20264

Chem

Pharm

Stat

AP

LBL

Dis

MICRO BIOLOGY

BIO

FONSI /EA

NDA 20-264

SEP 10 1993

Bristol-Myers Squibb Company
Attention: Marygayle Ritzert
Regulatory Affairs
2400 West Lloyd Expressway
Evansville, Indiana 47721-0001

Dear Ms. Ritzert:

Reference is made to your New Drug Application dated March 31, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Megace (megestrol acetate) Oral Suspension.

We also acknowledge receipt of your additional communications dated as follows:

March 31, 1992	December 4, 1992	April 1, 1993 (3)
September 19, 1992	January 14, 1993	April 23, 1993
September 20, 1992	January 26, 1993	April 28, 1993
September 21, 1992	February 12, 1993	May 12, 1993
October 6, 1992	March 5, 1993	May 21, 1993
November 16, 1992	March 8, 1993	June 25, 1993 (2)
November 25, 1992	March 11, 1993	July 12, 1993
December 3, 1992	March 31, 1993	August 6, 1993
		August 18, 1993

We have completed the review of this application, as amended, 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 draft labeling dated August 18, 1993. Accordingly, the application, with these labeling revisions, is approved, effective on the date of this letter.

These revisions are terms of the NDA approval. Marketing the product before making, exactly as agreedto, the revisions in the product's labeling may render the product misbranded and an unapproved drug.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 20-264." Approval of the submission by the FDA is not required before the labeling is used. Should additional

information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81.

Sincerely yours,

David W. Feigal 9-10-93

David W. Feigal, Jr., M.D., M.P.H.
Division Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Concurrences:
HFD-530/Director/Feigal
HFD-530/GL/Goldberger
HFD-530/SPharm/Farrelly
HFD-530/Pharm/KWu
HFD-530/SChem/Chen
HFD-530/Chem/Jarski
HFD-530/SMicro/Ramsey
HFD-530/Micro/Dempsey
HFD-530/SStat/Kammerman
HFD-530/Stat/Kammerman
HFD-226/SBiopharm/Lazor
HFD-226/Biopharm/Pelsor
HFD-530/ADPM/Lillie
HFD-530/SCSO/DeCicco
cc:
HFD-530 Orig NDA
HFD-530 Division File
HFD-530/Director/Feigal
HFD-530/GL/Goldberger
HFD-530/Pharm/KWu
HFD-530/Chem/Jarski
HFD-530/Micro/Dempsey
HFD-530/Stat/Kazempour
HFD-530/Biopharm/Lazor
HFD-530/DepDirector/Rosenstein
HFD-530/drafter/SCSO/DeCicco/6/15/93/8/24/93
HFD-53
HFD-80
HFD-130/JAllen
HFD-220
HFD-500
HFD-632
HFD-730
Approval Letter

P3296-00
MEGACE®
(megestrol acetate)
Oral Suspension

APPROVED

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

Megace® Oral Suspension
(megestrol acetate)

WARNING
THE USE OF MEGACE® (megestrol acetate) Oral Suspension IS CONTRAINDICATED IN PREGNANCY

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no evidence that the use of a high dose progestational agent such as MEGACE® (megestrol acetate) Oral Suspension during any phase of pregnancy is effective *for this purpose. Furthermore,* in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion.

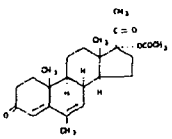
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses. Because of increased genital abnormalities in male and female fetuses induced by some progestational drugs, it is prudent to avoid the use of MEGACE® (megestrol acetate) Oral Suspension during pregnancy.

If the patient is exposed to MEGACE® (megestrol acetate) Oral Suspension during pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION

MEGACE® Oral Suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone progesterone. *Megestrol acetate is a white* crystalline solid chemically designated as 17α-(acetyloxy)-6-methylpregna-4,6-diene-3,20-dione. Solubility at 37°C in water is 2 µg per mL; solubility in plasma is 24 µg per mL. Its molecular weight is 384.51.

The empirical formula is $C_{24}H_{32}O_4$ and the *structural formula* is represented as follows:



MEGACE® (megestrol acetate) Oral Suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per mL.

MEGACE® (megestrol acetate) Oral Suspension contains the following inactive ingredients: alcohol (max. 0.06% v/v *from flavor*), *citric acid*, lemon-lime flavor, polyethylene glycol, polysorbate 80, purified water, sodium benzoate, sodium citrate, sucrose and xanthan gum.

CLINICAL PHARMACOLOGY

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

There are several analytical methods used to estimate megestrol acetate plasma concentrations, including gas chromatography-mass fragmentography (GC-MF), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MF and HPLC methods are specific for megestrol acetate and yield *equivalent concentrations. The* RIA method reacts to megestrol acetate metabolites and is, therefore, non-specific and indicates higher concentrations than *the GC-MF and HPLC methods*. Plasma concentrations are dependent, not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, *intestinal* bacteria, antibiotics administered, body weight, diet and liver function.

The major route of *drug elimination in humans* is urine. When radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 60.4%) and fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). *Megestrol acetate* metabolites which were identified in urine constituted 5% to 8% of the dose administered. Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in urine and feces.

Plasma steady state *pharmacokinetics of megestrol acetate* were evaluated in 10 adult, cachectic male patients with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline. Patients received single oral doses of 800 mg/day of MEGACE® Oral Suspension for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 *hours past the* last dose.

Mean (± 1SD) peak plasma concentration (C_{max}) of megestrol acetate was 753 (± 539) ng/mL. Mean area under the concentration time-curve (AUC) was 10476 (± 7788) ng x hr/mL. Median TMAX value was five hours. Seven of 10 patients gained weight in three weeks.

Additionally, 24 adult, asymptomatic HIV seropositive male subjects were dosed once daily with 750 mg of MEGACE® Oral Suspension. The treatment was administrated for 14 days. Mean C_{max} and AUC values were 490 (± 238) ng/mL and 6779 (± 3048) hr x ng/mL respectively. The median TMAX value was *three hours*. The mean C_{min} value was 202 (± 101) ng/mL. The mean %FL value was 107 (± 40).

The relative bioavailability of MEGACE® 40 mg tablets and MEGACE® Oral Suspension has not been evaluated. The effect of food on the bioavailability of MEGACE® Oral Suspension has not been *evaluated*.

DESCRIPTION OF CLINICAL *STUDIES*

The clinical efficacy of MEGACE® (megestrol acetate) Oral Suspension was assessed in two clinical trials. One was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate (MA) at doses of 100 mg, 400 mg, and 800 mg per day versus placebo *in AIDS patients with anorexia/cachexia* and significant weight loss. Of the 270 patients entered on study, 195 met all inclusive/exclusion criteria, had at least two additional post baseline weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. The percent of patients gaining five or more *pounds at maximum weight* gain in 12 study weeks was statistically significantly greater for the 800 mg (64%) and 400 mg (57%) MA-treated groups than for the placebo group (24%). Mean weight increased from baseline to last evaluation in 12 study weeks in the 800 mg MA-treated group by 7.8 pounds, the 400 mg MA group by 4.2 pounds, the 100 mg *MA group* by 1.9 *pounds and* decreased in the placebo group by 1.6 pounds. Mean weight changes at 4, 8 and 12 weeks for patients evaluable for efficacy in the two *clinical trials are* shown graphically. Changes in body composition during the 12 study weeks as measured by bioelectrical impedance analysis showed increases in non-water body weight in the MA-treated groups (*See clinical studies* table). In addition, edema developed or worsened in only 3 patients.

Greater percentages of MA-treated patients in the 800 mg group (89%), the 400 mg group (68%) and the 100 mg group (72%), than in the placebo group (50%), showed an improvement in appetite at last *evaluation during the* 12 study weeks. A statistically significant difference was observed between the 800 mg MA-treated group and the placebo group in *the change in caloric intake from* baseline to time of maximum weight change. Patients were asked to assess weight change, appetite, appearance, and overall perception of well-being in a 9-question survey. At maximum weight change only the 800 mg MA-treated group gave responses that were statistically significantly more favorable to all questions when compared to *the placebo-treated group*. A dose response was noted in the survey with positive responses correlating with higher dose for all questions.

The second trial was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol ace*tate 800 mg/day versus placebo in* AIDS patients with anorexia/cachexia and significant weight loss. Of the 100 pa*tients* entered on study, 65 met all inclusion/exclusion criteria, had at least two additional post *baseline weight mea*surements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. Patients in *the 800 mg MA-treated group had* a statistically significantly larger increase in mean maximum weight change than patients in the placebo group. From baseline to study week 12, mean weight increased by 11.2 pounds in the MA-treated group and decreased 2.1 pounds in the placebo group. Changes in body composition as measured by bioelectrical impedance analysis *showed increases in non-water* weight in the MA-treated group (See clinical studies table). No edema was reported in the MA-treated group. A greater percentage of MA-treated patients (67%) than placebo-treated patients (38%) showed an improvement in appetite at last evaluation during the 12 study weeks. This difference was statistically significant. *There were no* statistically significant differences between treatment groups in mean caloric change or in daily caloric intake at time to maximum weight change. In the same 9 question survey referenced in the first trial, patients' assessments of weight change, appetite, appearance, and overall perception of well being showed increases in mean scores in MA-treated *patients as compared* to the placebo group.

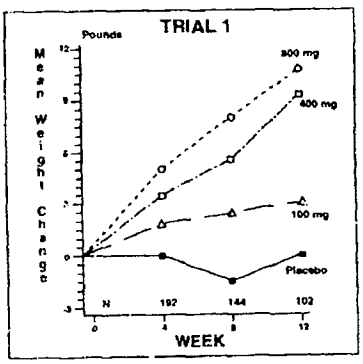
In both trials, patients tolerated the drug well and no statistically significant differences were seen between the treatment groups with regard to laboratory abnormalities, new opportunistic infections, lymphocyte counts, T_4 counts, T_8 counts, or skin reactivity tests (See Adverse Reactions).

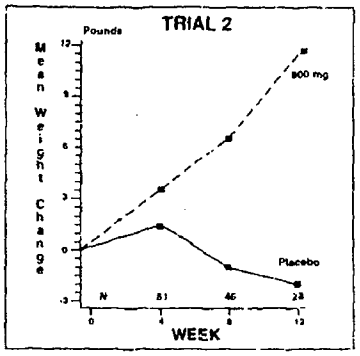
MEGACE® (*megestrol acetate*) *Oral Suspension* Clinical Efficacy Trials

	Trial 1 Study Accrual Dates 11/88 to 12/90				Trial 2 Study Accrual Date 5/89 to 4/91	
Megestrol Acetate mg/day	0	100	400	800	0	800
Entered Patients	38	82	75	75	48	52
Evaluable Patient	28	61	53	53	29	36
Mean Change in Weight (lb.) Baseline to 12 Weeks	0.0	2.9	9.3	10.7	-2.1	11.2
% Patients ≥ 5 Pound Gain at Last Evaluation in 12 Weeks	21	44	57	64	28	47
Mean changes in Body Composition*						
Fat Body Mass (lb.)	0.0	2.2	2.9	5.5	1.5	5.7
Lean Body Mass (lb.)	-1.7	-0.3	1.5	2.5	-1.6	-0.6
Water (liters)	-1.3	-0.3	0.0	0.0	-0.1	-0.1
% Patients With Improved Appetite						
At Time of Maximum Wt. Change	50	72	72	93	48	69
At Last Evaluation in 12 Weeks	50	72	68	89	38	67
Mean Change in Daily Caloric Intake						
Baseline to Time of Maximum Weight Change	-107	326	305	646	30	464

*Based on bioelectrical impedance analysis determinations at last evaluation in 12 weeks

Presented below are the results of mean weight changes for patients evaluable for efficacy in trials 1 and 2.





INDICATIONS AND USAGE
MEGACE® (megestrol acetate) Oral Suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS
As a diagnostic test for pregnancy
Known or suspected pregnancy

WARNINGS
Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, see the "Impairment of Fertility" section under PRECAUTIONS. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.
Megestrol acetate is not intended for prophylactic use to avoid weight loss.
See also "Carcinogenesis, Mutagenesis, and Impairment of Fertility" section under PRECAUTIONS.

PRECAUTIONS
General:
Therapy with MEGACE® (megestrol acetate) Oral Suspension for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric diseases.
Although the glucocorticoid effects of MEGACE® (megestrol acetate) Oral Suspension in HIV infected individuals have not been evaluated, laboratory evidence of adrenal suppression has been observed which is clinically insignificant.
Effects on HIV viral replication have not been determined.
Use with caution in patients with a history of thromboembolic disease.

Information for the Patient:
Patients using megestrol acetate should receive the following instructions:
1. This medication is to be used as directed by the physician.
2. Report any adverse reaction experiences while taking this medication.
3. Use contraception while taking this medication if you are a woman capable of becoming pregnant.
4. Notify your physician if you become pregnant while taking this medication.

Drug Interactions:
Possible interactions of MEGACE® with concomitant medications have not been investigated.

Animal Toxicology:
Long-term treatment with MEGACE® may increase the risk of respiratory infections. A trend toward increased frequency of respiratory infections, decreased lymphocyte counts and increased neutrophil counts was observed in a two-year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Carcinogenesis
Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times lower than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing MEGACE® Oral Suspension and in surveillance of patients on therapy. Also see **"WARNINGS"** section.

Mutagenesis
No mutagenesis data are currently available

Impairment of Fertility
Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05–12.5 mg/kg) less than that indicated for humans (13.3 mg/kg). In these low dose studies the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

Pregnancy:
Pregnancy Category X. See "**WARNINGS**" and "**Impairment of Fertility**" section. No adequate animal teratology information is available at clinically relevant doses.

Nursing Mothers:
Because of the potential for adverse effects on the newborn, nursing should be discontinued if MEGACE® (megestrol acetate) Oral Suspension is required.

Use in HIV Infected Women:
Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited.
All 10 women in the clinical trials reported breakthrough bleeding.

Pediatric Use:
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Clinical Adverse Events
Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial are listed below by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing MEGACE® (megestrol acetate) Oral Suspension.

ADVERSE EVENTS
% of Patients Reporting

	Trial 1 (N = 236)				Trial 2 (N = 87)		Open Label Trial
Megestrol Acetate mg/day	Placebo 0	100	400	800	Placebo 0	800	1200
No. of Patients	N = 34	N = 68	N = 69	N = 65	N = 38	N = 49	N = 176
Diarrhea	15	13	8	15	0	6	10
Impotence	3	4	6	14	0	4	7
Rash	9	9	4	12	3	2	6
Flatulence	9	0	1	9	3	10	6
Hypertension	0	0	0	8	0	0	4
Asthenia	3	2	3	6	8	4	5
Insomnia	0	3	4	6	0	0	1
Nausea	9	4	7	5	3	4	5
Anemia	6	3	3	5	0	0	0
Fever	3	6	4	5	3	2	1
Libido Decreased	3	4	0	5	0	2	1
Dyspepsia	0	0	3	3	5	4	2
Hyperglycemia	3	0	6	3	0	0	3
Headache	6	10	1	3	3	0	3
Pain	6	0	0	2	5	6	4
Vomiting	9	3	0	2	3	6	4
Pneumonia	6	2	0	2	3	0	1
Urinary Frequency	0	0	1	2	5	2	1

Adverse events which occurred in 1% to 3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than 1% are not included. There were no significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole: abdominal pain, chest pain, infection, moniliasis and sarcoma
Cardiovascular System: cardiomyopathy and palpitation
Digestive System: constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis
Hemic and Lymphatic System: leukopenia
Metabolic and Nutritional: LDH increased, edema and peripheral edema
Nervous System: paresthesia, confusion, convulsion, depression, neuropathy, hypesthesia and thinking abnormal
Respiratory System: dyspnea, cough, pharyngitis and lung disorder
Skin and Appendages: alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder
Special Senses: amblyopia
Urogenital System: albuminuria, urinary incontinence, urinary tract infection and gynecomastia

OVERDOSAGE
No serious unexpected side effects have resulted from studies involving MEGACE® (megestrol acetate) Oral Suspension administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability, however, due to its low solubility it is postulated that dialysis would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION
The recommended adult initial dosage of MEGACE® (megestrol acetate) Oral Suspension is 800 mg/day (20 mL/day).
Shake container well before using.
In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day were found to be clinically effective.
A plastic dosage cup with 10 mL and 20 mL markings is provided for convenience.

HOW SUPPLIED
MEGACE® (megestrol acetate) Oral Suspension is available as a lemon-lime flavored oral suspension containing 40 mg of micronized megestrol acetate per mL.
NDC 0015-0508-42 Bottles of 8 fl. oz. (236.5 mL)

STORAGE
Store MEGACE® (megestrol acetate) Oral Suspension at or below 25°C and dispense in a tight container. Protect from heat.

SPECIAL HANDLING
Health Hazard Data
There is no threshold limit value established by OSHA, NIOSH, or ACGIH.
Exposure or "overdose" at levels approaching recommended dosing levels could result in side effects described above (WARNINGS, ADVERSE REACTIONS). Women at risk of pregnancy should avoid such exposure.

Mead Johnson
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
U.S.A.

Issued September 1993

P3296-00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: September 14, 1993

FROM: Mary Ann Jarski MAJarski 9/14/93

SUBJECT: Methods Validation for Megace Applications

TO: File NDA 20-264 Megace(megestrol acetate oral suspension) 40mg/mL

On this date I discussed methods validation for these two NDAs with Marygayle Ritzert, Associate Director Regulatory Affairs (NDA 20-264 was approved September 10, 1993).

I indicated that our St. Louis laboratory would be doing the validation and the following material:

1. Samples of New Drug Substance, specify lot # and quantity.
2. Samples of Suspension (NDA 20-264), specify lot # and quantity.
3. Samples of . specify lot # and quantity.
4. Reference Standard(s), specify lot # and quantity.
5. Methods validation package for NDA 20-264.
6. Methods validation package for .

should be sent to:

Division of Drug Analysis and Testing
Attention: Thomas P. Layloff, Ph.D.
1114 Market Street
St. Louis, MO 63101

I also told her that prior to the submission of the samples, data and information to St. Louis the following material should be submitted to the NDA:

1. A record of the lot #'s and quantities of new drug substance, suspension, tablets, reference standard(s)
2. Copies of the Methods validation packages for NDA 20-264 and

Ms. Ritzert said there was no problem about samples, etc., for the suspension, however she was not sure about the status of the tablets. She also realized that additional information was required for the tablet application. I advised her that for chemistry, manufacturing and control an updated stability report was needed. Ms. Ritzert said that Steve Hawles would be assembling the necessary data and information and he would call before any material was sent to St. Louis.

CC:
Chi-wan Chen Supervisory Chemist-HFD-530
Tony DeCicco, Supervisory CSO-HFD-530

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL 27 1993

NDA #: 20-264
CHEMISTRY REVIEW #: 1 - Amended DATE REVIEWED: 21-Jul-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	31-Mar-92	01-Apr-92	06-Apr-92
Amendment	25-May-92	28-May-92	08-Jun-92
Amendment	19-Sep-92	22-Sep-92	22-Sep-92
Amendment	20-Sep-92	22-Sep-92	22-Sep-92
Amendment	03-Dec-92	07-Dec-92	15-Dec-92
Amendment	19-Jan-93	25-Jan-93	25-Jan-93
Amendment	26-Jan-93	27-Jan-93	27-Jan-93
Amendment	27-Jan-93	28-Jan-93	29-Jan-93
Amendment	12-Feb-93	16-Feb-93	
Amendment	08-Mar-93	09-Mar-93	11-Mar-93
Amendment	11-Mar-93	12-Mar-93	16-Mar-93
Amendment	31-Mar-93	06-Apr-93	09-Apr-93
Amendment	01-Apr-93A	06-Apr-93	09-Apr-93
Amendment	01-Apr-93B	06-Apr-93	09-Apr-93
Amendment	01-Apr-93C	06-Apr-93	09-Apr-93
Amendment	28-Apr-93	29-Apr-93	07-May-93
Amendment	07-May-93	11-May-93	18-May-93
Amendment	12-May-93	14-May-93	24-May-93
Amendment	21-May-93	28-May-93	04-Jun-93
Amendment	25-Jun-93	28-Jun-93	11-Jul-93
Amendment	12-Jul-93		

Also:
Meeting/Teleconference between Bristol-Myers Squibb and Division of Antiviral Drug Products on May 21, 1992.
Telephone communication between Ms. M. A Jarski and Ms. M. Ritzert of May 22, 1992.
Facsimile Correspondence of January 8, 1993 detailing Chemistry and Biopharmaceutics requests and recommendations.
Telephone conversation with applicant January 29, 1993
Pre-Advisory Committee Meeting with applicant of February 4, 1993
CMC presentation regarding Megace Oral Suspension at Advisory Committee meeting of February 14, 1993 and subsequent CMC discussions with applicant.
Teleconference between Bristol-Myers Squibb and Division of Antiviral Drug Products on May 13, 1993.

