of patients.

Skin: irritation at the injection site and rash occurred in 3% of patients.

Other: edema occurred in 4%, genitourinary and neuromuscular symptoms in 2%, and pulmonary symptoms in less than 1% of patients.

In addition, the following spontaneous adverse experiences have been reported during the marketing of flutamide: hemolytic anemia, macrocytic anemia, methemoglobinemia, photosensitivity reactions (including erythema, ulceration, bullous eruptions, and epidermal necrolysis), and urine discoloration. The urine was noted to change to an amber or yellow-green appearance which can be attributed to the flutamide and/or its metabolites. Also reported were cholestatic jaundice, hepatic encephalopathy, and hepatic necrosis. The hepatic conditions were often reversible after discontinuing therapy;

however, there have been reports of death following severe hepatic injury associated with use of flutamide.

Malignant breast neoplasms have occurred rarely in male patients being treated with EULEXIN.

Abnormal Laboratory Test Values: Laboratory abnormalities including elevated SGOT, SGPT, bilirubin values, SGGT, BUN, and serum creatinine have been reported.

OVERDOSAGE

In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquilization, emesis, and methemoglobinemia.

Clinical trials have been conducted with flutamide in doses up to 1500 mg per day for periods up to 36 weeks with no serious adverse effects reported. Those adverse reactions reported included gynecomastia, breast tenderness, and some increases in SGOT. The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established.

Flutamide is highly protein bound and is not cleared by hemodialysis. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The recommended dosage is 2 capsules 3 times a day at 8-hour intervals for a total daily dose of 750 mg.

HOW SUPPLIED

EULEXIN Capsules, 125 mg, are available as opaque, two-toned brown capsules, imprinted with "Schering 525". They are supplied as follows:

NDC 0085-0525-05 - Bottles of 500
NDC 0085-0525-03 - Unit Dose packages of 100 (10 x 10's)
NDC 0085-0525-06 - Bottles of 180

Store between 2• and 30• C (36• and 86• F).
Protect the Unit Dose packages from excessive moisture.

Schering Corporation
Kenilworth, NJ 07033 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-554/S-021

ADMINISTRATIVE DOCUMENTS

Division of Reproductive and Urologic Drug Products

Regulatory Project Manager Label Review

Application Number: NDA 18-554/S-021 Eulexin® (flutamide) Capsules, USP

Sponsor: Schering Corporation

Material Reviewed:

- Package Insert

Submission Date: March 5, 2001

Receipt Date: March 6, 2001

Background and Summary Description:
The sponsor submitted this "Special Supplement-Changes Being Effected" (CBE) to strengthen and further clarify the existing information contained in the **WARNINGS** section – **Use in Women.**

Review:

The **WARNINGS** section – **Use in Women** was revised as follows:

WARNINGS
Use in Women

> "EULEXIN Capsules are for use **only** in men. This product has no indication for women and should not be used in this population, particularly for nonserious or nonlife-threatening conditions."

Conclusions:
A sponsor may submit a CBE supplement to make changes to the labeling to "add or strengthen a contraindication, warning, precaution or adverse reaction" per CFR §314.70(2)(I). An Approval Letter should be issued for NDA 18-554/S-021.

Jeanine A. Best, M.S.N., R.N.
Regulatory Project Manager

Concurrence:

Terri Rumble, B.S.N.
Chief, Project Management Staff

Mark Hirsch, M.D.
Urology Team Leader

Susan Allen, M.D., M.P.H.
Director

APPEARS THIS WAY ON ORIGINAL

cc:
Orig. NDA 18-554
HFD-580/Div File
HFD-580/Best
Concurrence: Rumble,03.22.01/Hirsch,03.22.01/Allen,03.23.01
Drafted: JAB/March 22, 2001/N18554S21Labrev.doc
Final: JAB/March 23, 2001
REGULATORY MANAGER REVIEW

/s/

Jeanine Best
3/23/01 12:46:31 PM
CSO

Terri F. Rumble
3/23/01 01:46:40 PM
CSO

Mark S. Hirsch
3/27/01 02:06:09 PM
MEDICAL OFFICER

Susan Allen
3/30/01 04:17:34 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-554/S-021

CBE-0 SUPPLEMENT

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Eulexin® (flutamide) Capsules, USP

NDA Number: 18-554

Supplement Number: S-021

Date of Supplement: March 5, 2001

Date of Receipt: March 6, 2001

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following change: a revision of the **WARNINGS – Use in Women** section of the package insert to strengthen and further clarify the existing information contained in this section.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 5, 2001 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Jeanine Best
3/7/01 01:36:18 PM

APPEARS THIS WAY
ON ORIGINAL