

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

75-997

Generic Name: Megestrol Acetate Oral Suspension,
40mg/mL

Sponsor: Roxane Laboratories, Inc.

Approval Date: February 15, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-997

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AND RESEARCH**

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APPROVAL LETTER

ANDA 75-997

FEB 15 2002

Roxane Laboratories, Inc.
Attention: Elizabeth A. Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 27, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Megestrol Acetate Oral Suspension, 40 mg/mL.

Reference is also made to your amendments dated January 29, February 20, March 1, March 20, March 30, and November 30, 2001.

The listed drug referenced in your application, Megace Oral Suspension of Bristol Myers Squibb, is subject to a period of patent protection which will expire on August 16, 2011 [U.S. Patent No. 5,338,732 (the '732 patent)]. Your application contains a patent certification to the '732 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Roxane Laboratories, Inc. (Roxane) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Roxane within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Megestrol Acetate Oral Suspension, 40 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to

the listed drug Megace® Oral Suspension, 40 mg/mL, of Bristol Myers Squibb). The dissolution testing should be incorporated into your stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

A RSP *2/15/2002*
Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

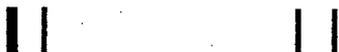
APPLICATION NUMBER:

75-997

Final Printed Labeling

MEGACE® Oral Suspension
Final Printed Labeling
NDA 20-264

Labeling: HFD-613
NDA No: 20264 Rec'd. 8/19/98
Reviewed by: [Signature]



P5745-02

MEGACE®
(megestrol acetate)
Oral Suspension

OR
SUSPENSION
OF
MEGESTROL
ACETATE

Rx only

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.

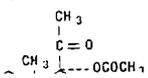
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure 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 17 α -(acetyloxy)-6-methylpregna-4,6-diene-3,20-dione. Solubility at 37° C in water is 2 μ g per mL, solubility in plasma is 24 μ g per mL. Its molecular weight is 384.51.

The empirical formula is C₂₄H₃₂O₄ and the structural formula is represented as follows:



**MEGESTROL
ACETATE**
Oral Suspension
40 mg/mL
NDC 0054-
3542-58
240 mL
(8 fl.oz.)

DC 0054- 240 mL
542-58 (8 fl.oz.)

**MEGESTROL
ACETATE**
Oral Suspension
40 mg/mL

Each mL contains
40 mg of micronized
megestrol acetate in
a lemon-lime
flavored oral suspension.

R_x only

 **Roxane**
Laboratories, Inc.
Columbus, Ohio 43216



FEB 15 2002

APPROVED

00000000/01
© RLI, 2001

NDC 0054- 240 mL
3542-58 (8 fl.oz.)

**MEGESTROL
ACETATE**
Oral Suspension
40 mg/mL

Each mL contains
40 mg of micronized
megestrol acetate in
a lemon-lime
flavored oral suspension.

R_x only

 **Roxane**
Laboratories, Inc.
Columbus, Ohio 43216

See Package I
Complete-Pre
Information.

Store the oral
suspension be
15° to 25°C (5
77°F) and disp
a tight contain

Protect from hu

Shake well imm
before dosing.

ROXANE LABORATORIES, INC.
MEGESTROL ACETATE
ORAL SUSPENSION

Rx only

WARNING

THE USE OF 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 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.

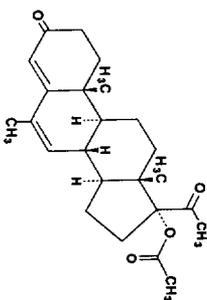
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If the patient is exposed to Megestrol Acetate Oral Suspension during pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION

Megestrol Acetate 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 17-Hydroxy-6-methylpregna-4, 6-diene-3, 20-dione acetate. Solubility at 37°C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.51.

The molecular formula is $C_{24}H_{32}O_6$, and the structural formula is represented as follows:



Megestrol Acetate Oral Suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per mL.

Megestrol Acetate Oral Suspension contains the following inactive ingredients: Avicel RC-591 (Microcrystalline Cellulose and Carboxymethylcellulose), NF7, citric acid, Cremophor EL, lemon-lime flavor, purified water, sodium benzoate, sodium citrate, and sucrose.

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 spectrometry (GC-MS), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MS 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-MS 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 66.4%) 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 Megestrol Acetate Oral Suspension for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 hours past the last dose. Mean (\pm SD) peak plasma concentration (C_{max}) of megestrol acetate was 753 (\pm 539) ng/mL. Mean area under the concentration time-curve (AUC) was 10476 (\pm 7788) ng x hr/mL. Median T_{max} 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 Megestrol Acetate Oral Suspension. The treatment was administered for 14 days. Mean C_{max} and AUC values were 490 (\pm 238) ng/mL and 6779 (\pm 3048) hr x ng/mL, respectively. The median T_{max} value was three hours. The mean C_{min} value was 202 (\pm 101) ng/mL. The mean % of fluctuation value was 107 (\pm 40).

The relative bioavailability of Megestrol Acetate Oral Suspension has not been evaluated. The effect of food on the bioavailability of Megestrol Acetate Oral Suspension has not been evaluated.

DESCRIPTION OF CLINICAL STUDIES

The clinical efficacy of 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 inclusion/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 7.9 pounds, the 400 mg MA group by 4.2 pounds, the 100 mg MA group by 1.6 pounds and decreased in the placebo group by 1.9 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 acetate 800 mg/day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 100 patients entered on study, 65 met all inclusion/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. 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 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, overall weight change, appetite, overall perception of well-being, and mean scores in MA-treated patients the placebo group. In both trials, patients tolerated the statistically significant differences in the treatment groups with regard to malaises, new opportunistic infections, T_e counts, T_s counts, or s (see ADVERSE REACTIONS).

Megestrol Acetate Oral Suspension
Clinical Efficacy Trial 1

Megestrol Acetate, mg/day	0	100	400	800
Entered Patients	38	82	71	71
Evaluable Patients	28	61	50	50
Mean Change in Weight (lb.)	0.0	2.9	7.9	11.2
Baseline to 12 Weeks	0.0	2.9	7.9	11.2
% Patients \geq 5 Pound Gain at Last Evaluation in 12 Weeks	21	44	50	65

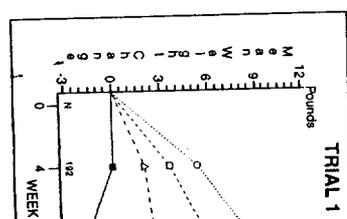
Mean Changes in Body Composition*	0	100	400	800
Fat Body Mass (lb.)	0.0	2.2	2.2	2.2
Lean Body Mass (lb.)	-1.7	-0.3	-0.3	-0.3
Water (liters)	-1.3	-0.3	-0.3	-0.3

% Patients With Improved Appetite At Time of Maximum Weight Change	50	72
At Last Evaluation in 12 Weeks	50	72

Mean Change in Daily Caloric Intake:	Baseline to time of Maximum Weight Change	-107	326
At Last Evaluation in 12 Weeks	-107 <td>326</td> <td>326</td>	326	326

* Based on bioelectrical impedance analysis evaluation in 12 weeks.

The following figures are the mean changes for patients evaluable for efficacy in 12 weeks.