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
U.S. Pharmaceutical Group
2400 W. Lloyd Expressway
Evansville, IN 47721-0001

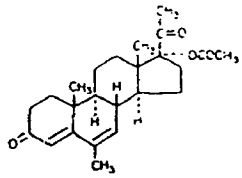
DRUG PRODUCT NAME

Proprietary:	MEGACE^R
Nonproprietary:	Megestrol acetate, U.S.P.
Code Name/#:	MJF 6056
Chem.Type/Ther.Class:	6P

PHARMACOLOGICAL CATEGORY: Progesterone, steroid hormone, derivative
INDICATION: Treatment of anorexia, cachexia, or significant weight loss in patients with AIDS

DOSAGE FORM/STRENGTH: Aqueous suspension/40 mg/mL
ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:



CAS: 595-33-5
Molecular formula: 384.51
Molecular weight: $C_{24}H_{32}O_4$

Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-.
17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate

SUPPORTING DOCUMENTS:

NDA 16-979 Bristol-Myers Squibb Co. - Megace in the treatment of endometrial cancer (approved 18-Aug-71) and breast cancer (approved 06-Jul-76)

ial

Authorizations are included for DMFs

RELATED DOCUMENTS:

PATENT INFORMATION:

With respect to any patent information which claims the drug, U.S. Patent 3,356,573 was issued on December 5, 1967 (assignment to the British Drug House Limited, London, England).

Orphan drug designation approval was granted on April 7, 1988 for use of megestrol acetate, USP, int the treatment of anorexia, cachexia, or a significant weight loss in patients with AIDS.

REMARKS/COMMENTS:

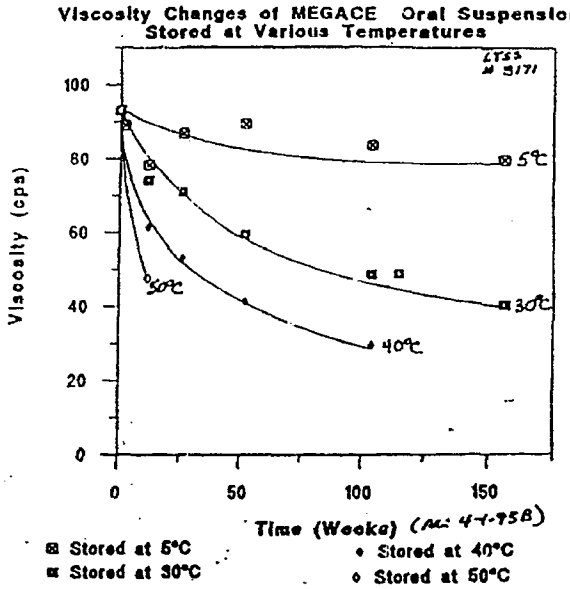
There are no outstanding issues regarding the synthesis, control or stability of megestrol acetate, thus the Review Notes for the new drug substance are concise. Bristol-Myers Squibb Company has manufactured megestrol acetat tablets for many years under NDA 16-979, with Upjohn as an approved source of the bulk drug Megestrol acetate is also the subject of a U.S.P. monograph (as is the tablet), thus there are compendial controls.

However, major chemistry, manufacturing and control (CMC) problems were associated with the preparation, control and stability of the oral suspension (not a U.S.P. dosage form). There were formulation problems. The applicant reported that following the manufacture of five clinical batches of product the second and third batches were found to have physical stability problems at approximately three months of age. The viscosities, specific gravities, pH and megestrol acetate particle sizes of these batches were the same as those of the normal ones but these batches exhibited caking and had poor redispersibility. It was subsequently determined that the concentration of the surfactant polysorbate 80 was critical to the formula and this was changed to its optimum value. Both formulas were used in clinical trials as documented in the Review Notes under INVESTIGATIONAL FORMULAS. No caked formula was distributed to patients and both formulas were completely redispersed prior to dosing.

The oral suspension is a pharmaceutical dosage form often selected for administration when a drug is very insoluble in water, as is the case with megestrol acetate. It may be operationally defined as a dosage form in which one phase, an insoluble solid, in this case micronized megestrol acetate, is uniformly dispersed in a second phase, a liquid. Micronization refers to reduction in the particle size and corresponding increase in the surface area of the solid megestrol acetate. In a well formulated pharmaceutical suspension the dispersed particles should be of such a size that they do not settle in the container. However, if they do settle, the sediment must not form a hard cake. Rather, the particles must be capable of redispersion with a minimum of effort on the part of the patient. Additionally the product should be easy to pour, pleasant to take, and resistant to microbial attack.

The processes involved in the formation of suspended particles may be described as follows:

In the Megace formula another ingredient, the thickening agent, xanthan gum, has also caused problems. From stability studies it was apparent that the viscosity of the vehicle was sharply decreasing with time and temperature. Added to this was a corresponding drop in the pH of the formula.



Decreased viscosity as postulated by the manufacturer of the gum, was a result of reduction in molecular weight caused by oxidizing agents or acids. "We know that contact with these, especially at elevated temperatures, and in the presence of transition metals, such as iron, can result in viscosity loss." Since viscosity loss was a consequence of aging it became necessary to now how long megestrol acetate particles would uniformly remain suspended in a vehicle with diminished viscosity. Through two sets of studies it was determined that there would be about a 30 minute dose uniformity after shaking with the minimum viscosity allowed for the vehicle, i.e., dosing will be uniform for 30 minutes after shaking and pouring. As added precautions labeling will carry the cautions "Store the oral suspension at or below 25°C and dispense in a tight container. Protect from heat." "Shake well immediately before dosing."

Initial stability reports also indicated the microbial failure of several of the initial British Pharmacopeia (BP) challenge tests because of apparent A.niger regrowth following 14 days of incubation. However, all challenged samples passed the USP Antimicrobial Preservatives Effectiveness Test and the microbial reduction between initial and days 14 and 28 always surpassed BP requirements. No consistent pattern of regrowth was evidenced in these results and results from the benzoic acid preservative assay tests showed no effect of package, test condition or storage interval. Microbial content had been a continuing source of discussion with respect to control specifications and stability. The final solution has been to allow 100 colony forming units (cfu) for standard plate count, mold and yeast at the time of release and to determine definitive specifications as experience is gained with production of the product.

With respect to manufacturing procedures, 300 liter clinical and stability supplies were made initially and CMC data in the NDA were based upon this material. Later limited data became available for an 1800 liter product batch. Comparative data for experimental and 'production' batches are outlined in the Review Notes under STABILITY of the dosage form. Physico-chemical profiles are similar. Additionally, as noted above, comparative dose uniformity (resuspendability) studies were performed on both types of batches showing similar profiles. For the 1800 liter batch in-process controls are extensive and clearly defined (Refer to the Review Notes). On the basis of such data and information it was concluded that scale-up would not be a problem. As an additional precaution a negotiated validation protocol for production batches has also been included in the NDA. However, because of the limited amount of data available for the production batch, the expiration date for marketed product is limited to 24 months (with storage below 25°C.) until full shelf-life data allows for and extension.

With respect to control procedures for the dosage form, the initial submission proposed only assay and identification. In early discussions the applicant was advised that such controls were insufficient. As a qconsequence methods had to be developed and although the original application was dated March 31, 1992, the completed CMC section was not available until September 19, 1992. Further, controls were not finalized until May 21, 1993. The final controls involve: Megestrol Acetate Assay (by HPLC); Megestrol Acetate Identification by both HPLC and TLC; pH determination; Resuspendability determination; Particle Size (median diameter and that of 90% of material) determination; Viscosity determination; Documentation of Physical Properties; specific gravity determination; Dissolution determination; and Plate Count determination. Specifications and test procedures are detailed in the Review Notes. Validation will be performed post-approval. This isn't considered a drawback since the HPLC assay procedure is equivalent to that for new drug substance and the tablets (and is in the USP) and other procedures are routine and instrumental in nature.

Thus, after a series of evaluations of the formula, production, packaging, controls and stability of this oral suspension and adjustments for the necessary parameters, Megace ® Oral Suspension (megestrol acetate oral suspension) is approvable from a chemistry, manufacturing and control standpoint. The product will initially be packaged in 8 ounce high density polyethylene containers with child-proof caps and will carry a two year expiration date.

Attachments to this Review include: A statement of composition of the lemon-lime flavor; A chemistry discussion on this drug product as given before the Antiviral Drugs Advisory Committee on February 18, 1993; A Finding Of No Significant Environmental Impact; Memoranda concerning Labeling Issues; Satisfactory Inspection Reports for All Firms Involved in the Operations.

CONCLUSIONS & RECOMMENDATIONS:

This application is approvable from a chemistry, manufacturing and control standpoint. The product will carry a 24 month expiration date.

Mary Ann Jarski 7/21/93
Mary Ann Jarski
Review Chemist, HFD-530

Concurrence:
HFD-530/LRosenstein 7/21/93
HFD-530/CChen CMC 7/23/93

cc:
Orig. NDA 20-264
HFD-530/Div. File
HFD-530/LRosenstein
HFD-530/CChen
HFD-530/MAJarski
HFD-530/DFeigal
HFD-530/Pharm
HFD-530/Micro
HFD-530/TDeCicco
HFD-102/CKumkumian

File: 20264.NDR

NDA 20-264
FAX of Deficiencies sent to the applicant Jan 8, 1993

1. A quantitative statement of composition will be required for the lemon-lime flavor.

2. A time frame for manufacturing operations, storage and packaging is necessary.

3. The applicant is to submit all data and information applicable to the experimental 'full scale' (1800 L) batch of Megace OS prepared. This should include the batch number, the batch record and QC reports. The applicant is also to submit their validation protocol for the scale up and the attendant data. In addition, a placebo batch was manufactured . Information on the size of this batch is also required.

4. The applicant is to address the specific control procedures performed at each of the three test stations noted in the manufacturing flow diagram. Applicable specifications and methods for "other in-house testing " are to be submitted.

5. With regard to specifications:

   a. There should be no "Specifications at time of release" or "Investigation required for batch release" categories in Regulatory Specifications. These specifications are valid for release of the product and throughout the shelf life of the product. Additionally, a justification for regulatory ranges should be provided (e.g., megestrol acetate, pH, viscosity).
   b. Description of the Product, Specific Gravity, Impurity Analysis and Microbial Testing should be included as regulatory specifications. With regard to Microbial Testing, in addition to the Canadian Procedure, USP and BP tests are available. The most stringent test is recommended and should be justified in a discussion for the file.
   c. Resuspendability is a Regulatory Procedure independent of a supervisor's disposition, thus the "Interpretation" should be unambiguous.
   d. The applicant should clarify why limits are given for the median diameter in particle size analysis, rather than an evaluation of actual particle size distribution limits.

It should be noted that "Specifications at time of release" and "Investigation required for batch release" are in-process controls.

6. With regard to the HPLC assay for dosage form, the evaluation of the method should be expanded to include probable degradation products and other impurities.

7. With regard to the resuspendability test, it should be a regulatory procedure for evaluation of 'caking' in the dosage form. As such it should be a Pass/Fail test within a reasonable time frame. If there is 'caking' the lot is rejected. However, it is unclear how visual observations can be made through an opaque (white) HDPE container.

8. With regard to particle size, provision should be made for a manual method.

9. Given the patient population for this drug product, the applicant is to discuss the most effective way to evaluate microbial contamination for the product.

10. With regard to dissolution, from a manufacturing and control standpoint other procedures are in place to monitor the physical stability of the dosage form, e.g., particle size, viscosity and dissolution should be taken up with Biopharmaceutics.

11. Again, given the patient population for this drug product, the applicant is to explain why an opaque bottle with a child resistant cap is proposed for packaging.

12. With regard to packaging components, the applicant is to:
    a. submit data on the interchangeability of HDPE resins used for bottles (re: USP procedures).
    b. submit data on the interchangeability of bottles from different sources (re: USP procedures, particularly moisture loss).
    c. submit schematics for packaging components that will be used that include critical dimensions and materials of construction applicable to this product. Clarification is also required as to whether the commitment solely to use a thick walled bottle made of

13. With regard to stability studies:
    a. sample was shaken on a paint shaker to resuspend the product. The applicant is to discuss the consequences of this procedure versus. wrist shaking on sampling for the various tests in stabil. y studies.
    b. degradation of the drug product is not addressed.
    c. loss of moisture from the container is not addressed (although superpotency is noted).
    d. the applicant is to provide evidence for the assertion that the breakdown of xanthan gum is responsible for viscosity and pH changes over time, and the effect of temperature on this breakdown.
    e. as noted above, the applicant is to further discuss microbial evaluation and the failure of BP tests for A. niger
    f. the applicant is to explain how measurements of sedimentation height, redispersibility, turbidity were made through the dark (amber) glass and why such measurements are not possible on opaque HDPE containers (and if they are not possible how will redispersibility be measures on marketed product.
    g. the applicant is to submit tables for turbidity data over time.

14. With regard to labeling:
    a. The trade name Megace OS is not acceptable, and the designation USP should not be used in conjunction with the dosage form.
    b. If HDPE bottles are used, the storage caution should be "Store below 30°C and dispense in a tight container. Protect from h t." rather than "Store at room temperature, protect from temperatures above 86°C and dispense in a tight container."

NDA 20-164

Additional deficiencies provided to the applicant in a Telecon on January 29, 1993

Unanswered Questions

The torque closure specification and attendant limits are to be provided.

With regard to scale up batch 8MGM291 , the applicant is to provide information on :

a. Packaging configurations used for this lot (composition and dimensions).
b. The dates that the QC data for the lot were obtained that provided assurance for the manufacturing procedure and an explanation of the time frames involved with the QC results as submitted to this application.
c. The information obtained from placebo lot 8MGM324 that guided the final details for processing the 1800L batch.
d. Stability data for the lot.

For sampling bulk product it would appear that the applicant actually means to sample from the Storage tank rather than the Mix tank, while it is undergoing agitation. This should be clarified (see flow diagram). Also, since the bulk may be stored up to 12 days between manufacture and packaging it would seem prudent to sample across this time frame and incorporate time limits into the manufacturing procedure.

In-process test procedures call for sampling #1 from the storage tank, #2 from the bottling stage and #3 after final package. Tests to be performed at #1 include assay, identification (HPLC), pH, viscosity and specific gravity. Tests to be perfor ed at #2 are assay, identification (TLC), Resuspendability, particle size, physical prope.ies and Standard Plate Count (Refer to Remarks and Comments Below). Such testing would allow an evaluation of chemical, physical and microbial product characteristics and would serve to confirm product specification ranges. (What is done at #3 is unclear) None of this is reflected in the validation protocol, nor is there a plan to deliberately challenge the limits of the manufacturing process.

In the FDA *Guideline on General Principles of Process Validation* a Validation protocol is defined as a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. Additionally, a worst case is defined, i.e.," a set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure." The important of worst case situations are emphasized throughout the *Guideline*.

It is recommended that the validation protocol be revised to more adequately reflect FDA Guidelines.

With regard to In-Process Testing:

a. In the Flow Chart Sampling Point #1 also contains the commentary "If indicated, rework bulk suspension per process development instructions". This comment should be clarified.
b. At Sampling Point #3 the applicant should clarify whether full monograph testing is done on stability samples to establish the initial values for stability studies.

Questions Discussed in Telephone Conversation of 13-May-93

1. Resolve Microbial Limit Test.
   Our proposal: on release
   Stability testing at 3,6,9,12 and expiry date. If test indicate greater than then it will be resolved with the FDA.

Agreed

2. With regard to particle size specifications, we concur with their latest proposal.
3. Discuss assay procedure aberrations in the submission of 12-May-93.

There is no ready explanation as to why the assay was low. It may have been analyst error. Precautions will be included in procedures to assure that sample is adequately dispersed.

4. Submit revised Specification/Test Sheet which includes dissolution testing

Agreed

5. Submit a revised validation protocol.

Agreed.

6. Submit a revised stability protocol which includes test stations, test procedures and storage conditions. On approval the expiry date will be 24 months.

Agreed

7. Prepare methods validation package for submission to St. Louis. Suspension and tablets. Include validating data. NDA approval will not be contingent on methods validation.

Agreed

8. Labeling is to state, "Store Megace below 25°C.

Agreed.

NDA 20-264

FINDING OF NO SIGNIFICANT IMPACT

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-264

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not have to be prepared.

The applicant is requesting approval to manufacture Megace (megestrol acetate) Oral Suspension, 40 mg per mL at its facilities in Evansville and Mt. Vernon, Indiana. This product is a liquid oral dosage form of megestrol acetate, proposed for the treatment of cachexia in AIDS patients. It will be supplied in high density polyethylene bottles of 4, 8, and 16 ounces and will be dispensed by pharmacies as a prescription product. An finished product or in-process material containing megestrol acetate which must be disposed of will be incinerated.

In support of their new drug application, Bristol - Myers Squibb Company prepared an abbreviated environmental assessment (21 CFR 25.31a(b)(3) (attached) which evaluated the potential environmental impacts of the manufacture and use of Megace Oral Suspension. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. The potential for adverse environmental effects from releases of megestrol acetate is unlikely. All processing and primary packaging will be performed in a special, controlled manufacturing suite at the Evansville facility. There are virtually no emissions associated with the manufacturing process and the facility is designed and constructed to protect employees and control emissions to air and water. The process generates no waste. Only an extremely small amount of product goes to sewer in cleaning equipment. Very little dust is created, owing to the nature of the product and process.

In addition, no wetland areas, significant cultural resources, threatened or endangered species, air quality, fish and wildlife resources, environmentally significant habitats, and water quality would be significantly affected. No significant changes in land use would occur.

July 21, 1993
DATE

Mary Ann Jarski
Mary Ann Jarski, Chemist HFD-530
Review Chemist
Center for Drug Evaluation and Research

DATE

Philip G. Vincent, Ph.D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

cc:
Charles S. Kumkumian, Ph.D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

3.4 Environmental Assessment

This section presents the environmental assessment for the anticipated MEGACE® OS manufactured by Bristol-Myers in Evansville, Indiana.

ENVIRONMENTAL ASSESSMENT

MEGACE ORAL SUSPENSION

1. Date: November 5, 1991

2. Name of Applicant: Bristol-Myers Squibb

3. Address: 2400 West Lloyd Expressway
Evansville, Indiana 47721-0001

4. Description of Proposed Action:

Bristol-Myers Squibb proposes to manufacture Megace Oral Suspension at its facilities in Evansville and Mt. Vernon, Indiana. This product is a liquid oral dosage form of megestrol acetate, proposed for use in treatment of cachexia, as for example with AIDS or cancer. The content of active drug is 40 mg/ml It is expected to be supplied in bottles of 4, 8, and 16 oz.

All processing and primary packaging will be performed in a special, controlled manufacturing suite at the Evansville facility (at the above address). The Evansville plant has been used for the production of many nutritional and pharmaceutical products for many years. It is located in an urban area, currently classified environmentally as follows:

Standard	Classification
PM_{10} Particulate	*
SO_2	Attainment
Ozone	**Marginal Non-Attainment
CO	***
NO_2	***

*The EPA has classified subject areas in Indiana as Group III. This indicates a Probable Attainment Status for the PM_{10} Standards adopted in 1987.

**The National Ambient Air Quality Standard was barely exceeded four times in three years.

***Cannot be classified or better than National Standards.

The Mt. Vernon facility, where secondary packaging will be performed, is located approximately two miles east of Mt. Vernon, Indiana. This is a rural area in southern Indiana, which is in attainment for the above pollutant standards. Many BMS products are currently packaged at this facility.

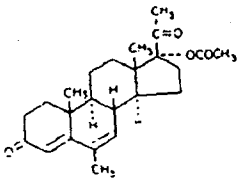
Both plants discharge wastewater to local Publicly Owned Treatment Works (POTW). The discharges are in substantial compliance with local ordinances and permits and pharmaceutical categorical standards requirements.

With respect to the active ingredient, megestrol acetate, any finished product or in-process material which must be disposed of will be incinerated.

5. Identification of Chemical Substances that are the Subject of the Proposed Action:

The sole active drug in Megace Oral Suspension is megestrol acetate.

MEGESTROL ACETATE

Chemical name:	17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate
CAS No.:	595-33-5
RTECS No.:	TU 4075000
Formula:	$C_{24}H_{32}O_4$
Molecular Weight:	384.51
Structure:	
Physical Description:	Crystals, m.p. 214°-216° C.
Hazardous Characteristics:	Antineoplastic; affects reproductive systems.
Toxicology:	IV LD50, mouse, 56 mg/kg.

The excipient ingredients in the formulation are:

Polyethylene glycol
Polysorbate 80
Xanthan gum
Citric acid
Sodium citrate
Sucrose
Sodium benzoate
Flavor, lemon-lime
Purified water

6. Introduction of Substances into the Environment

None of the product ingredients are on the consolidated hazardous substance list (40 CFR 302.4).

Introduction of substances involved into the environment will be very small. Annual production is forecast to total approximately [illegible] This represents [illegible] of active drug.

There are virtually no emissions associated with the manufacturing process. A solution is made of the polyethylene glycol, polysorbate 80, and water. The megestrol acetate is added, and the batch is mixed to form a suspension. The remaining ingredients are added, and the mixture is passed through a colloid mill to fully disperse the active drug.

All of the above operations are performed in a designated facility, specially designed and constructed to protect employees, and control emissions to air and water.

The process generates no wastes. Only an extremely small amount of product goes to sewer in cleaning equipment. Very little dust is created, owing to the nature of the product and process. Furthermore, atmospheric emissions from all operations are minimized through the use of dust control equipment (principally wet scrubbers) which are permitted by the Evansville EPA.

People exposed in the workplace are properly protected from any possible ill effect from handling these materials. All employees have received the required OSHA Hazard Communication Program training.

7. Fate of Emitted Substances in the Environment

(a) Air

For all practical purposes, there are no emissions of any of the substances into the air.

(b) Water

There will be very small emissions to water as a result of cleaning the facility. However, these will undergo treatment in the Evansville POTW before discharge to the Ohio river. Furthermore, it is expected that the concentration of active drug will not be detectable in the influent to the POTW.

(c) Terrestrial Ecosystems

Since only a very small quantity of this product would be disposed of in one year, the impact on the many sanitary landfills utilized is expected to be insignificant. In addition, it is expected that the components of this product would degrade in a landfill environment (through biodegradation and hydrolysis) to simple, relatively harmless molecules.

8. Environmental Effects of Released Substances

There will be no observable effect on the environment, because of the small quantities involved, very wide dispersion, and negligible toxicity of all ingredients.

9. Use of Resources and Energy

Only minimal materials and energy are required for the production of this pharmaceutical product. Land use is not affected, because the facilities involved are already in operation. No other property is affected, and no species are threatened. As the volumes are small, there will be no practical effect on transportation systems, and the effects of any disposals will be insignificant.

10. Mitigation Measures

Since all processes used to produce the product are properly controlled, and since production volumes are modest, mitigation measures beyond those described above are not necessary.

11. Alternatives to the Proposed Action

There are no practical alternatives to the proposal. This action will have no detectable effect upon the environment.

12. List of Preparers

This assessment has been prepared by R. D. Wood, Ph.D. Dr. Wood is a chemical engineer with degrees from Yale University and Northwestern University. He is a registered professional engineer in the state of Ohio.

Product and process information for this assessment was furnished by Bruce K. Long, a chemical engineer in the Pharmaceutical Process Development Department. Mr. Long has been employed by the company for more than twenty-five years, and is a registered professional engineer in the state of Indiana.

13. Certification

The undersigned certifies that the information presented herein is true, accurate, and complete to the best knowledge of Bristol-Myers Squibb.

November 6, 1991
Date

R. E. Hagen, Ph.D., Director, Environmental Management

MEGACE ORAL SUSPENSION

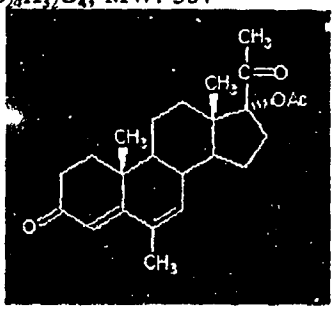
AUG 1 2 1993

PHARMACOLOGIST'S REVIEW

NDA 20-264 Pharmacology Amendment (BL)
Date Submitted: 8/9/93
Date Assigned: 8/11/93
Date Review Completed: 8/12/93
Reviewed by: Kuei-Meng Wu

SPONSOR: Bristol-Myers Squibb Company
2400 W. Lloyd Expressway
Evansville, IN 47721-0001

DRUG: MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3. 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384



RELATED NDA and IND: NDA 16-979
IND

FORMULATION: Oral Suspension (40 mg/ml)
Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.

INDICATIONS: Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS

This amendment to the pending NDA 20-264 MEGACE® OS (megestrol acetate oral suspension) provides a new version of the proposed label. It contains a new title in the BOX WARNING that is now in agreement with the Pregnancy Category X under the PRECAUTIONS section. The following changes on the (1) BOX WARNING (p. 8 of the submission), and (2) WARNINGS section (p. 26 of the submission) of MEGACE® OS are provided to reflect consistency with the preclinical pharmacology and toxicology information (recommended text shaded):

(1). **BOX WARNING** (page 8 of the submission)

CAUTION: FEDERAL LAW PROHIBITS
DISPENSING WITHOUT PRESCRIPTION
MEGACE® (megestrol acetate) Oral Suspension

WARNING
THE USE OF MEGACE® (megestrol acetate) Oral Suspension IS CONTRAINDICATED IN PREGNACY

~~The following warning is required for progestational agents:~~

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no ~~adequate~~ evidence that the use of a high dose progestational agent such as MEGACE® (megestrol acetate) Oral Suspension during any phase of pregnancy ~~such use~~ is effective for this purpose ~~when such drugs are given during the first 4 months of pregnancy~~. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. ~~Therefore, the use of such drugs during the first 4 months of pregnancy is not recommended.~~

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses. ~~fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.~~ Because of increased genital abnormalities in male and female fetuses induced by some progestational drugs, it is prudent to avoid the use of MEGACE® (megestrol acetate) Oral Suspension during pregnancy.

If the patient is exposed to MEGACE® (megestrol acetate) Oral Suspension during ~~the first 4 months of~~ pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

(2). **WARNINGS** (page 26 of the submission)

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, see the Impairment of Fertility section under **PRECAUTIONS**. ~~Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some male rat fetuses.~~ There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be appraised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Disk:
HFD-530/LRosenstein

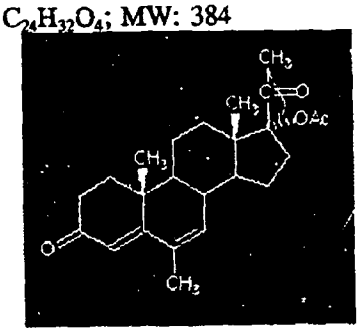
Concurrences:
HFD-530/Pre-Clin Dep/LRosenstein
HFD-530/SPharm/JFarrelly 8/12/93
Wu/Pharm/8/12/93

cc:
HFD-530 NDA 20-264(BL)
HFD-530/Division File
HFD-530/CSO/ADeCicco
HFD-530/MO/DFeigal
HFD-530/Chem/MJarski
HFD-530/Micro/WDempsey
HFD-530/Pharm/KWu
HFD-530/Biostat/KKazempour
HFD-710/Biometrics/Kelly
HFD-345/GJames

PHARMACOLOGIST'S REVIEW

MAY 7 1993

NDA 20-264	Pharmacology Amendment (AZ) Date Submitted: 4/26/93 Date Assigned: 4/26/93 Date Review Completed: 4/28/93 Reviewed by: Kuei-Meng Wu
SPONSOR:	Bristol-Myers Squibb Company 2400 W. Lloyd Expressway Evansville, IN 47721-0001
DRUG:	MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384
RELATED NDA and IND:	NDA 16-979 IND
FORMULATION:	Oral Suspension (40 mg/ml) Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.
INDICATIONS:	Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS



This amendment to the pending NDA 20-264 MEGACE® OS (megestrol acetate oral suspension) provides an updated version of the proposed labeling on preclinical pharmacology/toxicology. It incorporates the recommendations conveyed to the sponsor in a teleconference held on 3/25/93 (see attached PROPOSED LABELING CHANGES FOR MEGACE® OS). The sponsor has accepted and adopted nearly all recommended changes, except those described below that require further modifications.

Requirements

The following changes on the updated version of the proposed labeling on the preclinical pharmacology/toxicology portion of MEGACE® OS are needed (recommended text shaded):

PRECAUTIONS

Animal Toxicology

Long-term treatment with ~~megestrol acetate~~ MEGACE® may increase the risk of respiratory

infections. A ~~slight~~ trend toward increased frequency of respiratory infections, ~~decreases in~~ decreased lymphocyte counts and ~~increases in~~ increased neutrophil counts ~~were~~ was observed in a two-year chronic toxicity/carcinogenicity study of ~~MEGACE~~* megestrol acetate conducted in rats.

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Carcinogenesis

- - - - - Pituitary tumors were observed in ~~male~~ female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. - - - - -

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/Pre-Clin Dep/LRosenstein
HFD-530/Acting SPharm/JFarrelly
Wu/Pharm/4/29/93

cc:
HFD-530 NDA 20-264(AZ)
HFD-530/Division File
HFD-530/LRosenstein
HFD-530/CSO/ADeCicco
HFD-530/MO/DFeigal
HFD-530/Chem/MJarski
HFD-530/Micro/WDempsey
HFD-530/Pharm/KWu
HFD-530/Biostat/KKazempour
HFD-710/Biometrics/Kelly
HFD-345/GJames

ADDENDUM

PROPOSED LABELING CHANGES FOR MEGACE® OS: (faxed to and discussed with the sponsor on 3/20/93)

The following text represents recommended changes to the preclinical pharmacology/toxicology portion of the original labeling of MEGACE® OS. The recommended text is shaded.

PRECAUTIONS

Animal Toxicology

Long-term treatment with MEGACE® may increase the risk of infections. An increased frequency of respiratory infections, decreases in lymphocyte counts and increases in neutrophil counts were observed in a two-year chronic toxicity/carcinogenicity study of MEGACE® conducted in rats.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Carcinogenesis

~~Administration for up to seven years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast[11]. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors[OO] to humans is unknown but should be considered in assessing the benefit to risk ratio when prescribing MEGACE® OS and in surveillance of patients on therapy[11, 12].~~ Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times *lower* than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing MEGACE® OS and in surveillance of patients on therapy. Also see "WARNINGS" section.

Mutagenesis

No mutagenicity data are currently available.

Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05-12.5 mg/kg) *less* than that indicated for humans (13.3 mg/kg). In these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

~~*Pregnancy*~~ *Pregnancy - Teratology*

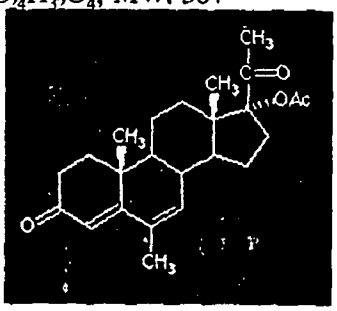
Pregnancy Category ~~D~~ X. See "WARNINGS" "and *Impairment of Fertility*" section. No adequate animal teratology information is available at clinically relevant doses.

OVERDOSAGE

No serious unexpected side effects have - - - - - as high as 1600 mg/day.[UU] ~~Oral administration of large, single doses of megestrol acetate (5 grams/kg) did not produce toxic effects in mice[10].~~

PHARMACOLOGIST'S REVIEW

NDA 20-264	Minor Pharmacology Amendment (BP) Date Submitted: 12/7/92 Date Assigned: 12/22/92 Date Review Completed: 12/29/92 Reviewed by: Kuei-Meng Wu	JAN 29 1993
SPONSOR:	Bristol-Myers Squibb Company 2400 W. Lloyd Expressway Evansville, IN 47721-0001	
DRUG:	MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384	
RELATED NDA and IND:	NDA 16-979 IND	
FORMULATION:	Oral Suspension (40 mg/ml) Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.	
INDICATIONS:	Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS	



The sponsor submitted survival data of the two-year carcinogenicity study in rats. Along with the data is an extensive statistical analysis of the survival data using the LIFETEST procedure. These data do not alter the conclusion of the study (please refer to the Pharmacologist's Reviews on the original submission and the supplement of this NDA, dated 6/1/92, 10/8/92 and 11/25/92). The statistical analysis of the data will be reviewed by Dr. Carl Lin of Statistical Analysis and Research Branch, CDER.

CONCLUSION

No regulatory action is needed at this moment.

Kuei-Meng Wu

12/29/92

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

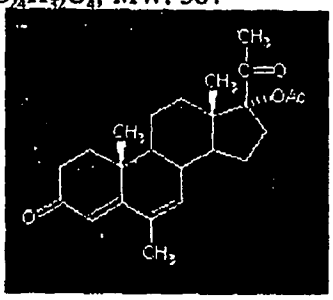
PHARMACOLOGIST'S REVIEW

DEC 1 4 1992

NDA 20-264 Minor Pharmacology Amendment (BP)
Date Submitted: 11/19/92
Date Assigned: 11/20/92
Date Review Completed: 11/25/92
Reviewed by: Kuei-Meng Wu

SPONSOR: Bristol-Myers Squibb Company
2400 W. Lloyd Expressway
Evansville, IN 47721-0001

DRUG: MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384



RELATED NDA and IND: NDA 16-979
IND

FORMULATION: Oral Suspension (40 mg/ml)
Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.

INDICATIONS: Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS

This amendment includes the sponsor's responses to a teleconference with Division reviewers in regard to the issues of pituitary tumors in the two-year carcinogenicity study of megestrol in rats. Comments on the sponsor's responses follows:

1. The sponsor has repeated the statistical test using trend analysis and concluded that the incidence of pituitary tumor is significant.

   This conclusion is consistent with that reached by Dr. Kazempour, the Divisional statistician, as indicated in the Pharmacologist Reviews on the original submission and the supplement of this NDA, dated 6/1/92 and 10/8/92, respectively. The detailed statistical computations submitted with this submission will be reviewed separately by the Statistical Application and Research Branch (SARB) of CDER. Dr. Kazempour will also provide his comments on this issue in his review.

2. In response to the Agency's request, the sponsor provided historical data on pituitary tumors of Mead Johnson colony rats in the 1960s. The data were obtained from an article published in *Toxicology and Applied Pharmacology (12:68-79)*. The paper showed that in a control group of 60 rats, there were 11 pituitary adenomas, but no such tumors in the 30 rats of the other control rats. Based

upon these data, the sponsor stated that "attributing the pituitary adenomas to the study drug (megace) cannot be justified."

The implication of pituitary tumors observed in female rats in this NDA has been discussed in the *Pharmacologist's Review on Supplement No. 1 dated 10/31/92*, regarding the fact that (1) the spontaneous occurrence of certain type of pituitary tumors in the rat is high and (2) the histologic nature of pituitary tumors and the strain of rats used were not described in the original NDA. It should be emphasized that although the spontaneous incidence of pituitary tumors in control rats was high and varied greatly, as outlined above, the pituitary tumor incidence in this NDA has been concluded to be treatment related. The concerns are that the tumor emerged in a relatively small sample size ($n < 25$) and at a dosage that is lower than the human dose (13.3 mg/kg). The sponsor does not have any relevant data indicating that at doses that are multiples of or equivalent to the proposed human dose, the pituitary and other tumors will not occur.

3. The sponsor has requested a waiver from any requirements to provide additional preclinical toxicology data because the drug has been in human use for over 20 years.

   The human experience on large doses of megace is scarce and animal toxicity data tested at a multiple of proposed human dose are lacking. The recommendations provided for this NDA in the Pharmacologist Reviews on the original submission and the supplement dated 6/1/92 and 10/8/92 respectively, should not be changed.

CONCLUSION

The sponsor should be informed of the *requirements* and *requests* (excluding the items on labeling changes) made in the conclusions of the reviews on the original NDA and supplement no. 1, dated 6/1/1992 and 10/8/1992, respectively.

Kuei-Meng Wu 12/8/1992

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/Pre-Clin Dep/LRosenstein
HFD-530/SPharm/MGreen 10/12/92
Wu/Pharm/11/25/92

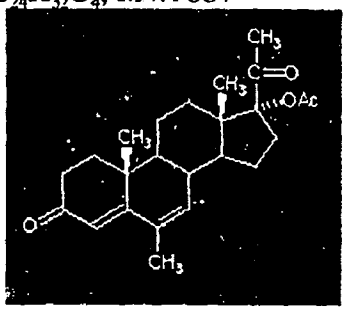
PHARMACOLOGIST'S REVIEW

NDA 20-264 Supplement No. 001 – BP
Date Submitted: 9/23/92
Date Assigned: 9/28/92
Date Review Completed: 10/8/92
Reviewed by: Kuei-Meng Wu

OCT 23 1992

SPONSOR: Bristol-Myers Squibb Company
2400 W. Lloyd Expressway
Evansville, IN 47721-0001

DRUG: MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384



RELATED NDA and IND: NDA 16-979
IND

FORMULATION: Oral Suspension (40 mg/ml)
Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.

INDICATIONS: Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS

INTRODUCTION

This amendment includes the sponsor's responses to the Agency's deficiency letter of 8/13/92 that contained four pharmacology/toxicology requests with respect to the original NDA. The sponsor's responses are as follows:

1. <u>The sponsor provided results of statistical analysis on the pituitary tumor incidence in the two-year carcinogenicity study of megestrol in rats. They concluded that there is no significant difference among treatment groups with respect to tumor incidence.</u>
   The sponsor has inappropriately pooled female and male animals together for the statistical analysis of tumor incidence. Additionally, Dr. K. Kazempour, the Division's statistician, pointed out that the *trend factor* was not included in the sponsor's analysis of the data. As he previously concluded (*see pharmacologist review on original NDA, dated 6/1/92*), the incidence of pituitary tumor is significant and is treatment-related when the *trend factor* is incorporated in the statistical test. Dr. C. Lin of the Statistical Application and Research Branch (SARB) of CDER was also consulted on this issue and he agreed with Dr. Kazempour.

The pituitary tumor incidence in rats during the two-year carcinogenicity study is summarized in the table below.

Table 1.
Pituitary Tumor Incidence in Rats Treated with Megestrol for Two Years.

Megestrol Dose (mg/kg)			
Control (14 f*, 13 m*)	1.5 (12 f, 10 m)	3.9 (12 f, 11 m)	10 (14 f, 13 m)
0	0	1 f	3 f

*: f= female, m= male.

It should be noted that the tumor emerged in a relatively small sample size ($n < 25$) and at a dosage that is lower than the human dose (13.3 mg/kg). Further, the MTD of this carcinogenicity study was not delineated.

The implication of pituitary tumors observed in female rats can not be determined at this time because (1) spontaneous occurrence of certain type of pituitary tumors in the rat is high (see table below), (2) the histologic nature of pituitary tumors and the strain of rats used were not described in the original NDA.

Table 2.
Percentage of 24-Month Spontaneous Pituitary Tumor in CDF/CrlBR and CD Strains of Female Rats. (Adapted from The Manuals of Charles River Laboratories, 1987, 1990)

Tumor Subtype	CDF/CrlBR (%)	CD (%)
adenoma (NS†)	8.9	57
adenoma, chromophobe	2.7	-
adenoma, pars distalis	17.4	-
adenoma, clear cell	-	0.1
adenocarcinoma	-	6
carcinoma (NS)	0.3	0.9
carcinoma, chromophobe	0.1	-
carcinoma, pars distalis	2.3	-

†: not specified.

2. The sponsor provided the location of mortality and survival data for the two year carcinogenicity data in their NDA files. The sponsor also indicated that information on gross and histopathology examination of fetuses in a teratology study in rabbits and data on food consumption in a twelve-week toxicity study in monkeys are either missing or not available.

   The sponsor's response regarding mortality/survival data in rats and food consumption data in monkeys is acknowledged by this reviewer. However, histopathology of the fetuses is needed for supporting sponsor's claim on the lack of teratologic effects in rabbits.

CONCLUSIONS

The statistics of tumor incidence in the pituitary of rats will be further investigated with the assistance of the Statistical Application and Research Branch (SARB) of CDER in a formal analysis.

Requests

(1) The sponsor should repeat the teratology study in rabbits using a sufficiently high dose range of megestrol, as compared to the proposed human dose (13.3 mg/kg). A MTD should be delineated for the dose range selected for the study. This should be included in the Phase IV plan of the NDA.

(2) The sponsor should provide historic control data on the incidence of pituitary tumors during the period that study was performed. The strain of rats used should be provided. In the Phase IV plan of the NDA, the sponsor should conduct a formal carcinogenicity study in rats using adequate dosage and number of animals to fully explore the carcinogenic potential of megestrol.

Kuei-Meng Wu 10/15/92

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/Pre-Clin Dep/LRosenstein 10/23/92
HFD-530/SPharm/MGreen 10/8/92
Wu/Pharm/10/8/92 10/15/92

Statistical Review and Evaluation

DATE: MAR 19 1993

NDA#: 20-264

APPLICANT: Bristol-Myers Squibb

NAME OF DRUG: Megace OS (megestrol acetate oral suspension)

DOCUMENTS REVIEWED: Amendments to NDA dated Nov. 16, 1992 and Dec. 4, 1992.

I. Background

The above submissions contain responses to FDA inquiries. The first amendment consists of a scientific paper, the sponsor's analysis of rat pituitary tumors, and a request for waiver from any requirements to provide additional preclinical toxicology/ pharmacology data because the drug has been used in humans for over 20 years. The more recent amendment contains preclinical pharmacology/toxicology information which was inadvertently omitted in the earlier amendment.

Dr. Kuei-Meng Wu (HFD-530) is the reviewing pharmacoligist. This reviewer discussed her findings with him and at a meeting with the sponsor. This product was deliberated at the 2/28/93 Antiviral Advisory Committee meeting. The tumor data, however, were not considered at this meeting.

II. The Rat Study

II.a. Design

This study was conducted over 20 years ago in Mead Johnson colony rats. Twenty-five animals each started in the control, the low, mid and high dose groups. The controls received the vehicle only, the actively treated animals received 1.5mg/kg, 3.9mg/kg, and 10mg/kg respectively. After 52 weeks on study, 10 animals in each of the dose and the control groups were sacrificed. The remaining animals continued on study until 107 weeks when all surviving animals were sacrificed, necropsied, and histopathologically examined. It is not totally clear, but the sponsor presumes from the records that were kept that tumors were only determined on the animals undergoing terminal sacrifice. Statistical analyses included survival analysis based on all animals and tumor analyses based on animals alive at week 54 and alive at terminal sacrifice.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis: Survival data were analyzed per sex treating the

animals sacrificed at week 53 and at the end of the study as censored. The sponsor found no statistical significant differences between dose groups, nor a statisically significant association of survival time with actual dose.