**FACTORIES, INC.
PLACETATE
SPENSION**

ING

**ESTROL ACETATE
S CONTRAINDICATED
NANCY**

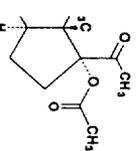
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PTION

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The second trial was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate 800 mg/day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 100 patients entered on study, 65 met all inclusion/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. 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, T₁ counts, T₂ counts, or skin reactivity tests (see ADVERSE REACTIONS).

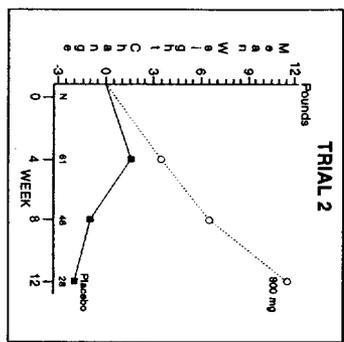
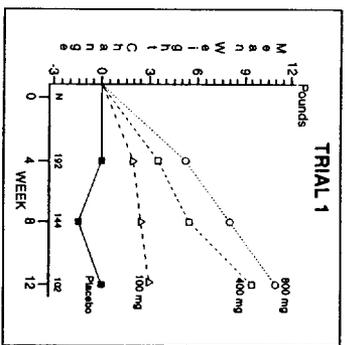
**Megestrol Acetate Oral Suspension
Clinical Efficacy Trials**

Megestrol Acetate, mg/day	Trial 1 Study Accrual Dates 11/88 to 12/90			Trial 2 Study Accrual Dates 5/89 to 4/91		
	0	100	400	800	0	800
Entered Patients	38	82	75	75	48	52
Evaluate Patients	28	61	53	53	29	36

Mean Change in Weight (lb.)	Trial 1			Trial 2		
	Baseline to 12 Weeks	Patients ≥ 5 Pound Gain at Last Evaluation in 12 Weeks	Patients with Improved Appetite	Baseline to Time of Maximum Weight Change	Patients with Improved Appetite	Patients with Improved Appetite
0.0	2.9	9.3	10.7	2.1	11.2	11.2
-1.7	-0.3	1.5	2.5	-1.6	-0.6	-0.6
-1.3	-0.3	0.0	0.0	-0.1	-0.1	-0.1
50	72	72	93	48	69	69
50	72	68	89	38	67	67
-107	326	308	646	30	464	464

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

The following figures are the results of mean weight changes for patients evaluable for efficacy in trials 1 and 2.



INDICATIONS AND USAGE

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

History of hypersensitivity to megestrol acetate oral suspension or any component of the formulation. Known or suspected pregnancy.

WARNINGS

Megestrol may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, (see PRECAUTIONS: Impairment of Fertility). 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 is not intended for prophyllactic use to avoid weight loss.

(See also PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility).

Although the glucocorticoid activity of megestrol has not been fully evaluated, evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in association with megestrol. Cases of clinically apparent adrenal insufficiency have also been reported in association with the use of megestrol acetate. The possibility of adrenal suppression should be considered in any patient taking or withdrawing from chronic megestrol acetate therapy who presents with symptoms of adrenal insufficiency such as hypotension, nausea, vomiting, dizziness, or weakness. Laboratory evaluation for adrenal insufficiency and replacement stress doses of a rapidly acting glucocorticoid may be indicated for such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death.

PRECAUTIONS

General:

Therapy with 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.

Effects on HIV viral replication have not been determined. Use with caution in patients with a history of thrombotic disease.

Use in Diabetics: Exacerbation of pre-existing diabetes with increased insulin requirements have been reported in association with the use of megestrol acetate.

Information for the Patients: 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:

Pharmacokinetic studies show that there are no significant alterations in pharmacokinetic parameters of zidovudine or ribavirin to warrant dosage adjustment when megestrol acetate is administered with these drugs. The effects of zidovudine or ribavirin on the pharmacokinetics of megestrol acetate were not studied.

Animal Toxicology:

Long-term treatment with megestrol acetate 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, 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, 20.6 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 Megestrol Acetate Oral Suspension and in surveillance of patients on therapy. (See **WARNINGS**)

Mutagenesis
No mutagenesis data are currently available.

Impairment of Fertility
Perinatal/postnatal (segment II) toxicity studies were performed in rats at doses (0.05 to 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: Teratogenic Effects; Pregnancy Category X. (See **WARNINGS** and **PRECAUTIONS**.)
(See **WARNINGS** and **PRECAUTIONS**.)
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 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 pediatric patients 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 Megestrol Acetate Oral Suspension.

ADVERSE EVENTS

	% of Patients Reporting				Open Label Trial		
	Trial 1 (N=236)	Trial 2 (N=87)					
Megestrol Acetate	0	100	400	800	0	800	1200
mg/day							
No. of Patients	N=34	N=69	N=69	N=69	N=69	N=176	
Dermatitis	15	13	8	15	8	6	7
Impotence	3	4	6	14	0	4	4
Rash	9	9	4	12	3	2	6
Fatigue	9	0	1	9	3	10	6
Hypertension	0	0	0	8	0	0	4
Asthma	3	2	3	6	8	4	5
Insomnia	0	3	4	6	0	1	1
Nausea	9	4	4	5	3	4	5
Artenia	6	3	2	5	0	0	0
Fever	3	6	6	5	0	2	1
Dyspnea	3	4	4	3	5	4	3
Hypotriglyceridemia	2	0	6	3	0	0	2
Headache	6	10	1	3	3	0	4
Pain	6	9	0	2	5	6	4
Vomiting	9	2	0	2	3	6	4
Pneumonia	8	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, hyposthesia and abnormal thinking

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

Postmarketing

Postmarketing reports associated with Megestrol Acetate Oral Suspension include thrombotic phenomena including thrombophlebitis and pulmonary embolism, and glucose intolerance (see **WARNINGS** and **PRECAUTIONS**).

OVERDOSAGE

No serious unexpected side effects have resulted from studies involving 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 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 5, 10, 15 and 20 mL markings is provided for convenience.

HOW SUPPLIED

Megestrol Acetate Oral Suspension is available as a lemon-flavored oral suspension containing 40 mg of micronized megestrol acetate per mL.

NDC 0054-3542-58 Bottles of 240 mL (8 fl. oz.)

Storage

Store between 15° to 25°C (59° to 77°F) and dispense in a tight container. Protected 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 (see **WARNINGS** and **ADVERSE REACTIONS**). Women at risk of pregnancy should avoid such exposure.

1000031202

November 2001
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NDC 0054-3542-58

240 mL
(8 fl.oz.)

LOT
EXP.

FEB 15 2002

**MEGESTROL
ACETATE**
Oral Suspension

40 mg/mL

Each mL contains 40 mg of
micronized megestrol acetate
in a lemon-lime
flavor.

APPROVED
Rx only



Roxane
Laboratories, Inc.
Columbus, Ohio 43216

00000000/01

© RLI, 2001

See Package Insert for Complete Prescribing Information.
Store the oral suspension between 15° to 25°C (59° to 77°F) and dispense in a
tight container. Protect from heat.
Shake well immediately before dosing.



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-997

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.1
2. ANDA # 75-997
3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc
P. O. Box 16532
Columbus, Ohio, 43216-6532
4. BASIS OF SUBMISSION
The listed drug product is Megace 40 mg/mL by Bristol-Myers Squibb held under NDA 16-979. The proposed drug product has same active ingredient, route of administration, and labeling is same as listed drug product.