Tumor Data Analysis: The rat pituitary tumor rates were analyzed via an extension of Fisher's exact test. There were no occurrences among the male rats, so no analysis was performed. The female tumor rates were analyzed for the total of 50 rats alive at week 54 and repeated for the 35 rats alive at the end of the two years (worst case scenario). The increase in tumor rates with increasing dose (trend test) was statistically significant (p=.047) at week 54 and more so (p=.031) at the end of the study. There were no statistically significant differences in tumor rates between the control and each of the treated groups at either time point (p>.05).

II.c. Reviewer's Analyses

Survival Analysis: The intercurrent mortality rates for both the male and female rats are given in Table 1. Among the male rats, 32%, 16%, 32%, and 32% survived until the terminal sacrifice from the control, low, mid, and high dose groups respectively. The corresponding survival rates till the end of study for the female rats were 40%, 32%, 32%, and 36%. As the sponsor noted, the dose groups were not statistically differentiable nor was the difference in survival experience between the male and the female rats. This reviewer did not perform an independent survival analysis. The sponsor's analyses appear valid and the study is so underpowered that only extreme differences in survival patterns would be detected. Visual inspection of the sponsor's survival curves also suggests similar survival experience across treatment and sex groups.

Tumor Data Analysis: This reviewer analyzed the pituitary tumors as requested by Dr. Wu. The analysis was not mortality adjusted, because according to the sponsor's assumption only the terminally sacrificed animals were necropsied. The pituitary tumor incidence rates among female rats appeared as follows:

	Dose			
	Control	1.5mg/kg	3.9mg/kg	10mg/kg
Female Rats	0/10	0/8	1/8	3/9

The trend statistic for these incidence rates is significant at the .05 level of significance (p=.0128). This level of significance is higher than the one given by the sponsor because the trend is weighted by the actual dose levels.

The study was conducted over 20 years ago, and it is difficult to

apply currently statistical methodology and standards to such old data. However, the following current approaches used by FDA statisticians seem applicable: Tumor types with 10 or less occurrences across treatment groups are generally analyzed by an exact permutation trend test. Treatment groups are weighted by the actual dose levels, i.e. 0, 1.5, 3.9, 10 mg/kg. Tumors with $\leq$ 1.00 % of occurrence in the control group are considered rare and a trend test is statistically significant when it reaches a p-value of $\leq$ .05. Higher tumor occurrences in the control group are considered common for these animals and a trend is statistically significant when its p-value is less than .01.

Applying these criteria, the pituitary tumors would be considered rare (no occurrences among the control animals) and the trend test is highly statistically significant. The sponsor argued, however, that pituitary tumors are not rare in Mead Johnson colony rats and quoted background rates ranging from 0 to 33 percent. This wide spread of spontaneous rates raises doubts about the validity of these estimates. Nonetheless, if we assume that pituitary tumors are common in this species, the level of the observed statistical significance (p=.0128) almost satisfies the current criterion for common tumors to reach significance at the .01 level.

The study started with only 25 animals per treatment group. After the intermittant sacrifice at 53 weeks there were only 10 - 14 animals remaining per treatment group to be at risk of developing late occurring tumors. The study as a whole has insufficient power to claim that the abscence of additional tumor findings represents lack of further tumor activity of the product. On the other hand, the general lack of power in this study makes the observed significant linear trend in pituitary tumors among female rats even more noteworthy.

III. Summary

This is a very old study, that is extremely underpowered. The study starts with half the number of animals that are nowadays considered necessary, and has an intermittant sacrifice that kills about half of the animals. Only 10 to 14 animals are at risk of developing late occurring tumors. An additional flaw of the study is, that to the sponsor's best knowledge, only animals that were sacrificed at the end of the study ($4 \leq n \leq 10$) were necropsied and microscopically examined. The resulting lack of power will make it unlikely to discover any tumor findings in this study.

Pituitary tumors in female rats were the main focus of this review. The incidence rates for this tumor showed a highly significant linear trend (p=.0128) with increasing dose. This finding would almost satisfy the current criterion of testing common tumors at p=.01, and certainly would be considered a statistically significant finding if the tumor is considered rare in this species. Additionally, this finding is of importance, as it shows

a significant result in a very underpowered study.

The level of significance reported by this reviewer is more extreme than the one reported by the sponsor. This is due to this reviewer using the actual doses administered as weights in the trend statistic. The sponsor did not use any weights in the calculation of his trend statistic.

The analysis for the pituitary tumor was not age adjusted, as their occurrence was observed only when animals were sacrificed at the end of the study. The sponsor's survival analyses appear appropriate, but again, only extreme differences between survival patterns would be detected in such an underpowered study.

From a statistical viewpoint, taking all available information of this study into account, there is a statistically significant linear trend in pituitary tumors among female rats.

Roswitha Kelly

Roswitha E. Kelly
Mathematical Statistician

Concur:

Karl K. Lin 3/17/93

Karl K. Lin, Ph. D.
Group III Leader

cc:HFD-530/Original NDA 20-264
HFD-530/Dr. Wu
HFD-710/Chron.
HFD-715/Chron.
HFD-715/Dr. Lin
HFD-715/Ms. Kelly
HFD-715/DRU 2.1.1 Megace OS, Bristal-Myers Squibb
HFD-715/RKELLY/02/24/93/megace-wp51

Table 1
INTERCURRENT MORTALITY RATES
RAT STUDY

Sex	Time (wks.)	Control	mg/kg		
		0	1.5	3.9	10
MALES	0 - 52	2/25 (8%)	5/25 (20%)	4/25 (16%)	2/25 (8%)
	Interm. Sacr.	10/23 (43%)	10/20 (50%)	10/21 (48%)	10/23 (43%)
	54 - 106	5/13 (38%)	6/10 (60%)	3/11 (27%)	5/13 (38%)
	Term. Sacr.	8/25 (32%)	4/25 (16%)	8/25 (32%)	8/25 (32%)
FEMALES	0 - 52	3/25 (12%)	3/25 (12%)	3/25 (12%)	1/25 (4%)
	Interm. Sacr.	10/22 (45%)	10/22 (45%)	10/22 (45%)	10/24 (42%)
	54 - 106	2/12 (17%)	4/12 (33%)	4/12 (33%)	5/14 (36%)
	Term. Sacr.	10/25 (40%)	8/25 (32%)	8/25 (32%)	9/25 (36%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parenthesis for this row represents the number of animals surviving to terminal sacrifice.

PHARMACOLOGIST'S REVIEW

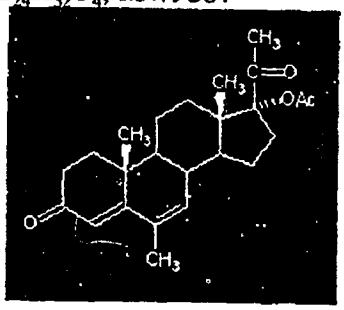
NDA 20-264

Date Submitted: 4/1/92
Date Assigned: 4/4/92
Date Review Completed: 6/1/92
Reviewed by: Kuei-Meng Wu

JUL 29 1992

SPONSOR: Bristol-Myers Squibb Company
2400 W. Lloyd Expressway
Evansville, IN 47721-0001

DRUG: MEGACE® OS (megestrol acetate oral suspension); B.D.H. 1298; Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-methyl acetate; 17-hydroxy-6-methyl-pregna-4, 6-diene-3, 20-dione acetate; CAS No.: CAS-595-33-5, CAS-3562-63-8; Formula: $C_{24}H_{32}O_4$; MW: 384



RELATED NDA and IND: NDA 16-979
IND .

FORMULATION: Oral Suspension (40 mg/ml)
Excipient: polyethylene glycol, polysorbate 80, sodium benzoate, sodium citrate, sucrose and xanthan gum.

INDICATIONS: Treatment of Anorexia, Cachexia or a Significant Weight Loss in Patients With AIDS

INTRODUCTION

Megestrol acetate (megestrol) is marketed by the current sponsor under NDA 16-979 as an antineoplastic agent for the treatment of endometrial cancer (40~320 mg/day) and breast cancer (160 mg/day). This NDA was submitted for the treatment of anorexia and cachexia in AIDS patients using an oral suspension formulation of megestrol. The proposed dose is 800 mg/day. The original IND had been allowed to go into effect by the Division of Oncology (HFD-150).

BACKGROUND

Megestrol is a synthetic analog of the naturally occurring progestin. In the US, megestrol was approved for palliative treatment of endometrial and breast cancer. One of the major side effects in these cancer treatments is gain in weight, associated not with fluid retention but with an *increased appetite*. Since cachexia often is a severe problem in cancer patients, the use of megestrol had been considered valuable in the treatment by virtue of the increase in appetite and weight gain that occurs with its use. The mechanism, however, by which megestrol produced appetite stimulation and increased weight gain is not known. This NDA was submitted in support of the use of 800 mg dose of megestrol (oral suspension) in the treatment of AIDS-related anorexia and cachexia.

NON-CLINICAL TOXICITY STUDIES

All non-clinical toxicity studies were completed prior to the year of 1980 and none of these studies were performed under the conditions of GLP.

TOXICITY STUDIES SUMMARY

A total of 2 single-dose, 6 repeat-dose and 3 chronic toxicity/carcinogenicity and 8 reproduction/mutagenicity studies was submitted. They are listed as follows:

Single-Dose Acute Toxicity

1. Single-Dose PO Toxicity Study in Mice
2. Single-Dose SC Toxicity Study in Mice

Repeat-Dose Chronic Toxicity

1. Two-Week PO Toxicity Study in Male Rats
2. Four-Week PO Toxicity Study in Female Rats
3. Twelve-Week PO Toxicity Study in Rats
4. Twelve-Week PO Toxicity Study in Squirrel Monkeys
5. Six-Month PO Toxicity Study in Beagle Dogs
6. One-Year PO Toxicity Study in Rats

Chronic Toxicity/Carcinogenicity

1. Two-Year PO Chronic Toxicity/Carcinogenicity Study in Rats
2. Four-Year PO Chronic Toxicity/Carcinogenicity Study in Female Beagles
3. Seven-Year PO Chronic Toxicity/Carcinogenicity Study in Female Beagles

Reproduction and Teratology

1. Reproduction Study in Female Rats
2. Reproduction Study in Female Rats
3. Reproduction Study in Female Rats
4. Teratology Study in Rabbits
5. Teratology Study in Rabbits
6. Teratology Study in Rats
7. Perinatal/Postnatal Toxicology Study in Rats
8. Perinatal/Postnatal Toxicology Study in Rats

TOXICITY STUDIES REVIEW

The information provided at the end of the title of each study are report code, site of experimentation and year of report followed by file codes. No information regarding the lot or batch number of the compound used was submitted. Report code of many studies was not designated. All single-dose, two repeat-dose and three reproduction/teratology studies were reported in England in the years 1960-1963. B.D.H. 1298 was used as the name for megestrol in some of these reports.

A. Single-Dose Acute Toxicity:

1. **Single-Dose PO Toxicity Study in Mice (1961, 7-05-304, 7-05-309)**

   Ten mice of both sexes were fed by gavage at a 5 g/kg dose of megestrol in an aqueous suspension and were kept under observation for 7 days. No toxicities were reported.

   COMMENTS: This study was a part of a paper attached along with the submission (*J. Reprod. Fertil. 5:331-346, 1963*). No detailed data were submitted.

2. **Single-Dose SC Toxicity Study in Mice (1961, 7-05-361)**

   Five mice of both sexes were injected subcutaneously with a 5 g/kg dose of megestrol suspended in water containing Tween-80. No signs of toxicities were observed for 48 hr following administration of the drug.

B. Repeat-Dose Chronic Toxicity:

1. **Two-Week PO Toxicity Study in Male Rats (1960 7-05-361)**

   Five immature male mice were administered 0 or 20 mg/kg/day of megestrol for 14 days. No toxicities were reported. Body weight gains were similar for the treated and control groups.

2. **Four-Week PO Toxicity Study in Female Rats (1960, Mead Johnson, 7-05-345)**

   Seven female rats of McCollum strain were fed with 0, 1.3, 4.2 or 12.7 mg/kg/day of megestrol in the diet for 4 weeks Animals in the high dose group showed decreased leukocyte counts and atrophy of ovary, uterus and adrenal gland. No other toxicities were reported.

3. **Twelve-Week PO Toxicity Study in Rats (1961, 7-05-304, 7-05-309)**

   METHODS. Twenty rats of both sexes were fed with megestrol by gavage at 0 (vehicle), 1, or 20 mg/kg/day 5 days a week for 12 weeks. Megestrol was

suspended in a vehicle containing arachis oil, 20% polyethylene glycol and water. Five animals of both sexes were randomly selected for histopathology. A total of 15 different organs/tissues was examined.

RESULTS. The uterine sections showed endometrial hyperplasia in the treated groups. Adrenal atrophy and an increased colloid storage in the thyroid gland were observed in females of the high dose group. No other toxicities were reported.

COMMENTS: This study was a part of a paper attached along with the submission (*J. Reprod. Fertil. 5:331-346, 1963*). No detailed data were submitted.

4. **Twelve-Week PO Toxicity Study in Squirrel Monkeys (1963, Mead Johnson Research Center, 9-05-1063)**

METHODS. Three groups of three female and one male squirrel monkeys were fed with megestrol by stomach tube at dosage levels of 0, 0.5, or 2.5 mg/kg/day seven days a week for a period of twelve weeks. Megestrol was suspended in a normal saline vehicle containing 0.5% carboxymethylcellulose, 0.4% Tween 80 and 1.5% benzyl alcohol.

MEASUREMENTS. Body weights were recorded weekly. Hematological studies were performed at the fourth, eighth and fifteenth weeks of treatment. Clinical chemistry was performed at the fifteenth week of the study. A total of twelve organs and at least nineteen tissues from each monkey at the terminal sacrifice was weighed and fixed for histopathology study.

RESULTS. The *body weight gains* were significant in the high dose group as compared to the pretreatment values. In treated males, *organ weights* of adrenals and testes were less than controls. The weight of adrenal and thyroid glands in one female from each treated group (1/3 females) was reduced. All ovaries from treated females weighed heavier than controls. *Histological examinations* of the ovary showed cystic follicles in two of the low and all of the high dose group animals. No other significant histopathological findings were related to the above organ weight changes and considered to be treatment-related. No hyperplastic or *neoplastic changes* were found in any of the tissues examined in all the monkeys.

COMMENTS: The apparent non-toxic profile in the non-reproductive tissues of the monkey reflected the inadequate and relatively low doses tested (0.5~2.5 mg/kg) as compared to the proposed human dose (13.3 mg/kg). Non-endocrine toxicity should be explored at levels 2~10 folds the proposed human dose. The number of male monkey used is also inadequate since only one male was used in each dosage group. In regard to the weight gain, the sponsor should provide food consumption data for analysis of the source of gain in weight.

5. Six-Month PO Toxicity Study in Beagle Dogs (WEIK-JH-02659, 1963, Mead Johnson Research Center, 9-05-1063)

METHODS. Megestrol was given to five groups of two beagle dogs of both sexes by mouth at dosage levels of 0 (group 1), 0.04 (group 2), 1 (group 3), 2.5 (group 4), or 6 mg/kg/day (group 5) seven days a week for six months. One part of megestrol was triturated with five parts of lactose and contained in the capsule for oral administration. All dogs except one male and one female from group 1, 4 and 5 were sacrificed after 28 weeks of drug administration. The 6 dogs that were not sacrificed at the 28th week were used for recovery study for 6 months.

MEASUREMENTS. Body weights were recorded monthly. Clinical laboratory studies (hematology, chemistry, and urine analysis) were determined in all dogs at week 4, 9, 16 and 24. A total of ten organs and at least sixteen tissues was obtained at the terminal sacrifice for their weights and histology.

RESULTS.

No deaths occurred during the experimental period. *Body weight gains* increased significantly in all treatment groups. The average percent gains for groups 1 through 5 were 9, 21, 28, 50 and 89%, respectively. These increases were more profound in females. *Clinical laboratory tests* showed decreased erythrocyte counts, packed cell volume and hemoglobin concentrations in one, two and three dogs from group 3, 4 and 5, respectively. Serum alkaline phosphatase was elevated in all dogs of group 5. Serum glutamic pyruvic transaminase (SGPT) was increased in 3 of group 5 and 1 of group 4 dogs.

Liver *organ weights* were increased (hepatomegaly) in all of group 5 and the females of group 4 dogs. In all treated animals, adrenal, prostate and ovary were atrophied and their weights were less than controls.

Major *histopathology findings* in the treated animals included *thyroid* hypertrophy, *liver* vacuolization, *mammary* hyperplasia, cystic endometrial hyperplasia in the *uterine horns*, and atrophy in the inner cortical zone of *adrenal gland*. The severity and frequency of these toxicities increased with the dose (see table below).

Table 1.
Incidence of major histopathologic findings in beagle dogs treated with megestrol for six months

Organs	Megestrol Dose (mg/kg/day)				
	0	0.4	1	2.5	6
Liver Vacuolization	0/4	0/4	0/4	1/2 (f)	2/2 (1 f, 1 m)
Adrenal Atrophy	0/4	3/4 (2 f, 1 m)	4/4	2/2 (1 f, 1 m)	2/2
Prostate Atrophy	0/4	2/4 (m)	2/4 (m)	1/2 (m)	1/2 (m)
Uterus Hyperplasia	0/4	2/4 (f)	2/4 (f)	1/2 (f)	1/2 (f)
Mammary Hyperplasia	0/4	2/4 (f)	2/4 (f)	1/2 (f)	1/2 (f)
Thyroid Hyperplasia	0/4	2/4 (1 m, 1 f)	3/4 (2 m, 1 f)	2/2	2/2

f: female; m: male

During *recovery period*, values of erythrocyte parameters, SGPT and alkaline phosphatase levels returned to the normal range after 4 weeks of drug withdrawal. Adrenal and testis of treated animals remained small.

Histological examination of the two recovery dogs from group 4 and 5 showed: (1) no evidence of vacuolization of liver, (2) borderline and minimal abnormalities in the cortical zone of adrenal gland, and (3) no residual histological changes in mammary gland, uterus and ovary. The prostate gland was, however, still in an atrophied state.

Breeding experiment was performed in the recovery animals. The control females mated with males from group 4 after 17 weeks of recovery had 4 female pups whelped, one undeveloped, one stillborn and one died after one week. The males from group 5 appeared to be impotent and would not mate during this period. The megestrol-treated females did not have estrous activities during the 6 month recovery period.

COMMENTS: Major target non-reproductive organs of toxicity in the beagle are *liver, adrenal and thyroid glands*. The severity and spectrum of toxicity might have been expanded if the dose had escalated to 13.3 mg/kg, the proposed human dose, or higher. Histopathology of the recovery animals suggested that organ toxicity in females recovered faster than that of the males. The

depression of erythrocyte parameters could not be reflected in bone marrow histology. Breeding experiments performed in recovery animals demonstrated a clear *reproduction toxicity* in both females and males that were previously treated with megestrol. The significance of mammary tumor may be discounted here because various reports have considered the beagle an inappropriate model for progestogen, particularly regarding the tumorigenicity of the breast (Please see "*Facts about injectable contraceptives: Memorandum from a WHO meeting. Bull. WHO 60:192, 1982*" and "*Safety Requirements for Contraceptive Steroids. by F. Michael, 1989 W.H.O.*").

6. One-Year Chronic PO Toxicity Study in Rats (WEIK-JH-02659, 1963, Mead Johnson Research Center, 9-05-1063, 9-05-1256)

METHODS. Four groups of twenty-five male and female rats of McCollum strain were fed with 0, 1.5, 3.9 or 10 mg/kg/day megestrol for 52 weeks. The test diet was prepared from a stock containing 1 mg of megestrol per gram of Purina Laboratory Chow in meal form. The drug/feed ratio was adjusted weekly to maintain desired dosing levels. The control received only Purina Laboratory Chow.

MEASUREMENTS. Body weights were recorded monthly. Clinical hematology study was determined in ten rats from each dose at week 4, 8, 16, 25, 36 and 52. A total of twelve organs and tissues was obtained from ten males and females at the terminal sacrifice for their weights and histology study. The remainder of the animals was used for recovery examinations.

RESULTS.

Body weights of female rats in middle and high dose groups increased significantly, with an appearance of *obesity*. A significant amount of subcutaneous and mesenteric fat was found in these females rats. No difference in average food consumption was observed. *Ataxia* and *depression* were observed in middle and high dose group rats after three weeks of treatment. *Alopecia* also occurred in the treated groups after 14 weeks of treatment. The *organ weight* of spleen, liver and heart was increased whereas the weight of adrenal and ovary decreased in females of the high dose group.

Histopathologic examinations showed hypoplasia of *adrenal* glands (cortex), *ovaries* and *uteri* in the females and *prostate* in the males of middle and high dose group rats. The severity of these findings increased with dose. In high dose rats, two males had small and hydropic testes with spermatocele granulomas.

Two *mammary tumors* were visible at 33 and 52 week of treatment in a female from the middle dose group. Histology showed the tumor was fibro-adenoma type. The third tumor was observed in a female from the high dose group at 48 week of treatment.

COMMENTS: The major target non-reproductive organs of toxicity in the rat are *CNS and adrenal gland*. Since no difference in average food consumption was observed, weight gains should result from decreases in calorie output. It is likely that the depression and ataxia seen in the same group of rats had contributed to the weight gain, possibly by reducing physical activities. The uterine findings (hypoplasia) in rats are in marked contrast to the consistent and conspicuous tubular dilation and uterine enlargement (glandular hyperplasia) observed in dogs given megestrol. Histopathological findings might have become evident in the liver, heart and spleen if the dose had escalated to 2~10 fold of the proposed human dose (13.3 mg/kg). The weight of these organs had already increased in high dose female rats.

C. Chronic/Carcinogenicity Studies:

1. Two-Year Chronic Toxicity/Carcinogenicity Study in Rats (WEIK-JH-02659, 1963, Mead Johnson Research Center, 9-05-1213, 9-05-1309)

METHODS. This is an extension study of the one-year toxicity study performed in two hundred rats as reviewed above. Four groups of 10~13 male and 12~14 female rats of McCollum strain (total forty-seven) were fed with megestrol at dosage levels of 0, 1.5, 3.9 or 10 mg/kg/day for 2 years. The test diets and its adjustments were the same as those used in the one-year rat study, as described above.

MEASUREMENTS. Body weights were recorded monthly. Clinical hematology was performed at week 77 and 104. Clinical chemistry was conducted at the conclusion of the study. At least twelve organs/tissues were obtained at terminal sacrifice (week 105) for their weights and histology.

RESULTS.

Ataxia, alopecia, depression and *obesity* observed in the one-year study continued to be present. Respiratory infections had increased to 24% by 78th week and to 51% during the 102 week and its incidence in treated groups was higher than controls. A decrease in lymphocyte and increase in neutrophil counts were evident in males of the high dose group. *Body weights* of female rats at the 105 week remained higher and were dose-related. The *organ weight* of adrenals, uteri and ovaries decreased in females of middle and high dose groups. The spleen weights were increased in treated females and pituitaries were heavier in high dose females.

Tumors were found in various tissues including pituitary, salivary gland, lung, liver, adrenal, spleen, kidney and mammary gland. The incidence is summarized in the table below.

Table 2.
Tumor incidence of rats treated with megestrol for two years.

Organs	Megestrol Dose (mg/kg)			
	Control (9 f*, 8 m*)	1.5 (8 f, 4 m)	3.9 (8 f, 6 m)	10 (9 f, 8 m)
Pituitary	0	0	1 f	3 f
Salivary gland	0	0	0	1 m
Lung	2 f	1 f	1 f	2 m, 2 f
Liver	1 f	0	0	0
Adrenal	1 m	1 f	1 m	0
Spleen	0	1 f	0	0
Mammary gland	5 f	3 f	2 f	8 f

*: *f = female, m = male*

Histopathologic examinations of tumors and other lesions in the organs/systems are presented as follows: *Mammary tumor* and hyperplasia in treatment groups were adenomatous type, in contrast to the fibrous type observed in controls. The *pituitary* in treated animals (a total of 2, 3 and 6 rats in low, middle and high groups, respectively) showed hyperplasia with associated concavity and depression of adjacent brain. The *ovary* in females of treated groups was hypoplastic, with the severity and frequency of incidence increased with dose. The finding in *uterus* was unremarkable, with only one incidence of cystic endometrial hyperplasia. The *adrenal gland* in both males and females of the high dose group did not show significant morphological changes. Both the secretions and cellular elements of *male reproductive tissues* were found decreased in group 3 and 4 males. The testis, prostate, seminal vesicle, and epididymis showed dose-related atrophies in these rats.

COMMENTS: Immunotoxicity of megestrol is evidenced in this study by the emergence of long-term treatment-related respiratory infections and other related syndromes (i.e., decreases in lymphocytes and increases in neutrophils). Megestrol-induced adrenal atrophy may also play a role in the cause of the increases in respiratory infections. The dose-related increase in the incidence of pituitary tumor is significant according to the Fisher Exact Test (consulted with Dr. Kazem Kazempour, the Statistician). This carcinogenicity study is deficient in certain information that is required to allow for full assessment of tumorigenic potentials of megestrol. For example, no mortality/survival data were provided, the number of animal used and the dosage selected were inadequate. Other concerns on the toxicity are listed in the "Comments" portion of the review of the one-year rat study presented above.

2. Four-Year Mammary Tumorigenicity Study in Female Beagles (1980, 7-05-319, 7-05-363)

METHODS. This is the fourth year interim report of a seven-year toxicity/carcinogenicity study conducted in female dogs (*see below*). Four groups of 20 female beagle dogs were treated with megestrol in capsules at dosage levels of 0, 0.01, 0.1 or 0.25 mg/kg/day. The control group was consisted of 10 animals treated with coconut oil tablets and 10 with lactose tablets. Megestrol was dissolved in coconut oil and contained in the capsule for oral administration. Four dogs from each group were sacrificed at the end of the second and fourth year, with the exception that in middle dose group, only two dogs were sacrificed at the end of fourth year for evaluation of mammary gland tumorigenicity.

RESULTS.

Palpable mammary nodules were observed at 18th month in high dose group, and at 27th month in middle dose group animals. The cumulative number of animals with nodules is listed in the table below.

Table 3.
Incidence of mammary nodules in female beagles treated with megestrol for four years.

Control	Megestrol mg/kg		
	0.01	0.1	0.25
4*/20	0/20‡	12/14	15/20

*: *Transitory nodule palpable only for 1~3 months.*
‡: *Number of Animals With Mammary Nodule/Total Examined.*

Histopathology of tissue sections prepared from 38 nodules of megestrol-treated dogs showed that 27 of them were hyperplasia, 3 were ductal dilations, 5 were benign mixed tumor, the remainder was either lymph node or fatty necrosis. The *benign mixed tumor* was found in 5 dogs of the high dose group. The size of tumor increased slowly but progressively. All tumors were encapsulated and consisted of epithelial and myoepithelial cellular components. Osseous metaplasia with marrow formation was found in one tumor. The largest mammary tumor was palpable at a size of 6×7.5 cm.

COMMENTS: This report is in a published paper format (*J. Nat'l Cancer Inst. 51:1303-1307, 1973*) that dealt solely with the mammary nodules in dogs during four years treatment with megestrol. No raw data were included.

4. **Seven-Year Chronic Toxicity/Carcinogenicity Study in Female Beagles (NELS-LW-05859, 1968~1975 7-05-363)**

METHODS. Four groups of 20 female beagle dogs were given by mouth 0 (vehicle control), 0.01, 0.1, or 0.25 mg/kg/day of megestrol in capsules. The control group was subdivided into 10 animals treated with coco nut oil tablets and another 10 with lactose tablets. Megestrol was dissolved in coconut oil and contained in the capsule for oral administration. Four dogs from each group were sacrificed at the end of the second and fourth year, with the exception that in middle dose group, only two dogs were sacrificed at the end of fourth year (*see above Four-Year Study*). At the end of seventh year, a total of 12, 10, 9 and 4 dogs from control, low, middle and high dose groups completed the study. Of these, 2, 3 and 3 dogs in low, middle and high dose groups did not receive treatments from the fifth to the seventh year and were used as recovery animals.

MEASUREMENTS. Body weights were recorded monthly. Breasts were examined monthly during the first four years and bimonthly thereafter. Eye examinations were performed at a six-month interval. Clinical laboratory studies (hematology, chemistry, and urine analysis) were determined in all dogs at week 364. A total of nine organs and forty one tissues from each dog was weighed and fixed for histopathology study at the end of seventh year. Histopathology was performed at Mead Johnson Research Center.

RESULTS.

Liver, kidney and adrenal *organ weights* were markedly heavier than controls. Liver and kidney weights in the middle dose dogs were also increased. Other differences from controls in organ weights included: low ovary weights in two middle dose dogs and higher ovary weights in a high dose dog; and heavier uterus weights in two low dose, two middle and one high dose animals.

Clinical laboratory examinations showed an elevated sedimentation rate in all treated dogs. Lowered levels of hematocrit, hemoglobin and erythrocyte count were noted in one of the low dose and all of the dogs in middle and high dose dogs. In the high dose group, blood glucose and total cholesterol levels were elevated and serum calcium and total proteins were decreased.

Ocular, renal and pancreatic changes were indicative of *diabetes mellitus* and evident in four dogs each of the middle and high dose groups. The changes included lenticular degeneration (vacuoles and granular areas in the cortical region of the lens), glomerulosclerosis, cytoplasmic vacuolation and atrophy of both pancreatic islet cells and renal tubular epithelium. During the seventh year, bilateral cataracts in one of the high dose and lenticular opacities in three of the middle dose dogs were considered treatment-related.

A decreased incidence of *estrus activity* in the low dose group and a complete cessation of estrus cycle in middle and high dose groups were recorded. The

amount of mucoid discharges from vagina in treated dogs were higher than controls. *Ovulations* were suppressed in 4/8 of the low dose and all middle and high dose group dogs. Histologic findings of *uteri* included: cystic glandular hyperplasia, luminal dilation, endometritis, myometritis, endometrial atrophy and mineralization, and mucoid glandular dilatation in the cervix. These changes were observed at an increased incidence with dose in treated groups.

Other treatment-related histology findings included cystic mucinous hyperplasia in the *gallbladders* of low (3/12), middle (10/12) and high dose (5/12) dogs, with the severity of toxicity increased with dose. Liver showed lesions such as pericholangitis, vacuolation, hyperplasia and congestions in low (7/12), middle (5/12) and high (7/12) dose groups. Two dogs from the middle dose group had atrophy of the skin and skeletal muscles.

Mammary nodules were present in 6/12 of controls, one low dose, and all middle and high dose dogs. In the low dose group, only hyperplasia was found. In middle and high dose groups, nodular hyperplasia, tumors, carcinomas, ductal papilloma, epidermoid cyst and ductal dilatation were noted. The number and severity of nodules increased with dose.

Table 4.
Incidence of mammary nodules in female beagles treated with megestrol for seven years.

Control	Megestrol mg/kg		
	0.01	0.1	0.25
6*/12 (13)	1/8 (2); 0/4* (0)	8/8 (168); 3/4 (7)	8/8 (169); 4/4 (21)

*: *Transitory nodule palpable only for 1-3 months.*
‡: *Frequency of nodule occurrence is expressed by:*
Number of animals showing a mammary nodule/total examined
Two sets of frequency are included for each dose, the first set is the treated group followed by the second set for recovery group. Numbers in the parenthesis represent counts of nodules and regions of hyperplasia.

Benign mixed tumors of the mammary gland were found in one control, four middle and four high dose group dogs. *Mammary carcinoma* was found in four of the middle and three of the high dose group dogs. The tumor increased slowly but progressively in size. *Neoplasms* other than mammary tumors in the megestrol-treated dogs included an ovarian granulosa cell tumor for one and hemangioma in the skin for another in the high dose dogs.

Thirteen dogs died or were sacrificed in a moribund condition during the fifth to seventh years of the study, as shown in the following *mortality* table:

Table 5.
Death statistics of female beagles during fifth to seventh year of study under treatment with megestrol.

Cause of Death	Number of Death	Dosage Group
Metritis	2	Low dose (recovery group)
Mammary Carcinoma	5	2 Middle dose group, 2 High dose group, 1 High dose (recovery group)
Ulcerated Mammary Hyperplasia	1	Middle dose (recovery group)
Acute Pneumonia	3	High dose group
Chronic Nephritis	1	High dose group
Intestinal Strangulation	1	High dose group

Of the 13 dogs that died, 2, 3 and 8 were from low, middle and high dose groups, respectively. Excluding the ones from the recovery group, the mortality rates were estimated to be 22% (2/9) and 78% (7/9) for middle and high dose megestrol-treated groups.

COMMENTS: Major target non-reproductive organs of toxicity are liver, pancreas and adrenal. The treatment-induced diabetes mellitus also caused injuries in the kidney and eye. Diabetes mellitus was not seen in the six-month beagle study (*see above repeat-dose chronic toxicity study no. 5*). The maximum dose used in this study was 0.25 mg/kg and is lower than the 6 mg/kg dose used in the six-month dog study. The significance of neoplastic changes of megestrol in dogs may not be a useful predictor for human (Please see "*Facts about injectable contraceptives: Memorandum from a WHO meeting. Bull. WHO 60:192, 1982*" and "*Safety Requirements for Contraceptive Steroids. by F. Michael, 1989 W.H.O.*"). For the non-endocrine toxicity information, the study should be performed in male animals with dosage selected at least 50 times higher than the current levels to fully explore the profile of toxicity.

5. Ten-Year Chronic Toxicity/Carcinogenicity Study in Female Rhesus Monkeys (GEIS-JG-08161, 1980, 8-05-758)

METHODS. Four groups of 20 female rhesus monkeys were fed by mouth at dosage levels of 0 (control), 0.01, 0.1, or 0.5 mg/kg/day of megestrol in a sugar cube. Megestrol was dissolved in coconut oil and administered at the prescribed levels on the sugar cube before being given to the animals. The control group was consisted of 10 animals treated with vehicle (coconut oil) and 10 untreated.

MEASUREMENTS. Body weights were recorded monthly. Breast and eye were examined bimonthly and biannually. Clinical laboratory studies and vaginal smears were performed at the ninth year or the termination of the study. A

total of eight organs and forty-one tissues from each monkey at the terminal sacrifice was weighed and fixed for histopathology.

RESULTS.

Three monkeys in the high dose group were found dead at the ninth and tenth year with the apparent cause of death being acute gastric dilation in all cases. Antemortem signs in animals that died included diarrhea, weight loss, thin and dehydrated condition with abdominal distention, and vomiting.

The mean *body weight gains* in all treatment groups increased significantly as compared to the control groups at the ninth and tenth year. *Menstrual activities* and mean *uterus weight* of all megestrol-treated groups were dose-dependently decreased. The middle and high dose group monkeys lacked ovarian corpora lutea but the incidence of cervical glandular dilatation, cervical mucoid secretions, and the number of hyalinized ovarian atretic follicles were increased.

Histopathological study showed no mammary hyperplastic or neoplastic changes in any of the monkeys. Occasional findings such as reactive hyperplasia in various lymph nodes, focal pericholangitis, hepatocellular vacuolation, interstitial myocarditis, thyroid and adrenal hyperplasia, and pituitary cysts occurred in both treatment and control animals and did not show any dose-related increases in severity.

COMMENTS: No food consumption data were provided to allow for the analysis of the source of weight gains in monkeys. The maximum dose employed, 0.5 mg/kg, is 5 and 26 times *lower* than the maximal dose used in twelve-week study in monkeys and the proposed human dose, respectively. The relative nontoxic finding in monkeys could be a reflection of inadequate doses. Additionally, the study lacks information on male animals. It is obvious that the nonendocrine toxicity of this drug has not been fully explored in both male and female monkeys.

OVERALL COMMENTS ON REPEAT-DOSE TOXICITY/CARCINOGENICITY STUDIES: Target non-reproductive organs/systems of toxicity in repeat-dose and chronic toxicity/carcinogenicity studies are listed in the table below.

Table 6.
Target non-reproductive organs/systems of toxicity in rats, dogs and monkeys.

Study	Target Non-Reproductive Organs/Systems of Toxicity	Toxicity Dose (mg/kg, po)	Maximum Dose Studied (mg/kg)
Rat, Twelve-Week	Thyroid, Adrenal gland	20	20

Study	Target Non-Reproductive Organs/Systems of Toxicity	Toxicity Dose (mg/kg, po)	Maximum Dose Studied (mg/kg)
Rat, One-Year	CNS, Adrenal Gland	3.9~10	10
Rat, Two-Year	CNS, Pituitary, Adrenal Gland, Spleen	3.9~10	10
Dog, Six-Month	Liver, Adrenal Gland	2.5~6	6
Dog (female), Seven-Year	Liver, Gallbladder, Pancreas, Kidney, Adrenal, Eye	0.1	0.25
Monkey (female), Twelve-Week	None	Not Achieved	2.5
Monkey (female), Ten-Year	None	Not Achieved	0.5

The maximum dose of these studies ranged from 0.5~2.5 mg/kg for monkeys, 0.25~6 mg/kg for dogs, and 10~20 mg/kg for rats. These levels are nearly equal or less than the maximum dose being used in AIDS patients (13.3 mg/kg at 800 mg/day). However, the toxicity profile in the non-endocrine system appeared to be species-specific. Both dog and monkey studies are deficient in that either the number of animal used is not enough (e.g., one male and one female per group in the six-month dog study) or the information regarding male-specific toxicities is lacking. Thus the animal data are insufficient and inadequate to predict the safety of the drug for human use at the highest dose proposed.

D. Reproduction and Teratology

There are seven studies performed during the 1960's. The design of these experiments was not fully conformed with the guideline for reproduction studies published by FDA in January, 1966 (*see also "COMMENTS" portion of the review of the studies*). The submissions were presented in a rather disorganized fashion, with different studies mingled together and reported in different length of details and clarity.

1. Reproduction Study in Female Rats (Mead Johnson Research Center, 1960, 9-05-1385)

METHODS. Three series of experiments were performed in rats of McCollum strain. In *the first series of experiments*, megestrol was given to three groups of pregnant female rats at doses of 0, 1 or 5 mg/kg/day on days 5 through 11 of pregnancy (n=8~11 each). In *the second series of experiments*, megestrol was given to four groups of pregnant female rats at doses of 0, 1, 5 or 12.5 mg/kg/day on days 12 through 18 of pregnancy (n=8~11 each). In the *third*

series of experiments, megestrol was given to two groups of 5 pregnant female rats at doses of 0 or 5 mg/kg/day on days 12 through 18 of the pregnancy. In the first two series of experiments, megestrol was suspended in 0.5% methylcellulose and given by intubation with a stomach tube once daily. In the third series of experiments, megestrol was suspended in sesame oil and injected subcutaneously once daily. The newborn rats were weighed and examined for sexual characteristics.

RESULTS. The number of newborns with a shortened anogenital distance ('intersexual') increased with the dose given to the pregnant mothers. However, these intersexuals matured anatomically as definitive males or females. In the third series of experiments, megestrol (12.5 mg/kg sc) caused a delay in paratus necessitating surgical delivery in 5 of 6 animals. The number and mean weight of fetuses were reduced by megestrol (12.5 mg/kg po) in the second series of experiments.

COMMENTS: Definitive fetal effects on weight and number of liver birth occurred at 12.5 mg/kg. The data thus speak against the running title of this study: "Lack of effect of megestrol acetate upon the uterus."

2. Reproduction Study in Female Rats (4/63, 1963, 9-05-1405)

METHODS. Two series of experiments were performed. In *the first series of experiments*, megestrol was given to five groups of pregnant rats by gavage at doses of 0, 0.05, 0.15, 1.5, or 15 mg/kg/day on days 15 through 20 of gestation (n=9~19). In *the second series of experiments*, megestrol was given to groups of pregnant rats at 0 or 3 mg/kg/day on days 13 through 20 of pregnancy, or at 0 and 3, 15 or 60 mg/kg/day on days 15 through 20 of pregnancy (n=5~10 each). Megestrol was in an aqueous suspension containing BDH TS-801 as the solvent.

RESULTS. In *the first series of experiments*, the percentage of newborns with a shortened anogenital distance ('intersexual') increased with the dose given to the pregnant mothers. Abnormalities of the sex organs of male newborns (feminization of the male) were evident in treated rats. The first filial generation (F_1) males from dams treated with 15 mg/kg megestrol showed a lower mating frequency and markedly reduced pregnancy rate. In *the second series of experiments*, a marked reduction in the proportion of males, as judged by abnormal anogenital distance and sexual characteristics, was observed. The findings included abnormal development of ejaculatory ducts, seminal vesicle and prostate gland. The feminizing effects in males occurred at 3 mg/kg dose with the severity increased with the treatment duration extended from 6 (i.e., 15~20th day) to 8 (i.e., 13~20th day) days. Thus the effects were both dose- and time-dependent. At 60 mg/kg given from day 15~20 there were no newborns identified as males and only a few 'intersex.' The percentage of resorption of the fetuses in breeding studies using F_1 males from dams treated with megestrol showed dose-related increments. Three F_1 males from dams treated with 60 mg/kg megestrol showed a small seminal vesicle and reduced body weight, and

did not produce fertile matings.

COMMENTS: The definitive dose of megestrol causing feminization of males was around 3 mg/kg. Toxicity of megestrol on the antenatal and postnatal development is obvious at this dose level. The identity of solvent BDH TS-801 was not provided.

3. **Teratology Study in Female Rabbits (3/63, 1963, 9-05-1383)**

METHODS. Megestrol was given to four groups of pregnant female New Zealand rabbits by gavage at doses of 0, 1, 3 or 9 mg/kg/day on days 8 through 29 of pregnancy (n=8~10 each). The does were killed on day 30 of gestation, the uteri opened and the contents examined for gross abnormalities.