Roxane certified that U.S. Patent no. 5,338,732 that expires on 8-16-2011 will not be infringed by the manufacture, use or sale of the Megestrol Acetate Suspension, 40 mg/mL. Roxane further stated that the marketing exclusivity expired on 9-10-00 in accordance with Orange Book, 20th Edition. In NC dated 1-19-01, Roxane submitted a copy of Patent Certification Notice to Bristol-Myers Squibb Company for the subject drug product.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
None used
7. NONPROPRIETARY NAME
Megestrol Acetate Oral Suspension
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 9-27-00
NC: 11-10-00
NC: 1-19-01

FDA:
Accepted for filing: 9-28-00 (Acknowledgment letter: 11-21-00)
Bio deficiency letter: 1-31-01
10. PHARMACOLOGICAL CATEGORY
For treatment of anorexia, cachexia, or weight loss in AIDS patients.
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

ANDA _____

DMF _____

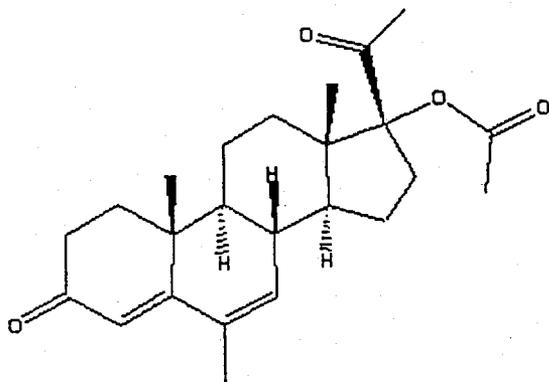
13. DOSAGE FORM
Suspension

14. POTENCY
40 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Name: 17-Hydroxy-6-methylpregna-4,6-diene-3,20,dione acetate

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS

1. DMF
Acetate is adequate per review conducted by this reviewer on 12-20-99.
2. Adequate information is provided for the manufacturing facility.
3. Megestrol Acetate is a USP 24 material. The proposed drug product is not a USP 24 material.
4. Roxane's specifications for Megestrol Acetate drug substance are based on USP 24.
5. Adequate information is submitted regarding executed batch and the intended production size batch.
6. Bio study - deficient. A deficiency letter was issued to the firm on 1-31-2001. Firm has not responded yet.

18. CONCLUSIONS AND RECOMMENDATIONS

A NA letter with major amendment is being sent to the firm citing all the comments identified in this review.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

2-21-01

Revised on 2-26-01 to include Mike Smela's comments

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ON ORIGINAL**

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1. CHEMISTRY REVIEW NO.2

2. ANDA # 75-997

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc
P. O. Box 16532
Columbus, Ohio, 43216-6532

4. BASIS OF SUBMISSION

The listed drug product is Megace 40 mg/mL by Bristol-Myers Squibb held under NDA 16-979. The proposed drug product has same active ingredient, route of administration, and labeling as listed drug product.

Roxane certified that U.S. Patent no. 5,338,732 that expires on 8-16-2011 will not be infringed by the manufacture, use or sale of the Megestrol Acetate Suspension, 40 mg/mL. Roxane further stated that the marketing exclusivity expired on 9-10-00 in accordance with Orange Book, 20th Edition. In NC dated 1-19-01, Roxane submitted a copy of Patent Certification Notice to Bristol-Myers Squibb Company for the subject drug product. They were not sued per 3/1/01 correspondence.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Megestrol Acetate Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 9-27-00

NC: 11-10-00

NC: 1-19-01

Amendment (BIO): 2-20-01

Amendment (Patent): 3-1-01

Amendment (BIO): 3-20-01

* Major Amendment (Chemistry + Labeling): 4-17-01

FDA:

Accepted for filing: 9-28-00 (Acknowledgment letter: 11-21-00)

Bio deficiency letter: 1-31-01

Deficiency letter: 3-7-01

10. PHARMACOLOGICAL CATEGORY

For treatment of anorexia, cachexia, or weight loss in AIDS patients.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF _____

13. DOSAGE FORM

Suspension

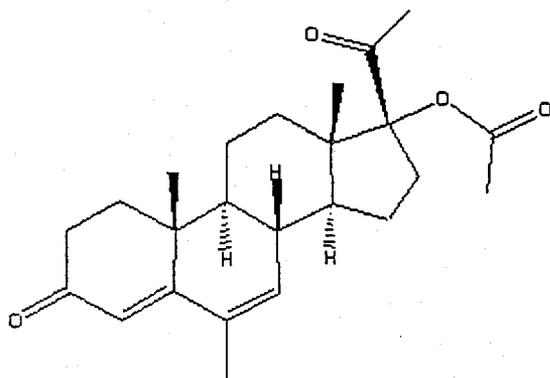
14. POTENCY

40 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Name: 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate

Structure:



16. RECORDS AND REPORTS

N/A

17. COMMENTS

1. DMF

Acetate is adequate per review conducted by this reviewer on 2-20-01.

2. Megestrol Acetate is a USP 24 material. The proposed drug product is not a USP 24 material. MV will be required.

3. Bio study - acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

A NA letter with Fax amendment is being sent to the firm citing all the comments identified in this review.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

10-10-01

Revised on 10-16-01

**APPEARS THIS WAY
ON ORIGINAL**

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1. CHEMISTRY REVIEW NO.3

2. ANDA # 75-997

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc
P. O. Box 16532
Columbus, Ohio, 43216-6532

4. BASIS OF SUBMISSION

The listed drug product is Megace 40 mg/mL by Bristol-Myers Squibb held under NDA 16-979. The proposed drug product has same active ingredient, route of administration, and labeling as listed drug product.

Roxane certified that U.S. Patent no. 5,338,732 that expires on 8-16-2011 will not be infringed by the manufacture, use or sale of the Megestrol Acetate Suspension, 40 mg/mL. Roxane further stated that the marketing exclusivity expired on 9-10-00 in accordance with Orange Book, 20th Edition. In NC dated 1-19-01, Roxane submitted a copy of Patent Certification Notice to Bristol-Myers Squibb Company for the subject drug product. They were not sued per 3/1/01 correspondence.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Megestrol Acetate Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 9-27-00

NC: 11-10-00

NC: 1-19-01

Amendment (BIO): 2-20-01

Amendment (Patent): 3-1-01

Amendment (BIO): 3-20-01

Amendment (BIO): 3-30-01

Major Amendment (Chemistry + Labeling): 4-17-01

Amendment (MVP samples): 11-9-01

* Minor Amendment: 11-30-01 (Response to NA letter dated 10-24-01)

FDA:

Accepted for filing: 9-28-00 (Acknowledgment letter: 11-21-00)

Bio deficiency letter: 1-31-01

Deficiency letter: 3-7-01

Deficiency letter: 10-24-01

10. PHARMACOLOGICAL CATEGORY

For treatment of anorexia, cachexia, or weight loss in AIDS patients.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF

DMF

DMF

DMF

DMF

DMF

DMF

DMF

DMF

13. DOSAGE FORM

Suspension

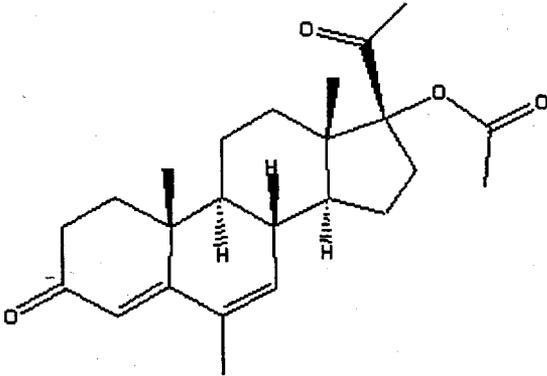
14. POTENCY

40 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Name: 17-Hydroxy-6-methylpregna-4,6-diene-3,20,dione acetate