RESULTS. A reduced number and weight of live fetuses and a concomitant increase in the number of resorbing fetuses in the two high dose groups were observed. The NOEL is 1 mg/kg. No gross abnormalities were found except that a dead fetus from the middle dose group had hydrocephalus and a cleft palate. The sponsor claimed that the significance of this finding is questionable since the fetus was "tightly compressed between two others."

COMMENTS: The sponsor indicated that the result of a more detailed examination of the fetuses "will be reported later" (page 1384, volume 9, printed in 1963). The report on this teratologic information is not available in the current submission.

4. **Teratology Study in Rabbits (HENN-DM-03938, Mead Johnson Research Center, 1970, 9-05-1448)**

METHODS. Megestrol was given to four groups of 17 pregnant Dutch rabbits by gavage at doses of 0, 0.05, 0.3 or 1.8 mg/kg/day on days 6 through 18 of pregnancy. Megestrol was in a suspension containing 0.5% methylcellulose. All does were killed on day 29 of gestation, the uteri opened and the contents examined.

RESULTS. An increase in the number of early resorption sites (placenta definable without recognizable fetus) was observed only in the low dose group. This effect was not dose-related and mean number of implantation sites per dam or mean live fetuses per dam were not changed. Skeletal abnormalities (defective ossification of parietal or sternum) were recorded in two of the low and one of the high dose groups, respectively.

COMMENTS: This study is different from the previous one in that the treatment duration was shorter and doses used were smaller. It is debatable that the drug lacked teratology effects in rabbits, as claimed by the sponsor. Although the report on detailed examination of fetuses (study #3) has not yet been submitted, a significant dose-related fetal toxicity (number and weight of

live fetuses decreased) and 4 cases of gross malformations (2 in 0.05 mg/kg and 1 each in 1.8 and 3 mg/kg dosage groups) were observed. The sponsor should repeat study no. 3 (with additional sufficiently high dosage group added) if they cannot provide the report on detailed fetal morphology.

5. **Teratology Study in Rats (11-12/63, 1963, 9-05-1445).**

METHODS. Megestrol was given to seven groups of 5-7 pregnant female Sprague-Dawley rats by gavage at doses of 0, 1.1, 3.3, 10, 30, 90, or 270 mg/kg/day on days 6 through 20 of pregnancy. Megestrol was suspended in solvent BDH TS-801. All animals were killed on day 21, the uteri opened and the live births examined.

RESULTS. The number of newborns that developed into males with a shortened anogenital distance ('intersexual') increased at dose levels 10 mg/kg and above. Skeletal abnormalities including shortened limb bones, irregular and incomplete calcification of ribs, sternum, vertebrae and cleft palate were observed in three fetuses of the 30 mg/kg group. No malformations, changes in litter size, fetal weight were observed in other treatment groups. The sponsor claimed that the findings observed in the 30 mg/kg group were not treatment-related.

COMMENTS: The teratologic effects that occurred in 50% of the fetuses in the 30 mg/kg group might have been a biphasic phenomena and should be repeated for clarification. This rat study is the only one that employed a reasonably high range of doses close to the projected human dose (13.3 mg/kg). Actual systemic exposure of the animal to drug, however, is uncertain. No blood concentrations of megestrol had been measured in this and other toxicity studies. In general, the rat study was different from that of the rabbit in that the later showed a reduction in litter size and fetal body weight at the *low dose* level.

6. **Perinatal/Postnatal Toxicology Study in Rats (HENN-DM-03938, Mead Johnson Research Center, 1970, 9-05-1448)**

METHODS. Megestrol was given to 4 groups of 30 pregnant female rats of the Charles River strain by gavage at doses of 0, 0.05, 0.3 or 1.8 mg/kg/day on day 15 of gestation and continued through parturition and the first 21 days postpartum. Megestrol was in an aqueous suspension containing 0.5% methylcellulose. Each pup was examined at parturition and observed for 21 days.

RESULTS. Megestrol caused a reduction in *littering index* (no. of liters ÷ no. of females mated) and *fertility index* (no. of live offspring ÷ no of females mated) in all treatment groups. Weanling index (no. of alive on day 21 ÷ no. of born alive) and lactation index (no. of alive on day 21 ÷ no. of alive on day 4) were not influenced by the drug. In the high dose group, one newborn had an ectopic left eye and distorted mouth.

COMMENTS: This result was consistent with study no. 1 and 2 conducted in rats that showed megestrol caused reduction in fetal weight and number of live birth.

7. **Perinatal/Postnatal Toxicology Study in Rats (Mead Johnson Research Center, 1960, 9-05-1385))**

METHODS. A series of crossover reproduction studies was carried out with the offspring (F_1) of female rats (F_0) given 0, 5, or 12.5 mg/kg of megestrol. Two groups of F_0 treated with megestrol in different dosing periods (day 5~11 or 12~18 of pregnancy) were used. Their offsprings were mated with controls or F_1 of treated F_0 of the opposite sex. The pregnancy rate, F_2 weight, sex characteristics and viability were recorded.

RESULTS. In all groups of the F_1, in which both male and female rats were derived from megestrol-treated F_0, the incidence of pregnancy was low. A smaller incidence of pregnancy was also found in the group that control females mated with F_1 males born of megestrol-treated females. Megestrol did not cause virilization of the F_1 females. F_2 rats born of the offspring of megestrol-treated F_0 were found to be of normal size weight and viability.

COMMENTS: This study showed that megestrol-treated F_0 caused impairment of reproductive capability in F_1 males but not females.

OVERALL COMMENTS ON REPRODUCTION/TERATOLOGY STUDIES: The doses used in these reproduction/teratology studies were originally intended and designed for providing safety information on the contraceptive indication of the drug. The fetal toxicity portion of the reproduction study was conducted, at a dose range that was just enough to cover the small doses required for contraception. No segment I reproduction study on female fertility was necessary because megestrol prevents ovulation. The new indication of megestrol involved the use of the drug in patient populations that are predominantly male. Safety information regarding male fertility is not currently available. Further, in many of the reproduction study presented, the sponsor had employed too low a dose range as compared to the proposed human dose. Reproductive toxicity information derived from the available data are summarized as follows:

(1) *Rat:* Fetal toxicity regarding weight and number of live birth occurred at 12.5 mg/kg. Feminization of males occurred at 3 mg/kg. Fetal malformation may occur at 30 mg/kg (the study needs to be repeated). Male offsprings of megestrol-treated pregnant females (5~12.5 mg/kg) showed impairments of reproductive capability.

(2) *Rabbit:* A reduced number and weight of live fetuses and a concomitant increase in the number of resorbing fetuses occurred at 3 mg/kg or higher.

NON-CLINICAL PHARMACOKINETICS

All pharmacokinetic data obtained from animal studies were submitted in a published paper format, without detailed data presented. The majority of these studies employed radioactive megestrol and drug levels were expressed in terms of the radioactivity measured.

Rat

The distribution of megestrol was studied in female rats after single and repeated oral doses of a combination of 10 mg/kg of megestrol-6-^{14}C and 0.125 mg/kg of unlabeled ethinyl estradiol. Peak plasma radioactivity occurred at 5~6 hours after dosing suggesting slow absorption of the drug. The tissue distribution four hours after drug was primarily in liver, fat, adrenal, ovary and kidney. At 24 hour, liver, fat and adrenals still contained high levels of radioactivity.

More than 75% of the radioactivity were recovered in the feces within 6 days after drug administration, suggesting high biliary excretion of radioactivity for the drug. One major metabolite excreted in the bile was identified as a glucuronide of the 6-hydroxy derivative of megestrol.

Megestrol could be metabolized by rat, mouse or rabbit liver microsomal enzyme preparations (*Biochem. J. 97:672, 1965*). Because of the 6α-methyl and 17α-acetoxy groups, megestrol is resistant to liver microsomal metabolism in both rats and rabbits as compared to progesterone. Less than 5% of megestrol was metabolized during incubation periods of up to 3~5 hours as compared to a complete metabolism of progesterone in 15 minutes under the same conditions.

Liver microsomal preparations from rats treated with repeated doses of megestrol and ethinyl estradiol metabolized megestrol at a greater rate than preparations from untreated animals. This finding suggested that microsomal enzyme induction had occurred. Induction of microsomal drug metabolizing enzymes by administration of megestrol alone has not been reported.

Rabbit

Recovery of radioactivity in urine and feces was 70% after administration of [1,2-$^{3}H_2$]megestrol and 40% after [6-methyl-^{14}C]megestrol. In urine, 20-30% of the drug was in conjugated form and 10-13% in free form. Fecal excretion accounted for 8 to 15 % of the dose. Two urinary metabolites excreted as conjugates with glucuronic acid were identified as the 2α-hydroxy derivative and the 6-hydroxy derivative (i.e., 17α-acetoxy-2α-hydroxy-6-hydroxymethylpregna-4, 6-diene-3, 20-dione, and 17α-acetoxy-6-hydroxymethylpregna-4, 6-diene-3, 20-dione) of megestrol.

COMMENTS: The two metabolites characterized in rabbits are identical to two of the three major glucuronidated metabolites in humans.

Dog

Excretion of radioactivity in female dogs following eight daily oral doses of 2 mg/kg of [6-methyl-^{14}C]megestrol was found mainly in feces. No unchanged megestrol was detected in urine or feces. Four unidentified metabolites of the drug were detected in the urine and feces.

OVERALL COMMENTS: Neither time-plasma concentration plots nor bioavailability of the drug could be derived from these studies. Time-plasma concentrations data are useful in obtaining AUC, C_{max}, T_{max} and $T_{1/2}$ parameters for toxicokinetic analysis of the toxicity studies performed in animals.

PROPOSED LABELING OF MEGACE® OS (megestrol acetate, USP)

Under the title of **PRECAUTIONS** of the proposed labeling, the sections of *Carcinogenesis, Mutagenesis, and Impairment of Fertility* (vol. 1, page 02 00014) and *Pregnancy* (vol. 1, page 02 00015) contain a similar text to that appeared in the labeling of MEGACE® Tablets indicated for the treatment of breast cancer and endometrial cancer, as quoted below:

" Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Administration for up to seven years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast[11]. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors[OO] to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing MEGACE® OS and in surveillance of patients on therapy[11, 12]. Also see "WARNINGS" section.

Pregnancy
Pregnancy Category D. See "WARNINGS" section. "

COMMENTS:

The proposed labeling of this NDA is inadequate because (1) the statements are inconsistent with the submitted data and (2) the preclinical data are insufficient in supporting statements in the sections of *Carcinogenesis, Mutagenesis, and Impairment of Fertility* and *Pregnancy*. The specific comments are addressed as follows:

(1) In the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* section, the labeling should caution that information on carcinogenesis was obtained from studies performed in female dogs, female monkeys and rats of both sexes treated with megestrol at dosages 53.2, 26.6 and 1.3 times *lower* than the proposed dose for humans. The labeling should point out that there is no information on carcinogenesis currently available from studies conducted in animals, especially males, at dosage sufficiently high as compared to the proposed human dose. The sponsor should emphasize the incompleteness of carcinogenicity studies in animals and conclude that it is not known whether the risk of cancer formation will be increased at the high dose

indicated for cachectic HIV positive patients.

(2) In the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* section, the labeling should mention the dose-related increase in the occurrence of the pituitary tumors in the rat.

(3) In the *Pregnancy* section, consideration on the Pregnancy Category should be given to a change from D to X Category since at this high dose the benefits may be outweighed by teratogenic risks of the drug. The title of this section should be altered to *Pregnancy - Teratogenic Effects* to include reproduction/teratology findings in animals. The sponsor should indicate that reproduction and perinatal/postnatal toxicity studies were performed in animals (rats and rabbits) at doses less than that is indicated for humans. The sponsor should point out that no toxicity information on male reproduction (spermatogenesis) are currently available. The apparent fertility impairments observed in male offspring of animals treated with megestrol (e.g., six-month repeat-dose study in dogs and reproduction studies in rats) should be presented in this section of the labeling.

(4) The sponsor should submit equivalent bioavailability data for mice and humans to sustain the statement made under the title of **OVERDOSAGE** (vol. 1 page 02 00019): "Oral administration of large, single doses of megestrol acetate (5 grams/kg) did not produce toxic effects in mice.[10]"

PROPOSED WORDING:

The following text represents recommended labeling changes which address certain deficiencies in the original labeling of MEGACE® OS, as commented above. The inappropriate portion of original label was strikeout with the added text shaded.

PRECAUTIONS

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Carcinogenesis

~~Administration for up to seven years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast[11]. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors[CC] to humans is unknown but should be considered in assessing the benefit to risk ratio when prescribing MEGACE® OS and in surveillance of patients on therapy[11, 12].~~ Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at dosages 53.2, 26.6 and 1.3 times *lower* than the proposed dose (13.3 mg/kg/day) for humans. No males were used in these dog and monkey studies. In female beagles, megestrol (0.01, 0.1 and 0.25 mg/kg/day) induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10

years treatments of 0.01, 0.1 and 0.5 mg/kg/day megestrol. In rats treated with 1.5, 3.9 and 10 mg/kg/day of megestrol for 2 years, pituitary tumors were observed. Because of the inadequacy of doses and lacks of information on male species, the risk of cancer in cachectic HIV positive patients can not be determined based on currently available data. Also see "WARNINGS" section.

Mutagenesis

No mutagenicity data are currently available.

Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies was performed in rats at doses (0.05~12.5 mg/kg) *less* than that indicated for humans (13.3 mg/kg). In these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were also obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live birth, and feminization of male fetus. No toxicity data are currently available on male reproduction (spermatogenesis).

~~*Pregnancy*~~ *Pregnancy - Teratology*

Pregnancy Category ~~D~~ X. See "WARNINGS" "and *Impairment of Fertility*" section. No adequate animal teratology information are available. The teratologic potential could not be determined from current animal data.

OVERDOSAGE

No serious unexpected side effects have — as high as 1600 mg/day.[UU] ~~Oral administration of large, single doses of megestrol acetate (5 grams/kg) did not produce toxic effects in mice[10].~~

CONCLUSION

This NDA in its present form does not provide adequate preclinical safety information to support its approval and labeling. The sponsor did not employ adequate levels of dosage and number of animals of both sexes in their studies. The conclusion made by the sponsor on the toxicity profile of megestrol may be misleading because no additional studies were carried out to support and extend the data obtained under non-GLP conditions in early studies (1950~70s). The sponsor has failed to fully explore the toxicity of megestrol. Specific concerns include tumor formation potential and adverse effects on male fertility. Additionally, the long term safety of high-dose megestrol in immune-compromised, HIV positive patients has not been adequately established.

Issues of preclinical information aside, human experience gained from HIV positive patients treated with 800 (n=127) and 1200 mg/day (n=149) megestrol in clinical trials showed a different spectrum of adverse drug reactions and the regimens appeared to be well-tolerated.

REQUIREMENTS:

(1) The labeling of this NDA needs to be rewritten to appropriately reflect deficiencies in preclinical data submitted in support of the sponsor's statements in the labeling. The comments and recommended wordings are listed in the review of the **LABELING** section above.

(2) The sponsor should perform three Phase IV studies, one carcinogenicity, one teratology and one male fertility study. The drug should be administered at sufficiently high doses in animals of both sexes (two to five times higher than the human doses). This will fully explore the toxicity of the drug and assure that the historic toxicology data obtained under a non-GLP environment are reliable. Along with these studies, the sponsor should provide toxicokinetic information on the high dose megestrol. Specifically, oral bioavailability and dose-response by AUC curve will be needed for the evaluation of drug exposure in animals.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/Pre-Clin Dep/LRosenstein
HFD-530/SPharm/MGreen for MDG 7/27/92
Wu/Pharm/6/1/92 7/27/92

cc:
HFD-530 Original NDA
HFD-530/Division File
HFD-530/LRosenstein
HFN-340
HFD-502
HFD-530/Pharm/KWu
HFD-530/CSO/ADeCicco
HFD-530/MO/DFeigal
HFD-530/Chem/MJarski
HFD-530/Biostat/KKazempour
HFD-530/Micro/WDempsey
HFD-345/GJames

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA #: 20-264

NOV 12 1992

REVIEWER : Dempsey
CORRESPONDENCE DATE : 03/31/92
CDER RECEIPT DATE : 04/01/92
REVIEW ASSIGN DATE : 04/29/92
REVIEW COMPLETE DATE: 11/03/92

SPONSOR: Bristol Meyers Squibb Co.
U.S. Pharmaceutical Group
2400 W. Lloyd Expressway
Evansville, IN 47721-0001
(812) 429-5584

SUBMISSION REVIEWED: NDA

DRUG CATEGORY: steroid hormone derivative

INDICATION: Treatment of anorexia, cachexia, or a significant weight loss in patients with AIDS

DOSAGE FORM: oral suspension (40 mg/ml)

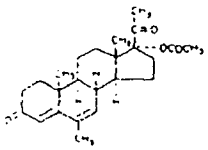
PRODUCT NAMES:

a. **PROPRIETARY:** MEGACE

b. **NONPROPRIETARY:** Megestrol acetate

c. **CHEMICAL:** Pregna-4,6-diene-3,20-dione,17-(acetyloxy)-6-methyl

STRUCTURAL FORMULA:



BACKGROUND: Megace was evaluated in two clinical trials for amelioration of weight loss in AIDS patients. Megace is currently

approved for use in the treatment of endometrial or breast carcinoma. In the clinical trials in AIDS patients, the primary endpoints of efficacy were weight changes and lean body mass changes. Immune status was measured by total lymphocyte and lymphocyte subset determinations and by delayed type hypersensitivity skin reactivity tests. The IND for this indication was originated in another division. No pre-clinical microbiology studies were completed.

SUMMARY:
No pre-clinical microbiology studies were completed, nor were any measurements of viral burden done in the clinical trials with HIV+ patients. Two questions with respect to microbiology had been posed following a pre-NDA meeting with the sponsor. The sponsor was asked to specify any efforts to quality control the flow cytometric lymphocyte subset analyses in the trials. The sponsor reported that the assays completed at each site in the trial were the complete responsibility of the individual site facility. Four sites in the 8807 study used AIDS Cooperative Treatment Group (ACTG) certified laboratories and six sites in the 8809 study also used ACTG certified laboratories. Also in 8809, one site was a CDC reference laboratory and one was subject to the College of American Pathologists Quality Control. Two addition sites in 8807 used Met Path, Inc. The sponsor was also asked to address the question of missing data points for many of the immunologic markers. The sponsor indicated that the reports submitted previously were preliminary and that the reports included with this NDA are more complete.

CONCLUSIONS:
The time on treatment in the two pivotal clinical studies was designed to be 12 weeks. However, it is likely that most patients will receive Megace therapy for a much longer duration. In the studies submitted with this NDA, no measures of viral burden were included in any of the trials. If phase 4 clinical studies are conducted, the effects of Megace on virologic markers of HIV disease should be measured.

RECOMMENDATIONS:

With respect to Microbiology, this NDA is approved. However, it is recommended that because no determinations of the effect of Megace on the underlying viral etiology of HIV disease have been made, any phase 4 trials of Megace should include measurements of viral burden.

Walla L. Dempsey
Microbiologist

CONCURRENCES:
HFD-530/Pre-Clin Dep _____ Signature 11/12/92 Date
HFD-530/SMicro _____ Signature 11/16/92 Date
cc:
HFD-530/Original IND
HFD-530/Division File
HFD-530/Div Dir Reading file
HFD-530/Pre-Clin Dep
HFD-530/MO
HFD-530/Pharm
HFD-530/Chem
HFD-530/SMicro
HFD-530/Review Micro
HFD-530/CSO

BIOPHARMACEUTICS REVIEW

NDA: 20 264, 20 296 MAY 14 1993

Submission Date: April 1, 1992

Generic Name, Dose & Formulation: Megestrol Acetate (micronized) 40 mg/ml Suspension

Brand Name: MEGACE® ORAL SUSPENSION

Sponsor: Bristol-Myers Squibb
U.S. Pharmaceutical Group
Evansville, IN 47721

Type of Submission: III-S

Reviewer: Francis R. Pelsor, Pharm.D.

SYNOPSIS: The sponsor has studied the multiple dose pharmacokinetics of the suspension formulation of micronized megestrol acetate. In addition, the sponsor has adequately studied the comparative bioavailability of the suspension and a of micronized megestrol acetate. Acceptable in vitro dissolution methods have been provided for both formulations. The sponsor provided analysis of the relationship between plasma megestrol acetate concentrations and weight gain.

The sponsor has not addressed the following issues: effect of food on the absorption of megestrol acetate from the proposed formulations, comparative bioavailability of the suspension formulation of micronized megestrol acetate and approved and drug-drug interactions with megestrol acetate.

RECOMMENDATION:

1. The Human Pharmacokinetics and Bioavailability Section of NDA 20 264 (and is acceptable.

2. The sponsor should include dissolution testing for MEGACE® ORAL SUSPENSION, 40 mg/ml in their manufacturing and controls procedures. As an **interim** specification the dissolution testing should be conducted using The Q value should be NLT in 30 minutes. The sponsor should continue to investigate the dissolution performance of MEGACE® ORAL SUSPENSION, 40 mg/ml as outlined in the **COMMENTS**.