Structure:



16. RECORDS AND REPORTS

N/A

17. COMMENTS

1. DMF
Acetate remains adequate per review conducted by this reviewer on 12-27-01.
2. Megestrol Acetate is a USP 24 material. The proposed drug product is not a USP 24 material. MVP was sent to Diane O'Brien on 10-16-01. The MVP is found satisfactory by PRLN in report dated 12/27/01.
3. Bio study - acceptable.
4. Labeling: Acceptable as of 12-10-01 review.
5. Release specifications for the drug product became acceptable. Also, acceptance specification for Megestrol Acetate became acceptable.
6. Expiration dating period of 24 month for the drug product is acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approved pending EER.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

12-31-0

Revised on 1-7-02

cc: AND 75-997
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/1/7/02

HFD-625/M.Smela/1/7/02

/S/
/S/
1/8/02
1/8/02

Project Manager:

HFD-617/M.Dillahunt/1/7/02

V:\firmnsnz\Roxane\ltrs&rev\75997.RV3

F/T by: gp/1/8/02

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10/24/01

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3/7/01

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**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

75-997

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-997

APPLICANT: Roxane Laboratories

DRUG PRODUCT: Megestrol Acetate Oral Suspension
40 mg/mL

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water at 37°C using USP Apparatus II (paddle) at 50 rpm. - The test product should meet the following specifications:

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,




Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Megestrol Acetate
40 mg/mL Oral Suspension
ANDA # 75-997
Reviewer: Kuldeep R. Dhariwal
V:\FIRMSNZ\ROXANE\LTRS&REV\75997SD.201

Roxane Laboratories
P.O.Box 16532
Columbus, Ohio 43216
Submission Dates:
February 20, 2001
March 20, 2001
March 30, 2001

Review of Amendments

The bioequivalence study and the dissolution data were reviewed on January 16, 2001 and the deficiencies were communicated to the firm on January 31, 2001. These amendments are in response to those deficiencies.

Deficiency 1: Please submit all clinical raw data. This should include test article dispensing records, records of dose administration with actual clock times, records of subject prohibitions (records of activity, fasting, water restrictions, release from confinement), records of final status of subjects on study, case report forms, etc.

Firm's response: The requested information is provided.

Reviewer's comments: The response is satisfactory.

Deficiency 2: You have not calculated elimination rate constant and AUC_{0-inf} for seven subjects on test drug and three subjects on reference drug. However it seems that, except for subject number 15 on test drug and 32 on reference drug, these parameters can be calculated. Please calculate the parameters and reanalyze the data. Also, provide the diskette with revised plasma and PK data including AUC_{0-inf} . You did not include AUC_{0-inf} data in the original diskette.

Firm's response: The firm reanalyzed the elimination rate constant and AUC_{0-inf} and have submitted the data.

Reviewer's comments: The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals based on the revised data. The 90% confidence intervals for log transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} are within acceptable limits of 80-125%. Subject #2 had pre-dose drug level (greater than 5% of C_{max}) in period 1 (test drug). The 90% confidence intervals remained within acceptable limits after dropping this subject.

Deficiency 3: Please state if nominal or actual sampling times were used for PK calculations.

Firm's response: Actual sample times were used for PK calculations.

Reviewer's comments: The response is satisfactory.

Deficiency 4: Please submit SOPs for accepting/rejecting a run and sample reassy procedure.

Firm's response: The requested SOPs are provided.

Reviewer's comments: The response is satisfactory.

Deficiency 5: The dissolution testing should be conducted in _____
_____ . The samples should be drawn
at 10, 20, 30 and 45 minutes.

Firm's response: The Roxane megestrol acetate oral suspension formulation contains Avicel RC-591 (microcrystalline cellulose and carboxymethylcellulose sodium) which _____

_____ The Avicel RC-591 r _____

_____ is defined as a _____

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #RD5052 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	4.67	_____	27.92	31.08	_____	21.84
20	6.42	_____	19.33	45.09	_____	11.94
30	8.25	_____	26.42	57.17	_____	6.28
45	11.08	_____	26.78	63.17	_____	2.85

Reviewer's comments: The reference product used in this dissolution testing is not from the same lot as used in the bio-study.

- (i)
- (ii)

The DBE also requested that the reference product used in the dissolution testing should be from the same lot as used in the bio-study. In an amendment dated March 20, 2001, the firm submitted the results of the dissolution testing conducted under the above conditions. The reference product used in the bio-study was used for the dissolution testing.

Medium: 900 mL 0.5% SLS
 Apparatus: 2 (paddle), 50 rpm

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #OC28807 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75		11	48		8
20	92		5	48		7
30	95		5	49		7
45	92		5	52		10

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #OC28807 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	5		69	23		17
20	6		61	40		15
30	7		57	58		10

45	7	56	76	1
----	---	----	----	---

On March 30, 2001, the firm submitted another amendment with additional dissolution data. The firm conducted dissolution testing under two additional conditions:

Medium: 900 mL 0.5% SLS
 Apparatus: 2 (paddle). — rpm

Results of <i>In Vitro</i> Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #OC28807 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	88		3	48		12
20	91		2	49		12
30	93		2	51		12
45	91		1	53		12

Medium: _____
 Apparatus: _____

Results of <i>In Vitro</i> Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #OC28807 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	99		1	99		1
20	99		1	100		0.9
30	100		1	99		1
45	101		1	101		1

These data suggest that a satisfactory dissolution profile of the test product can be obtained using 0.5% SLS at a paddle speed of 50. A specification of (Q) in 30 minutes is suggested.

The firm has satisfactorily responded to all the deficiencies.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Roxane Laboratories on its megestrol acetate oral suspension 40 mg/mL, lot # 009030A comparing it to Megace® 40 mg/mL, lot #OC28807 manufactured by Bristol-Myers Squibb (Mead Johnson) is acceptable to the Division of Bioequivalence. The study demonstrates that Roxane's megestrol acetate oral suspension 40 mg/mL is bioequivalent to the reference product Megace® 40 mg/mL manufactured by Bristol-Myers Squibb (Mead Johnson).
2. The dissolution testing conducted by the firm is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification:

Not less than $\frac{1}{Q}$ (Q) of the labeled amount of megestrol in the dosage form is dissolved in 30 minutes.

3. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

ISI
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

ISI
Date 4/26/2001

Concur ISI

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date 4/22/01

CC: ANDA 75-997
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 04/02/2001

Endorsements: (Final with Dates)

HFD-655/ Dhariwal

HFD-655/ Nerurkar

HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: 2/20/2001
3/20/2001
3/30/2001

1. STUDY AMENDMENT (STA)
2/20/2001

Strengths: 40 mg/mL
Outcome: AC

2. STUDY AMENDMENT (STA)
March 20, 2001
Telephone Amendment containing
dissolution testing results

Strengths: 40 mg/mL
Outcome: AC

3. STUDY AMENDMENT (STA)
March 30, 2001
Firm submitted another amendment
Containing new additional data

Strengths: 40 mg/mL
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 75-997

SPONSOR : Roxane Laboratories

DRUG AND DOSAGE FORM : Megestrol Acetate Oral Suspension

STRENGTH(S) : 40 mg/mL

TYPES OF STUDIES : Fasting

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : The fasting study is acceptable.

DISSOLUTION : The dissolution testing was conducted in 900 mL of 0.5% sodium lauryl sulfate in water using apparatus 2 (paddle) at 50 rpm. The test product meets the specification: NLT (Q) in 30 minutes.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic <u>No</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal BRANCH : II

INITIAL : ISI DATE : _____

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : ISI DATE : 4/26/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : ISI DATE : 4/27/01

JAN 31 2001

Thomas E

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-997

APPLICANT: Roxane Laboratories

DRUG PRODUCT: Megestrol Acetate Oral Suspension, 40 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit all clinical raw data. This should include test article dispensing records, records of dose administration with actual clock times, records of subject prohibitions (records of activity, fasting, water restrictions, release from confinement), records of final status of subjects on study, case report forms, etc.
2. You have not calculated elimination rate constant and $AUC_{0-\infty}$ for seven subjects on test drug and three subjects on reference drug. However it seems that, except for subject number 15 on test drug and 32 on reference drug, these parameters can be calculated. Please calculate the parameters and reanalyze the data. Also, provide the diskette with revised plasma and PK data including $AUC_{0-\infty}$. You did not include $AUC_{0-\infty}$ data in the original diskette.
3. Please state if nominal or actual sampling times were used for PK calculations.
4. Please submit SOPs for accepting/rejecting a run and sample reassay procedure.
5. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water using USP apparatus 2 (paddle) at rpm. The samples should be drawn at 10, 20, 30 and 45 minutes.

Sincerely yours,

^
-
|SI|

fr

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Megestrol Acetate
40 mg/mL Oral Suspension
ANDA # 75-997
Reviewer: Kuldeep R. Dhariwal/Alfredo R. Sancho
V:\FIRMSNZ\ROXANE\LTRS&REV\75997SD.900

Roxane Laboratories
P.O.Box 16532
Columbus, Ohio 43216
Submission Date:
September 27, 2000

Review of A Single Dose Bioequivalence Study and Dissolution Data

First Generic: No

Type of submission: Original submission

RLD: Megace®, Bristol-Myers Squibb (Mead Johnson)

Contents of Submission: Fasting study and dissolution data

Indication: Megestrol acetate 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). It is also indicated as an adjunctive therapy to certain cancers. Megestrol acetate is also indicated in the palliative treatment of advanced carcinoma of the breast or endometrium.

Recommended Dose: The recommended initial daily adult dose of Megace® Oral Suspension is 800 mg (20 mL).

Financial Disclosure: The principal investigator has no conflict of interest with the firm.

Background: Megestrol acetate is a synthetic derivative of progesterone with antineoplastic effects and appetite enhancing properties. Although the exact mechanism for megestrol-induced weight gain is unknown, the drug is thought to exert its effects via interference with the production or action of mediators such as cachectin, a hormone that inhibits adipocyte lipogenic enzymes.

Following oral administration, megestrol acetate is well absorbed from the gastrointestinal tract. The relative oral bioavailability of megestrol acetate suspension compared with the tablet formulation, and the effect of food on the bioavailability of the drug, have not been evaluated.

The following parameters were obtained following the administration of a single oral 80 mg (2 mL) dose of megestrol acetate suspension to healthy male subjects:

C_{max} (ng/mL)	— (CV% 30)
T_{max} (hours)	3.0 (CV% 40)
$T_{1/2}$ (hours)	25 (CV% 25)

The kinetics of megestrol acetate have been shown to follow a two compartment model.

Megestrol acetate is completely metabolized in the liver to free steroids and glucuronide conjugated metabolites, which may also be active in enhancing appetite. After oral administration of 4 to 90 mg of a radiolabelled dose, approximately 66% and 20% of the dose is excreted in the urine and in the feces respectively, within 10 days. Approximately 58% of the dose were excreted in the urine as metabolites.

Fasting Study:**Study Information****STUDY FACILITY INFORMATION**

Clinical Facility:	
Principal Investigator:	
Clinical Study Dates:	Period I June 24, 2000 Period II July 8, 2000
Analytical Facility	
Analytical Study Manager:	
Analytical Study Dates:	July 14-August 9, 2000
Storage Period:	45 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Megestrol Acetate	Megace [®]
Manufacturer:	Roxane Laboratories	Bristol-Myers Squibb (Mead Johnson)
Manufacture Date:	5/31/00	N/A
Expiration Date:	N/A	04/2002
ANDA Batch Size:		N/A
Batch/Lot Number:	009030A	0C28807
Potency:	98.3%	99.5%
Strength:	40 mg/mL	40 mg/mL
Dosage Form:	Oral Suspension	Oral Suspension
Dose Administered:	2x40 mg/mL (80 mg/2 mL)	2x40 mg/mL (80 mg/2 mL)
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION**DESIGN**

Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	Y
No. of Treatments:	2	Washout Period:	14 days

Randomization scheme:

AB: 2,4,5,8,9,11,13,16,17,20,21,24,26,28,30,31,33,36,38,40,41

BA: 1,3,6,7,10,12,14,15,18,19,22,23,25,27,29,32,34,35,37,39,42

DOSING**SUBJECTS**

Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	42

Route of Administration:	Oral	No. of Subjects Completing:	42
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	42
Number of Doses:	N/A	No. of Dropouts:	0
Loading Dose:	N/A	Sex(es) Included:	Male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	8

Dietary Restrictions:	Subjects were instructed to abstain from food or beverages containing xanthine (e.g. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.), and alcohol starting 48 hours prior to dosing and throughout the confinement period
Activity Restrictions:	Subjects engaged in normal activity for the first 4 hours after dosing avoiding complete rest. Vigorous physical activity was prohibited at all time during confinement.
Drug Restrictions:	No OTC drugs for 7 days prior to dosing and no prescription medications 14 days prior to dosing or during the study.
Blood Sampling:	Prior to dosing and at 0.5,1.0,1.50,2.0,2.50, 3.0, 3.5,4.0, 5.0, 6.0, 8.0, 10, 12,16,20,24,30,36,48 and 72 hours after dosing

Study Results

1) Clinical

Adverse Events: One subject complained of headache on test drug. Other events were unrelated to study drug.

Protocol Deviations:

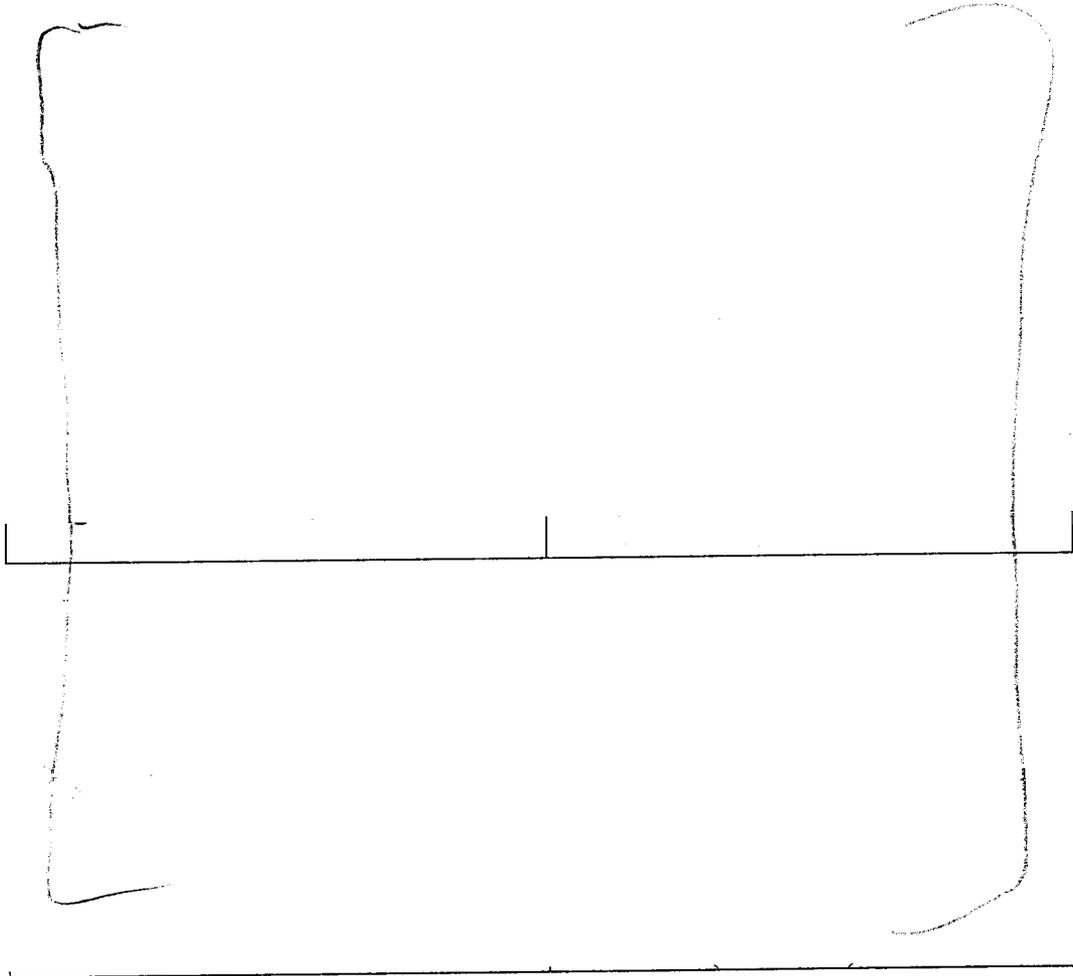
1. There were some sampling time deviations.
2. Two subjects consumed coffee/coke during the study.

Dropouts: None

2) Analytical (Not to be released Under FOI)

Pre-Study Assay Validation:





Reassays:

Three sample runs were repeated due to QC failures. Two samples were repeated for anomalous values. Since the reassay and the original values differed by greater than 30%, no concentration was reported for these samples, as per SOP.

3) Pharmacokinetics:

Mean Plasma Concentrations:	Table 1, Figure 1						
Pharmacokinetic Parameters:	Table 1						
90% Confidence Intervals:	<table border="0"> <tr> <td>LAUC_{0-t}</td> <td>92.60-105.94%</td> </tr> <tr> <td>LAUC_{0-inf}</td> <td>95.44-111.44%</td> </tr> <tr> <td>LC_{max}</td> <td>93.51-111.43%</td> </tr> </table>	LAUC _{0-t}	92.60-105.94%	LAUC _{0-inf}	95.44-111.44%	LC _{max}	93.51-111.43%
LAUC _{0-t}	92.60-105.94%						
LAUC _{0-inf}	95.44-111.44%						
LC _{max}	93.51-111.43%						
AUC_{0-t} / AUC_{0-inf} ratios:	<table border="0"> <tr> <td>Test</td> <td>0.90 (0.65-0.97)</td> </tr> <tr> <td>Ref</td> <td>0.90 (0.77-0.98)</td> </tr> </table>	Test	0.90 (0.65-0.97)	Ref	0.90 (0.77-0.98)		
Test	0.90 (0.65-0.97)						
Ref	0.90 (0.77-0.98)						
Root MSE:	<table border="0"> <tr> <td>LAUC_{0-t}</td> <td>0.183153</td> </tr> <tr> <td>LAUC_{0-inf}</td> <td>0.199169</td> </tr> <tr> <td>LC_{max}</td> <td>0.238617</td> </tr> </table>	LAUC _{0-t}	0.183153	LAUC _{0-inf}	0.199169	LC _{max}	0.238617
LAUC _{0-t}	0.183153						
LAUC _{0-inf}	0.199169						
LC _{max}	0.238617						

Comments:

1. The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.
2. The 90% confidence intervals for log transformed AUC_{0-t} , AUC_{0-inf} and C_{max} are within acceptable limits of 80-125%. There was no significant sequence, treatment or period effect for these parameters.
3. Subject #2 had pre-dose drug level (greater than 5% of C_{max}) in period 1 (test drug). The 90% confidence intervals remained within acceptable limits after dropping this subject.
4. The firm has not submitted clinical raw data. This includes test article dispensing records, records of dose administration with actual clock times, records of subject prohibitions (records of activity, fasting, water restrictions, release from confinement), records of final status of subjects on study, case report forms, etc.
5. The firm has not calculated elimination rate constant and AUC_{0-inf} for seven subjects on test drug and three subjects on reference drug. However it seems that, except for subject number 15 on test drug and 32 on reference drug, these parameters can be calculated. The firm should calculate the parameters and reanalyze the data.
6. It is not clear if nominal or actual sampling times were used for PK calculations.

Conclusion: The fasting study is incomplete.

Formulation:

Ingredients	Amount per mL
Megestrol Acetate, USP micronized	40 mg
Avicel RC-591 (Microcrystalline Cellulose And Carboxymethylcellulose NF)	_____
Sodium Benzoate, NF	_____
Citric Acid, USP	_____
Sodium Citrate, USP	_____
Sucrose, NF	_____
Lemon Lime Flavor	_____
Cremophor EL	_____
Water, USP	_____

Comments on formulation:

1. Lemon Lime Flavor is not listed in IIG. It has the following composition:

Ingredient	% by weight
_____	_____
_____	_____
_____	_____

The concentration of _____ is within the IIG limits. _____ and _____ constitute less than _____ of the total formulation.

Dissolution:

Method:

Medium: _____

Apparatus: 2 (Paddle), 50 rpm

Dissolution results: Table 2

Dissolution comments: The Agency recommends the dissolution testing for the test and reference products be conducted in 900 mL of 0.5% sodium lauryl sulfate using USP 24 apparatus 2 (paddle) at _____ rpm. The firm did not use the FDA recommended method.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Roxane Laboratories on its megestrol acetate oral suspension 40 mg/mL, lot # 009030A comparing it to Megace[®] 40 mg/mL, lot #OC28807 manufactured by Bristol-Myers Squibb (Mead Johnson) has been found incomplete by the Division of Bioequivalence.
2. The dissolution testing conducted by the firm is unacceptable. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water using USP apparatus 2 (paddle) at _____ rpm.