3. The sponsor should be asked to commit to the following:

i.) undertake a study of the effect of food on the bioavailability of MEGACE® micronized formulations.

ii.) undertake a comparative bioavailability study of MEGACE® ORAL SUSPENSION and the approved MEGACE® 40 mg tablet.

iii.) undertake a drug-drug interaction study of megestrol acetate and zidovudine.

iv.) undertake a drug-drug interaction study of megestrol acetate and fluconazole.

v.) undertake a drug-drug interaction study of megestrol acetate and dapsone.

vi.) undertake a drug-drug interaction study of megestrol acetate and trimethoprim-sulfamethoxazole.

vii.) undertake a drug-drug interaction study of megestrol acetate and rifabutin.

TABLE OF CONTENTS:

BACKGROUND: Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically designated as 17α-acetyloxy-6-methyl-pregna-4, 6-diene-3, 20-dione. Its molecular weight is 384.51. Solubility in water is 2 mcg/ml.

Megestrol acetate appears to be well absorbed from the GI tract. Early human pharmacokinetics studies using ^{14}C-labelled megestrol acetate demonstrated that the primary excretion route in humans is urinary (Cooper, JM. and Kellie, AE. (1968) *Steroids* **11**: 133-149). After oral administration of 4 to 91 mg of radiolabelled steroid, 57-78% of the radioactivity was found in the urine and 8-30% in feces over a period of 7 days . Metabolites found in urine accounted for only 5-8% of the administered dose. The metabolites were identified as the following: 2α-hydroxy, 6-hydroxymethyl, and 2α-hydroxy-6-hydroxymethyl. A more specific method using a mass fragmentographic technique confirmed the existence of 2-hydroxy and 6-hydroxymethyl metabolites, however, hydroxylation and partial reduction of the 4,6-diene were postulated (Adlercreutz *et al* (1974) *J. Steroid Biochem.* 5: 619-626). Both glucuronide-conjugated metabolites and unconjugated metabolites were found in the urine whereas the metabolites found in bile were almost all glucuronide-conjugated.

In healthy male volunteers (N=24) who received 160 mg of megestrol acetate given as a 40 mg tablet (MEGACE®) qid, the peak plasma concentration (about 30 ng/ml) was obtained in 2.5 hours after the first dose (Gaver *et al* (1986) *J. Biopharm. Drug Dispos.* 7: 35-46). After the fourth dose, the average peak plasma concentration was 107 ng/ml. Plasma elimination half-life ranged from 8.5 to 104.9 hours (mean = 33.2 hours)

In the same study, the bioequivalence of two investigational one (containing regular megestrol acetate and the

4/21/93

other micronized megestrol acetate, was determined relative to a 40 mg MEGACE® tablet. The average peak plasma concentration for the 160 mg tablet of regular megestrol acetate was 89 +/- 37 ng/ml compared to 107 +/- 30 ng/ml after the fourth dose of MEGACE® 40 mg tablets. The average peak plasma concentration for the 160 mg tablet of micronized megestrol acetate was 135 +/- 35 ng/ml. The time to maximum concentration was the same for the 3 formulations. The average bioavailability of the 160 mg regular megestrol acetate tablet was 97% relative to 4 doses of the 40 mg MEGACE® tablet. The average relative bioavailability of the micronized megestrol acetate tablet was 118%.

No serious side effects have resulted from studies involving Megace administered in dosages as high as 1600 mg/day.

MEGACE® is approved for the palliative treatment of advanced carcinoma of the breast or endometrium. The recommended dose is 160 mg/day (40 mg qid) for breast cancer and 40 to 320 mg/day (in divided doses) for endometrial carcinoma. MEGACE® is available as scored tablets containing 20 mg (NDA 16,979) or 40 mg (NDA 16,979) of regular megestrol acetate.

Megestrol acetate is proposed for the treatment of anorexia, cachexia, or a significant weight loss in HIV positive patients. The proposed dosing is 400 to 800 mg micronized megestrol acetate (MEGACE® ORAL SUSPENSION, 40 mg/ml or) per day.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

I. BIOAVAILABILITY/BIOEQUIVALENCE

A. Absolute Bioavailability: Not studied.

B. Comparative Bioavailability: Study 8811 showed that steady-state minimum plasma megestrol acetate concentrations were significantly greater (90% CL = 1.13, 1.34) following daily doses of 750 mg of the tablet formulation (micronized megestrol acetate) compared to 750 mg of the suspension formulation (micronized megestrol acetate). The average percent fluctuation of plasma megestrol acetate concentrations was significantly smaller (90% CL = 0.61, 0.79) for the tablet compared to the suspension. The average bioavailability of the tablet tended to be greater than the suspension (90% CL = 1.01, 1.24), but maximum plasma megestrol concentrations were the same (90% CL =

0.85, 1.09).

C. Food Effect: Not studied.

II. PHARMACOKINETICS: After 800 mg oral doses of megestrol acetate suspension daily for 21 days the average CMAX was 753 ng/ml, the average AUC(SS) 10476 hr*ng/ml, the median TMAX 4 hours, the CMIN 315 ng/ml, and the fluctuation was 98% (Study 8810). The average apparent oral clearance (Cl/F) was calculated by the reviewer to be 137 L/hr (Range: 40 - 516 L/hr). The average half-life was estimated by the investigator to be 30 hr (Range: 19 - 53 hr).

III. METABOLISM: See **BACKGROUND.**

IV. DOSE AND DOSAGE FORM PROPORTIONALITY: In study 8810, 24 adult asymptomatic HIV seropositive males subjects were dosed once daily with 750 mg

The average steady state (14 days) AUC was 7650 (+/- 3780) hr x ng/ml for the 24-hour dosing interval. The median AUC was 7306 hr x ng/ml. Gaver *et al* evaluated an investigational tablet formulation of micronized megestrol acetate in 24 healthy male volunteers ((1986) *J. Biopharm. Drug Dispos.* 7: 35-46). In this study each subject received a single dose of a 160 mg tablet. The average AUC(0-∞) was 2474 (+/- 531) hr x ng/ml and the median AUC(0-∞) was 2354 hr x ng/ml. From the results of these studies, a 5-fold increase in dose yielded about a 3-fold increase in AUC.

V. SPECIAL POPULATIONS

A. AIDS: The pharmacokinetics in adult, male, cachectic AIDS patients was assessed in study 8810. The results are summarized under II (See above).

VI. DRUG INTERACTIONS: Not studied.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: As part of the analyses of study 8810, the investigators explored relationships between megestrol acetate exposure and weight gain. They reported a statistically significant ($p < 0.05$) correlation between the ratio of weight gained after 3 weeks on treatment with MEGACE® ORAL SUSPENSION 800 mg qd and the

percent of dose interval when plasma megestrol acetate concentrations exceeded 300 ng/ml (N = 10 observations). Our review of the data revealed that the correlation between weight gain and plasma exposure to megestrol acetate in excess of 300 ng/ml was not statistically significant. The difference in analyses is indicative of the influence which one or two observations may have on the results from small studies. In any event these data should be used as a basis to further investigate the relationship between the pharmacokinetics of megestrol acetate and weight gain.

VIII. FORMULATIONS: The formulation for MEGACE® ORAL SUSPENSION, 40 mg/ml is listed in the review of study 8810 (See Appendix 1). The formulation for is listed in the review of study 8811 (See Appendix 1).

IX. DISSOLUTION: The dissolution of MEGACE® ORAL SUSPENSION, 40 mg/ml in 0.5% or 1% sodium lauryl sulfate (SLS) was studied using The

The dissolution testing for the suspension should be explored further. The dissolution testing for the is acceptable.

X. ASSAY: Plasma samples were analyzed for intact megestrol acetate according to an HPLC method. Plasma standard curves were in the range 10 - 2000 ng/ml. The lower limit of quantitation was 10 ng/ml and the upper limit was 2000 ng/ml. The analytical method validation is acceptable.

GENERAL COMMENTS (Need not be sent to the firm):

1. In our analysis of study 8810, we found significantly different values than the investigator, for 2 patients, in the percent of dose interval that the subject's plasma concentration was greater than 300 ng/ml. We calculated the percent of dose interval greater than 300 ng/ml from each subject's observed data. During a telecon with the investigator, we conveyed our findings. We learned that the investigator fit the plasma concentrations of each subject using nonlinear least squares and calculated the percent of the dose interval above 300 ng/ml from the fitted curve. Further, the investigator did not include one subject who gained weight but had very low plasma concentrations of megestrol acetate. Furthermore, the investigator reported that there were data entry errors in their original analysis.

From our analysis of 10 patients we obtained a p value of 0.11 for the correlation between weight gain and exposure to megestrol acetate concentrations greater than 300 ng/ml. The investigator obtained a p value of 0.07 from reanalysis of the corrected data from 9 patients.

COMMENTS TO BE FORWARDED TO THE FIRM:

1. The analysis of weight gain and plasma megestrol acetate exposure undertaken by the investigators of study 8810, looks interesting. The sponsor should investigate the relationship further.

2. The sponsor should undertake a study of the effect of food on the bioavailability of MEGACE® formulations (40 mg/ml suspension [redacted] In lieu of a study, the final product label should state that the food effect has not been studied.

3. The sponsor should undertake a comparative bioavailability study of MEGACE® Oral Suspension and the approved MEGACE® 40 mg tablet. In lieu of a study, the final product label should state that comparative bioavailability of formulations of megestrol acetate and micronized megestrol acetate have not been studied.

4. Several pharmacokinetics drug-drug interaction studies have been requested for post-approval investigations. The sponsor should conduct some in vitro studies with liver enzyme systems to explore potential drug interactions. As candidates for clinically relevant interactions are identified, the sponsor should investigate the utility of a population pharmacokinetics approach. In this manner, it may be possible to evaluate several interactions in a single study under clinically relevant conditions.

5. Comments regarding final product label will be addressed separate from this review.

6. The sponsor should further evaluate the dissolution of MEGACE® Oral Suspension. The dissolution testing should be conducted on 12 units each, of the lot used in Study 8811, in 900 ml of 0.0%, 0.1%, 0.5%, and 1.0% sodium lauryl sulfate (SLS) using . Samples should be drawn at 5, 10, 15, 30, and 60 minutes to generate dissolution profiles.

7. The NDA 20, 264 does not provide any information regarding the effect of gender on the human pharmacokinetics of megestrol acetate. The sponsor should include gender effects as part of the post-approval investigations proposed above.

Francis R. Pelsor 5/14/93
Francis R. Pelsor, Pharm.D.
Division of Biopharmaceutics

Biopharm Day on March 31, 1993, Attendees: T. Ludden, Ph.D.
H. Malinowski, Ph.D.
N. Fleischer, Ph.D.
F. Pelsor, Pharm.D.

Final Type Initialed by M F Pelsor 6/24/93

cc:
~~NDA 20-264~~

HFD-530/Division
HFD-530/DIR/DFeigal
HFD-530/CHEM/MJarski
HFD-530/CSO/ADeCicco
HFD-530/PHARM/KWu
HFD-530/BIOPHARM/FPelsor
HFD-426/DRUG, NFleischer
HFD-340/Viswanathan

APPENDIX 1

STEADY-STATE PHARMACOKINETICS STUDY:

STUDY NO: 8810 VOLUME: 10 PAGES: 06 00057 - 06 00170

INVESTIGATOR and LOCATION: The clinical phase was conducted by

performed under the direction

FORMULATION: Micronized megestrol acetate suspension (40 mg/ml), Lot E89G309 (E89G253).

Ingredient	Concentration, gm/L	
Megestrol Acetate, micronized	40[B]	40[A]
Polysorbate 80		
Polyethylene glycol 1450		
Sucrose		
Sodium Benzoate		
Sodium Chloride		
Citric Acid		
Sodium Citrate		
Xanthine Gum		
N&A Lemon-Lime Flavor		
Purified Water *qs ad*		

Note: Formulation A was used in clinical Study 8807 in addition to B. The ratio of units supplied for the study was about 2:1 (A:B). A combination of formulations was also used in clinical Study 8809. The ratio of units supplied for 8809 was about 1:1 (A:B).

STUDY DESIGN: Ten, adult, male, cachectic AIDS patients with an involuntary weight loss greater than 10% of baseline received daily oral doses of 800 mg of a megestrol acetate (micronized) suspension for 21 days. Patients were permitted to receive drug treatment as needed for their disease. However, they could not be receiving corticosteroids or anabolic steroids. They could not have physical or functional obstruction of the GI tract, dementia, uncontrollable diarrhea, ascites or pleural effusions, and they could not have a disease for which high-dose megestrol acetate is contraindicated.

Patients were provided with unit dose bottles of megestrol acetate suspension. The patients were instructed to shake the bottle well and drink the contents, then rinse the bottle once with tap water, shake well, and drink the contents of the bottle again, followed by 6 oz. of tap water. Further, patients were instructed to take the dose every morning 2 hours before breakfast. Patients were confined to the study facility from 6 PM on the evening prior to day 21 and until 48 hours after taking the dose of megestrol acetate on day 21.

Blood samples were obtained just prior to dosing on days 19, 20 and 21 and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours after dosing on day 21.

ASSAY: Plasma samples were analyzed for intact megestrol acetate according to an HPLC method. Plasma standard curves were in the range 10 - 600 ng/ml. The lower limit of quantitation of the assay was 10 ng/ml and the upper limit was 600 ng/ml. Quality control (QC) samples were prepared in blank human plasma at concentrations of 25 and 500 ng/ml.

The variation (%CV) about duplicate samples of the 10 ng/ml standard was 16.4 and 24.3 for standard curves 1 and 2, whereas the %CV was 2.0 and 9.0 at 300 ng/ml, respectively. For standard curve 1, the %CV was 6 at 600 ng/ml; no value was available for curve 2. The within-day %CV was 15 for 25ng/ml QC samples and 2 for 500 ng/ml QC samples. The between-day (n = 2 days) %CV was 14 and 7 for 25 ng/ml and 500 ng/ml QC samples, respectively.

DATA ANALYSIS: Plasma concentrations, C, versus time, t, data were analyzed by noncompartmental methods. The highest observed C was defined as CMAX and the time of its occurrence as TMAX. CMIN was the observed C just before dosing on days 19, 20, 21 and 24 hours after day 21 dose. The 0-24 hour steady-state area under the C *vs* t curve, AUC(SS), was calculated using linear trapezoidal rule. The average C on day 21, C(AV), was calculated as AUC(SS)/24. The percent of fluctuation between CMAX and CMIN on day 21, %FL, was calculated as 100 x (CMAX - CMIN)/C(AV).

RESULTS: Data from 10 male cachectic AIDS patients were available for pharmacokinetic analysis. The medical history indicated that all patients except #2 and #8, received zidovudine. Patient #8 had a history of disseminated *Mycobacterium avium* infection and received numerous antibiotics. Patient #2, #6, #7, #9 and #10 received aerosolized pentamidine therapy.

Table 1 lists the demographic data for each patient. Figure 1 shows the mean steady-state plasma megestrol acetate concentrations for all patients. The CMIN values are listed in

Table 2 and Figure 2 shows a breakdown of mean plasma concentrations into 3 distinct groups: high, medium, and low concentrations. Table 3 lists the steady-state pharmacokinetic parameters for each patient.

Figure 3 shows a plot of individual AUC(SS) values (labeled by patient #) and their dose in terms of mg/Kg total body weight. Correlation analysis suggested an association between dose and AUC(SS) ($r = 0.59$, $p = 0.07$).

Figures 4 and 5 show plots of the weight gain in each subject after 21 days of MEGACE versus the plasma megestrol acetate exposure (AUC(SS)) or dose. No significant relationships were found. Further analysis of individual megestrol acetate concentration time-profiles (See Attachments) was carried out to determine if plasma exposure was predictive of response (weight gain) to the drug. Figure 7 shows the investigator's analysis. They reported a statistically significant correlation between weight gain and the percent of the 24-hour dosing interval where plasma megestrol acetate concentrations exceeded 300 ng/ml. Our analysis of the individual profiles is summarized by the plot shown in Figure 6. Correlation and regression analysis of these data did not show a statistically significant relationship between weight gain and exposure to concentrations of megestrol acetate greater than 300 ng/ml ($r = 0.53$, slope = 0.00074, $p = 0.11$).

CONCLUSIONS: The results of this study demonstrate significant inter-subject variation in steady-state plasma megestrol acetate concentrations following a dose of MEGACE ORAL SUSPENSION 800 mg qd. The pharmacokinetics of megestrol acetate may be confounded by drug-drug interactions due to other drug therapy which the subjects received. Potential drug-drug interactions should be investigated further.

Furthermore, the results of the study suggest that there may be a relationship between plasma megestrol acetate exposure and weight gain. This relationship should be explored further.

Table 1.

Patient Demographic Data
(N = 10)

Patient	Race	Age(yr)	Height, cm	Weight, kg		%IBW	
				Pre	Post	Pre	Post
1							
2							
5							
6							
7							
8							
9							
10							
109							
110							
Mean		39	176.1	60.0	62.2	85.6	88.5
SD		8	12.2	6.1	7.1	15.4	14.8

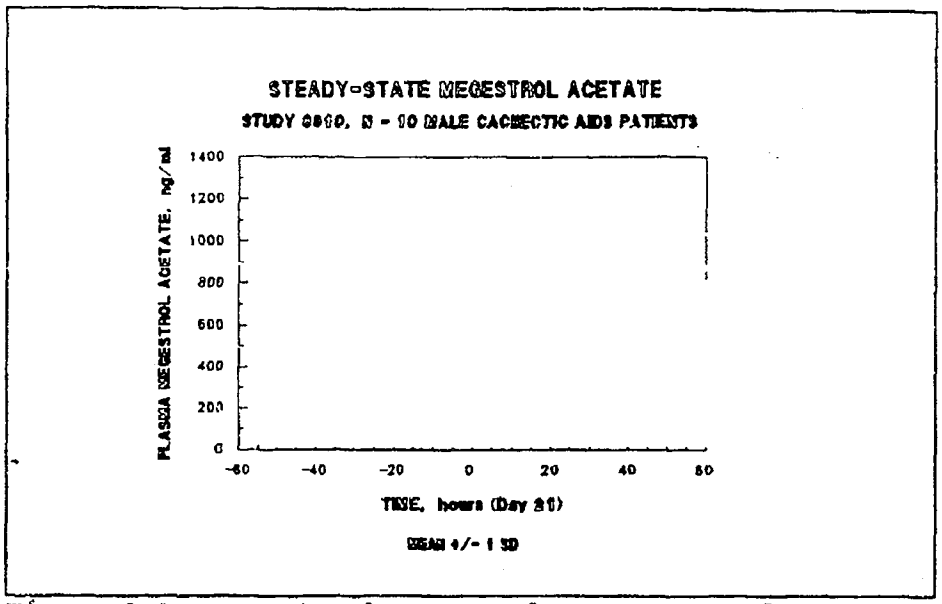


Figure 1 Average steady-state plasma megestrol acetate concentrations.

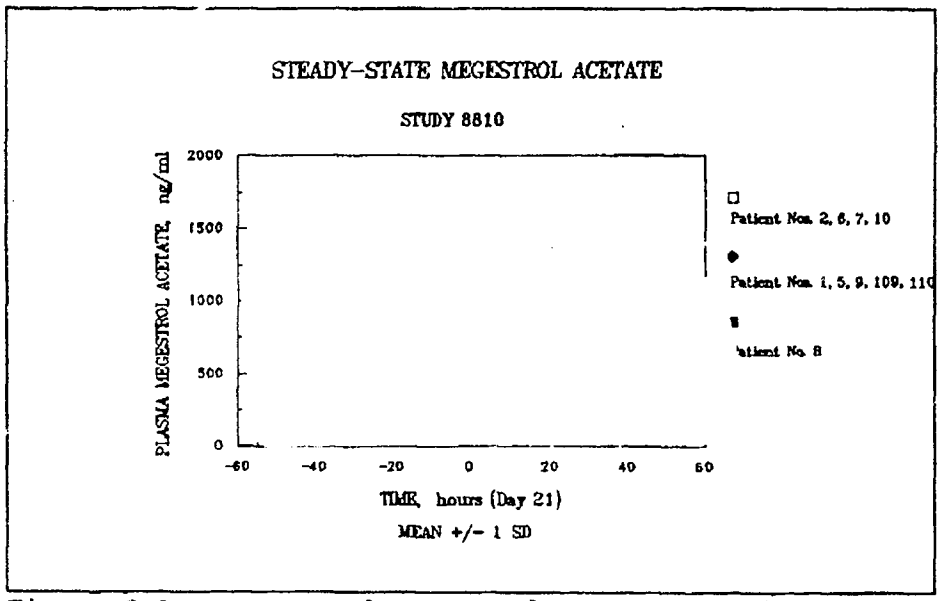


Figure 2 Average steady-state plasma megestrol acetate concentrations by group: high, medium, and low.

Table 2.

Trough Concentrations (CMIN) of Megestrol Acetate, ng/ml

	Day,Time (hour)						
Patient	19,0	20,0	21,0	21,24	Mean	SD	N
1							
2							
5							
6							
7							
8							
9							
10							
109							
110							
Mean	325	335	307	338			
SD	180	252	256	307			
N	7	5	9	8			

*Value excluded.

Table 3.

Megestrol Acetate
Steady-State Pharmacokinetic Parameters
(Concentration = ng/ml, Time = hours)

Patient	TMAX	CMAX	CMIN*	AUC(SS)	C(AV)	%FL
1						
2						
5						
6						
7						
8						
9						
10						
109						
110						
Mean	4	753	315	10476	436	98
SD	2.6	539	243	7788	324	30
N	10	10	10	10	10	10
Median	5	602	245	7547	314	92

*Value used to calculate %FL.

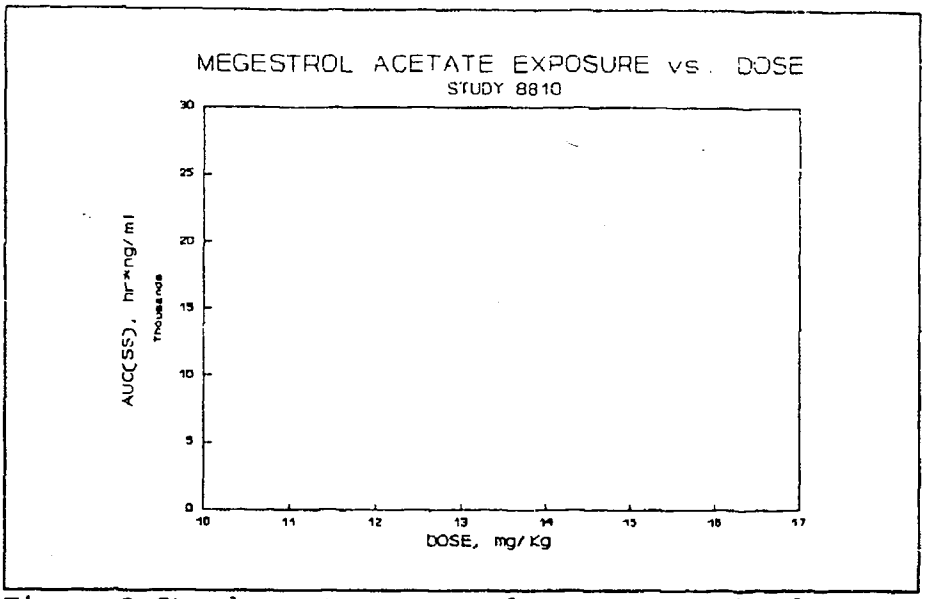


Figure 3 Steady-state megestrol acetate AUC by dose (800 mg/ total body weight) for each patient. Each data point labeled by patient number.

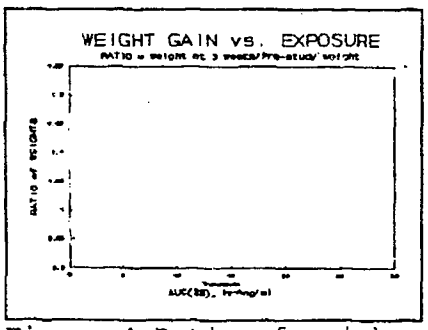


Figure 4 Ratio of weight gained after 3 weeks on treatment vs. steady-state AUC.

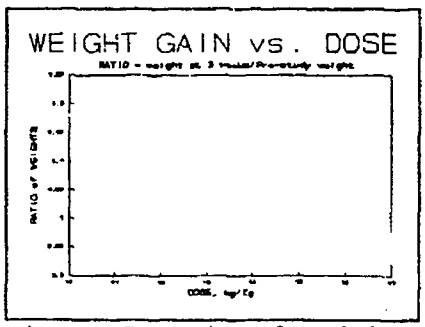


Figure 5 Ratio of weight gained after 3 weeks on treatment vs. dose (800 mg/total body weight).

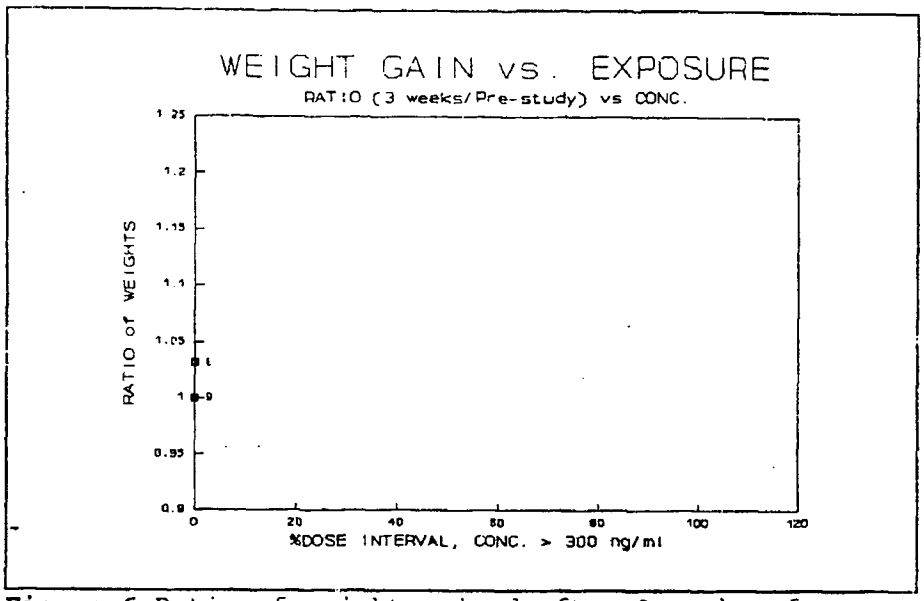


Figure 6 Ratio of weight gained after 3 weeks of treatment vs. the % of dosing interval (24 hours) that each patients' plasma megestrol acetate concentration was greater than 300 ng/ml.

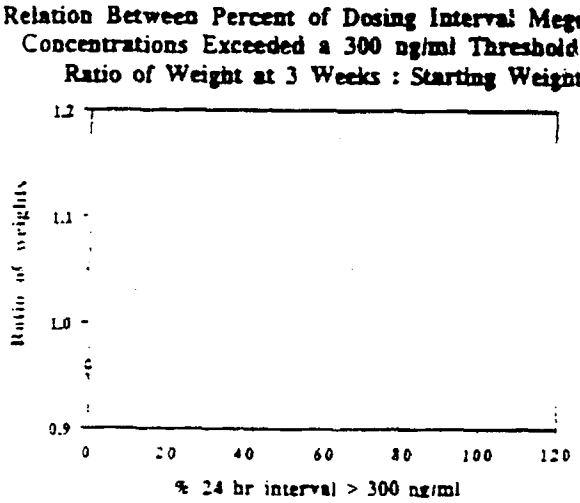
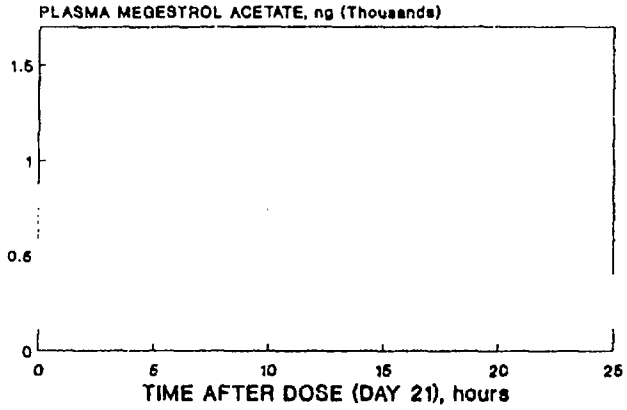


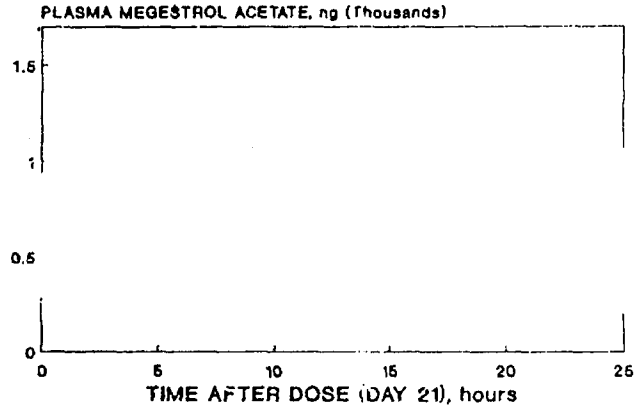
FIGURE 7

ATTACHMENTS

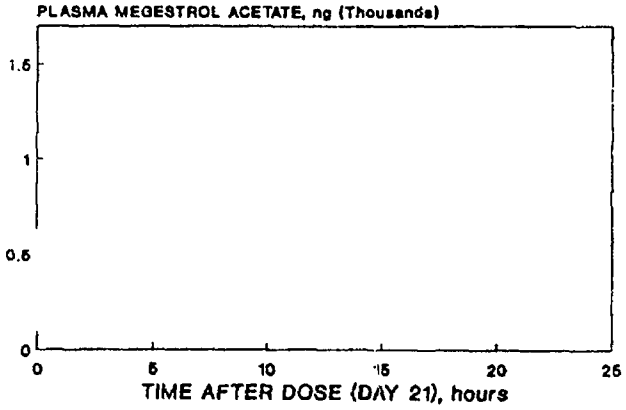
STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 1 CONCENTRATIONS > 300 ng/ml



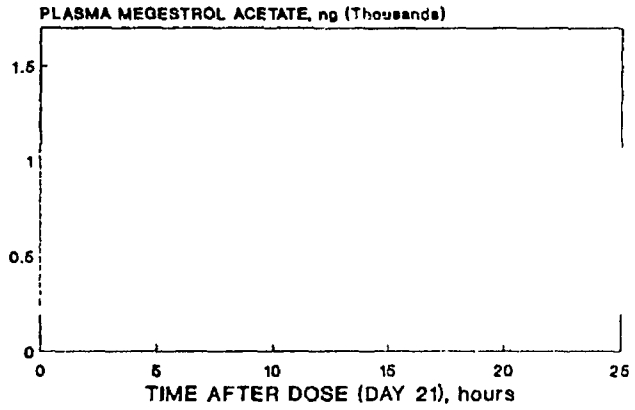
STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 2 CONCENTRATIONS > 300 ng/ml



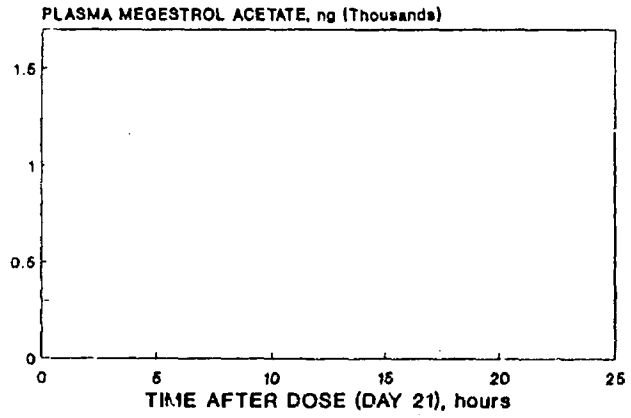
STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 5 CONCENTRATIONS > 300 ng/ml



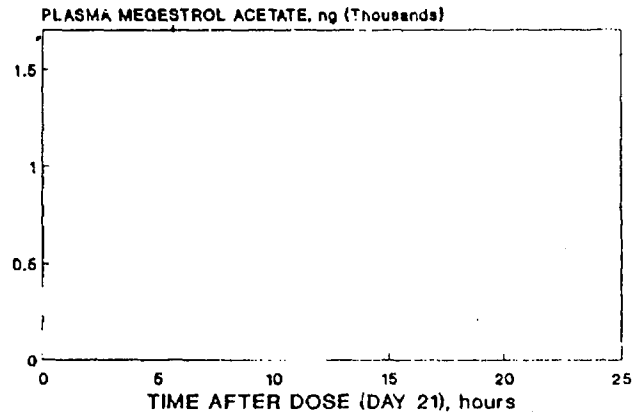
STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 6 CONCENTRATIONS > 300 ng/ml



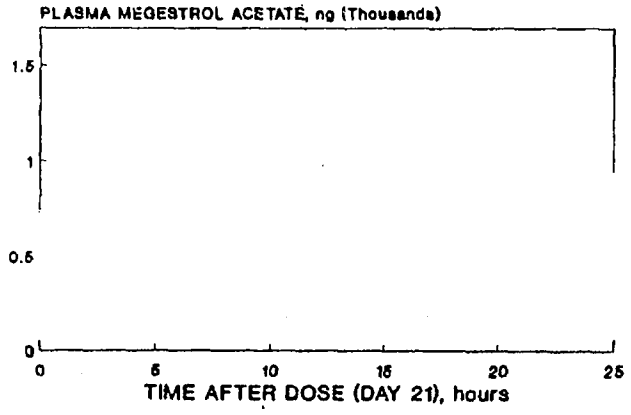
STEADY-STATE MEGESTROL ACETATE - STUDY SUBJECT 7 CONCENTRATIONS > 300 ng/ml



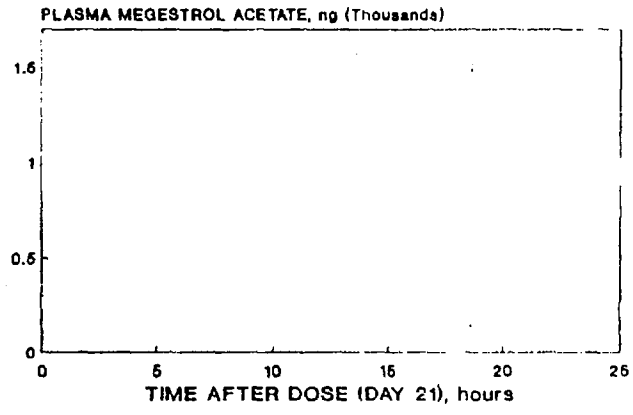
STEADY-STATE MEGESTROL ACETATE - STUDY SUBJECT 8 CONCENTRATIONS > 300 ng/ml



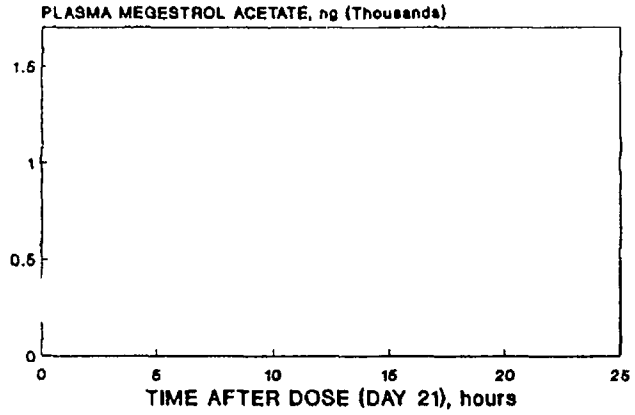
STEADY-STATE MEGESTROL ACETATE - STUDY SUBJECT 9 CONCENTRATIONS > 300 ng/ml



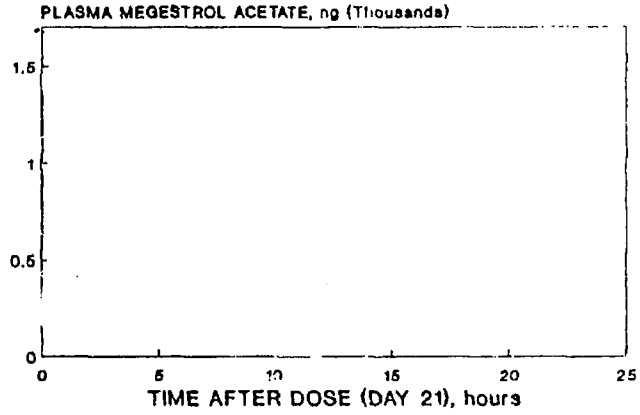
STEADY-STATE MEGESTROL ACETATE - STUDY SUBJECT 10 CONCENTRATIONS > 300 ng/ml



STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 109 CONCENTRATIONS > 300 ng/ml



STEADY-STATE MEGESTROL ACETATE - STUDY
SUBJECT 110 CONCENTRATIONS > 300 ng/ml



11 pages
purged

OCT 13 1993

NDA 20-264

Bristol-Myers Squibb Company
Attention: Marygayle Ritzert
Regulatory Affairs
2400 West Lloyd Expressway
Evansville, Indiana 47721-0001

Dear Ms. Ritzert:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Megace (megestrol acetate) Oral Suspension.

We acknowledge the receipt of your September 17, 1993, submission of final printed labeling (FPL).

We have reviewed the FPL that you have submitted in accordance with our approval letter dated September 10, 1993, and we find it acceptable.

Sincerely yours,

10-6-93

David W. Feigal Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and
Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-264

JUN 9 1993

Bristol-Myers Squibb Company
Attention: Marygayle Ritzert
Regulatory Affairs
2400 West Lloyd Expressway
Evansville, IN 47721-0001

Dear Ms. Ritzert:

Please refer to your New Drug Application (NDA) for Megace® OS , and to your submissions dated April 23, 1993, and May 3, 1993.

We consider your submissions major amendments under 21 CFR 314.60, and have determined that 120 additional days will be required for their reviews.

The new due date for NDA 20-264 is September 3, 1993.

Should you have any questions regarding either of these NDA applications, please contact Mr. Antony DeCicco, Supervisory Consumer Safety Officer, at (301) 443-9553.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and
Research

14

NDA 20-264

AUG 13 1992

Bristol-Myers Squibb Company
Attention: Marygayle Ritzert
Regulatory Affairs
2400 W. Lloyd Expressway
Evansville, Indiana 47721-0001

Dear Ms. Ritzert:

Please refer to your New Drug Application (NDA) for MEGACE® OS (megestrol acetate) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act on March 31, 1992.

We have reviewed your submission and request the following information:

Pharmacology/Toxicology:

1) Please submit results of appropriate statistical tests on the significance of pituitary tumor incidence in two-year carcinogenicity study of megestrol in rats (vol. 1.9, p. 05 01253).

2) Please submit mortality/survival data on two-year carcinogenicity study in the rats (vol. 1.9, p. 05 01213).

3) Please submit the report on detailed examination of fetuses in teratology study in rabbits. You mentioned that this information "will be reported later", as indicated in volume 9, page 1389, dated 1963.

4) Please submit food consumption data on twelve-week toxicity study in monkeys (vol. 1.9, p. 05 01063). This data will be useful for the analysis of the body weight gains in monkeys.

Statistics:

The variables in the data sets (diskettes) that you sent to us are not labeled. Please provide us with:

1) Labeled variables data sets.

2) A hard copy indicating where each variable is located.

3) Codes of treatment assignment for study No. 8809.

If you have any questions, please contact Mr. Anthony DeCicco, Consumer Safety Officer, at (301) 443-9559.

Sincerely yours,

8/12/5

David Feigal Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation
and Research

Concurrences:
HFD-530/DepDir/LRosenstein/
HFD-530/MO/DFeigal/ 8/11/92
HFD-530/Pharm/KWu/ 8.11.92
HFD-530/SCSO/ADeCicco/ 8-11-92
HFD-715/Stat/ KKazempour/

cc:
HFD-530 Orig NDA
HFD-530 Division File
HFD-530/MO/DFeigal

HFD-530/GL/MGoldberger
HFD-530/SChem/CChen
HFD-530/Chem/MJarski
HFD-530/SMicro/JRamsey
HFD-530/Micro/WDempsey
HFD-530/SPharm/DGreen
HFD-530/Chem/KWu
HFD-715/Stat/LHauptman
HFD-715/Stat/KKazempour 8-11-92
HFD-530/SCSO/ADeCicco

Information Request

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-264

-8

MARYGAYLE RITZERT
ASSISTANT DIRECTOR REGULATORY AFFAIRS
BRISTOL-MYERS SQUIBB COMPANY
2400 WEST LLOYD EXPRESSWAY
EVANSVILLE, IN 47721-0001

DEAR SIR/MADAM: MARYGAYLE RITZERT

WE HAVE RECEIVED YOUR NEW DRUG APPLICATION (NDA) SUBMITTED PURSUANT TO SECTION 505(B)/507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT FOR THE FOLLOWING:

NAME OF DRUG PRODUCT: MEGACE OS (MEGESTROL ACETATE, USP)

DATE OF APPLICATION: MARCH 31, 1992

DATE OF RECEIPT: APRIL 1, 1992

OUR REFERENCE NUMBER: 20-264

UNLESS WE FIND THE APPLICATION NOT ACCEPTABLE FOR FILLING, THE FILLING DATE WILL BE MAY 31, 1992.

PLEASE BEGIN ANY COMMUNICATIONS COCERNING THIS APPLICATION BY CITING THE NDA NUMBER LISTED ABOVE AND ADDRESSED AS FOLLOWES:

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH, HFD-530
ATTENTION: DOCUMENT CONTROL ROOM (15B45)
5600 FISHERS LANE
ROCKVILLE, MD 2085,

SHOULD YOU HAVE ANY QUESTIONS CONCERNING THE NDA, PLEASE CONTACT:
CLAUDETTE ELLIS
CONSUMER SAFETY OFFICER
(301) 443-9559

SINCERELY YOURS,

SUPERVISORY CONSUMER SAFETY OFFICER
DIVISION OF ANTIVIRAL DRUG PRODUCTS
CENTER FOR DRUG EVALUATION AND RESEARCH