^m
ISI 1/11/01
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

ISI
Date 01/12/2001

ISI
Concur: _____
fw Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date 1/16/2000

Table 1

MEAN PLASMA MEGESTROL LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, N=42

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.26	1.68	0.00	0.00	.
0.5	18.84	13.13	15.08	9.81	1.25
1	52.57	41.12	51.35	41.75	1.02
1.5	76.50	68.27	71.38	52.76	1.07
2	84.08	70.68	83.99	58.12	1.00
2.5	85.89	66.86	84.22	54.89	1.02
3	84.67	55.76	81.31	46.02	1.04
3.5	81.33	49.66	76.28	41.51	1.07
4	74.83	41.45	69.41	34.35	1.08
5	67.95	32.25	61.96	24.90	1.10
6	57.61	24.82	55.40	22.39	1.04
8	39.28	14.39	42.78	20.39	0.92
10	32.50	11.97	35.14	14.81	0.93
12	26.51	12.54	31.05	18.49	0.85
16	22.85	16.09	23.43	9.99	0.98
20	19.49	15.35	19.05	8.62	1.02
24	19.98	15.32	19.90	9.13	1.00
30	18.41	15.28	15.72	8.56	1.17
36	12.70	10.52	11.71	6.63	1.08
48	7.13	3.59	7.45	4.22	0.96
72	4.03	2.32	4.44	2.79	0.91

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1589.91	818.73	1490.44	614.09	1.07
AUCT	1331.49	581.11	1330.91	502.72	1.00
CMAX	100.27	68.72	96.34	56.30	1.04
KE	0.03	0.01	0.03**	0.01	1.03
LAUCI	1430.05*	0.45	1367.43**	0.43	1.05
LAUCT	1225.20	0.41	1236.96	0.40	0.99
LCMAX	86.65	0.51	84.89	0.49	1.02
THALF	24.93	8.49	25.48	7.24	0.98
TMAX	3.03	1.42	3.39	2.11	0.89

*N=34, **N=39

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1547.70	1475.75	1.05	94.17	115.58
AUCT	1331.49	1330.91	1.00	92.89	107.20
CMAX	100.27	96.34	1.04	93.82	114.33
LAUCI	1397.80	1355.43	1.03	95.44	111.44
LAUCT	1225.20	1236.96	0.99	92.60	105.94
LCMAX	86.65	84.89	1.02	93.51	111.43

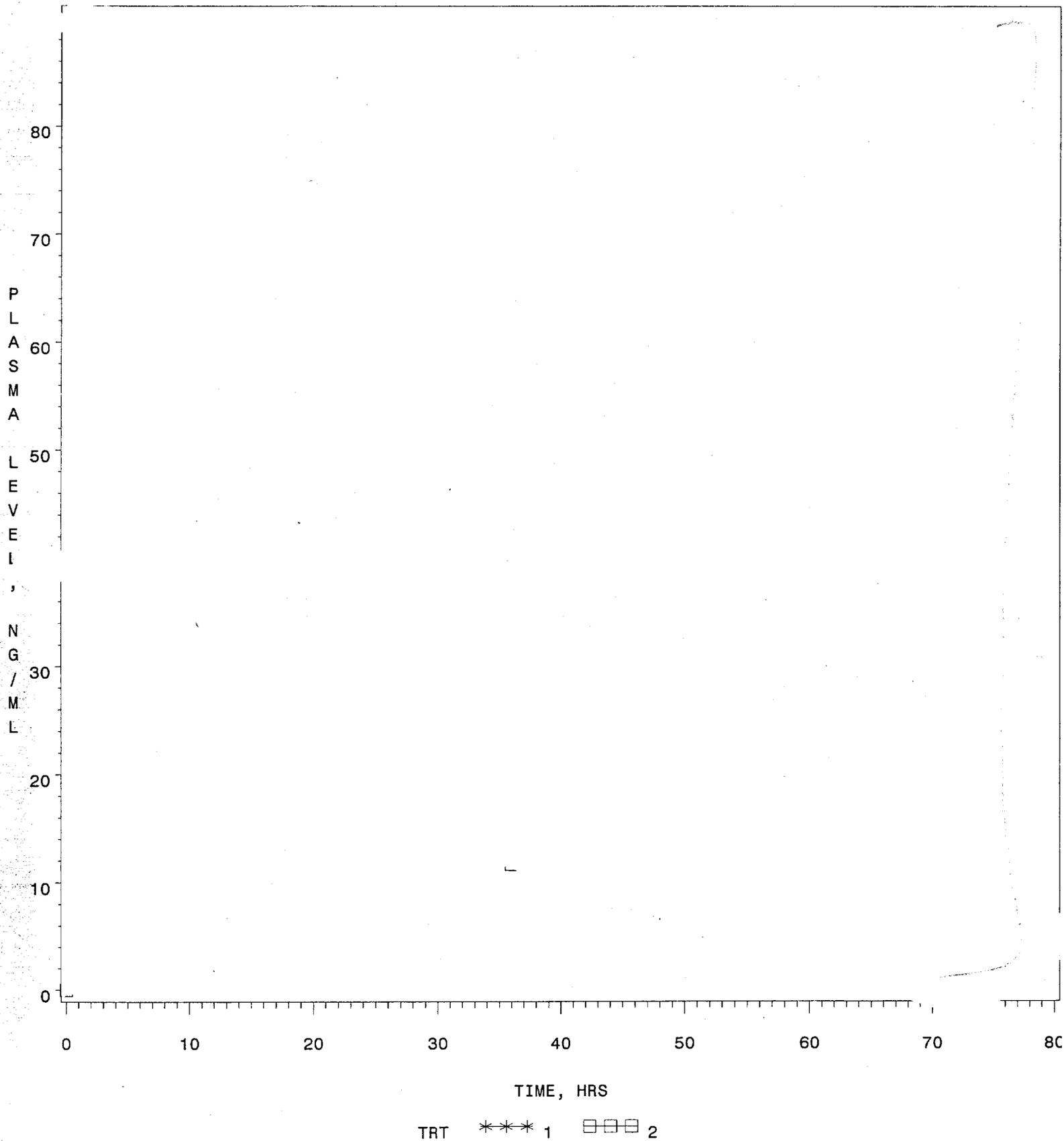
Table 2. In Vitro Dissolution Testing						
Drug (Generic Name): Megestrol acetate oral suspension Dose Strength: 40 mg/mL ANDA No.: 75-997 Firm: Roxane Submission Date: September 27, 2000 File Name: \\CDS008\WP51F99\FIRMSNZ\ROXANE\LTRS&REV\75997SD.900						
I. Conditions for Dissolution Testing:						
USP XXIII Basket: Paddle: x RPM: 50 No. Units Tested: 12 Medium: _____ Specifications: NLT _____ (%) in 30 minutes (Roxane) Reference Drug: Megace® Oral Suspension Assay Methodology: _____						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #009030A Strength 40 mg/mL			Reference Product Lot #OC28807 Strength 40 mg/mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97	_____	4.0	98	_____	1.1
20	97	_____	1.9	99	_____	0.8
30	99	_____	1.6	99	_____	0.9
Sampling Times (Minutes)	Test Product Lot # Strength (mg)			Reference Product Lot # Strength (mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

FIG 1. PLASMA MEGESTROL LEVELS

MEGESTROL ACETATE ORAL SUSPENSION, 40 MG/ML, ANDA #75-997

UNDER FASTING CONDITIONS

DOSE=2 X 40 MG/ML



1=TEST (ROXANE) 2=REF (BRISTOL-MYERS)

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-997

APPLICANT: Roxane Laboratories

DRUG PRODUCT: Megestrol Acetate Oral Suspension, 40 mg/mL

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5. The dissolution testing should be conducted in 900 mL of 0.5% sodium lauryl sulfate in water using USP apparatus 2 (paddle) at \sim rpm. The samples should be drawn at 10, 20, 30 and 45 minutes.

Sincerely yours,

fr *ISI*
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

75-997

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-997

FIRM: Roxane Laboratories
Columbus, OH 43216

DOSAGE FORM: Suspension

STRENGTH: 40 mg/mL

DRUG: Megestrol Acetate Oral Suspension

CGMP STATEMENT/EIR UPDATED STATUS:

EER for all facilities listed in section # 33 of this ANDA (CR # 2) is pending as of January 7, 2002.

BIO STUDY:

Bio status: Acceptable.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

MV: Satisfactory on 12-27-01.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Containers used in the stability studies are identical to those listed in container section.

LABELING:

Acceptable for approval per A. Payne's review and signed off on 12-10-01.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):

Bio/stability batch is lot # 009030 and its size is _____

Source of NDS:

DMF # _____ : Adequate per review completed on 12-27-01.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Stability batch is lot # 009030 and its size is _____

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

Intended production batch size: _____ (Equivalent to _____)

Manufacturing process for the intended production size batch is identical to that used for the exhibit/bio/stability batch.

cc: ANDA 75-997
Endorsements:
HFD-625/M.Shaikh/
HFD-M.Smela/1/7/02

/S/ 1/9/02
/S/ 1/9/02

V:\firmsnz\Roxane\ltrs&rev\75997.appsum

APPEARS THIS WAY
ON ORIGINAL

**FIRST GENERIC #2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-997

Date of Submission: April 17, 2001

Applicant's Name: Roxane Laboratories

Established Name: Megestrol Acetate Oral Suspension 40 mg/ mL

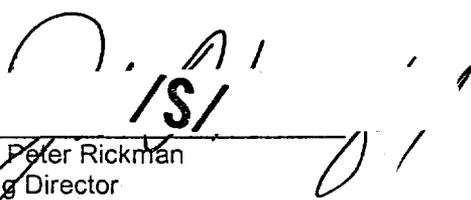
Labeling Deficiencies:

INSERT : You deleted the BLACK BOX WARNING information in your proposed revised insert labeling. We note your comment that you revised your insert labeling to be in accord with the insert labeling for the RLD (Megace Oral Suspension; approved on 2/2000). We do not have record of a 2/2000 insert being approved for the RLD. Please revise to include the black box warning information. We have included a copy of the text from the reference listed drug insert labeling for your convenience.

Please revise your insert labeling, as instructed above, and submit 12 final printed insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Megace

**FIRST GENERIC
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-997

Date of Submission: Sept 27, 2000

Applicant's Name: Roxane Laboratories

Established Name: Megestrol Oral Suspension 40 mg/ mL

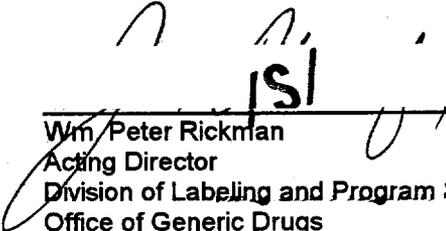
Labeling Deficiencies:

1. CONTAINER (240 mL) - Delete the period behind "Rx only".
2. CARTON (1 X 240 mL) - Please site the name of the product on the flap as per CFR 201.15(a)(1)
3. INSERT
 - a. TITLE
 - i. Delete the _____ that follows "Rx only"
 - ii. Black Box Warning, last two paragraphs - Use " _____" rather than Megestrol Acetate Oral suspension".
 - b. DESCRIPTIONS - List the USP names for Avicel as well as alphabetize the inactive ingredients.
 - c. CLINICAL PHARMACOLOGY
7th, paragraph - delete reference to the _____
 - d. CONTRAINDICATIONS
"... to megestrol acetate oral suspension or any...". (add oral suspension)
 - e. WARNINGS
You may use "megestrol" rather than the salt or dosage form throughout this section.
 - f. HOW SUPPLIED
You have designated "Storage" as a section heading. Please note it is consider as part of the how supplied section and therefore you a may designate it as a subsection heading. In addition, we encourage you to delete " the product name from the storage statement.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

75-997

CORRESPONDENCE



Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/A M

Attention: Michelle Dillahunt

November 30, 2001

ANDA 75-997
Megestrol Acetate Oral Suspension, 40mg/mL

MINOR AMENDMENT
Chemistry/Labeling Deficiencies

Dear Ms. Dillahunt:

We wish to amend ANDA 75-997. Enclosed please find a point-by-point response to the questions in the facsimile deficiency letter dated October 24, 2001.

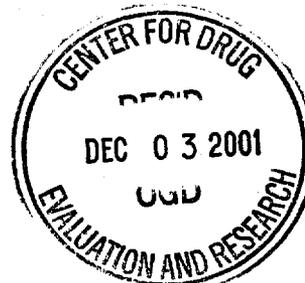
This amendment contains 12 copies of the revised final labeling for your review.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director of Regulatory Affairs, Roxane Laboratories, Inc. or me. Elizabeth can be reached by telephone at (614)272-4785 and by telefax at (614)276-2470. I can be reached at (614)241-4131.

Respectfully,

Elizabeth A. Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products



12/11/01
12/11/01



Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

November 9, 2001

NEW CORRESP

NC

MSK
/S
11/19/01

Attention: Michelle Dillahunt

**ANDA75-997
Megestrol Acetate Oral Suspension, 40 mg/mL**

Amendment – Response to Sample Request for Method Validation

Dear Ms. Dillahunt:

We wish to amend ANDA 75-997. Enclosed is a copy of the Amendment to the ANDA for Megestrol Acetate Oral Suspension, 40 mg/mL. This is in response to the October 29, 2001 request by FDA that samples be sent to the Pacific Regional Lab-Northwest for method validation studies.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Marilyn Davis, Clinical Research Associate, Regulatory Affairs at (614) 241-4123.

Respectfully,

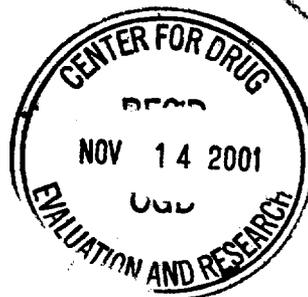
Elizabeth Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

Elizabeth A. Ernst, R.N.,
B.S.N.
Associate Director, Regulatory
Affairs, DRA-Multisource
Products for Roxane
Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail
ernst@col.boehringer-
ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532



151
11/19/01



Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Ms. Nina Nwaba
OGD/CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG. AMENDMENT

AB

March 30, 2001

**Re: ANDA 75-997, Megestrol Acetate Oral Suspension, 40 mg/mL
Bioequivalency Amendment**

Dear Ms. Nwaba,

Attached is the hard copy of the amendment that was faxed to you today.

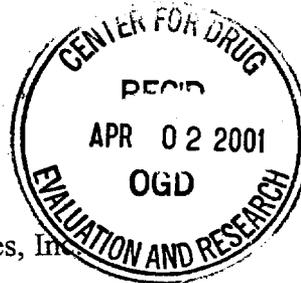
Correspondence concerning this request should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. I can be reached at (614) 241-4131.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Respectfully,

Marilyn J. Davis for

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.





Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Ms. Nina Nwaba
OGD/CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

N/A/B
ORIG AMENDMENT
PRODUCTION

March 20, 2001

**Re: ANDA 75-997, Megestrol Acetate Oral Suspension, 40 mg/mL
Bioequivalency Amendment**

Dear Ms. Nwaba,

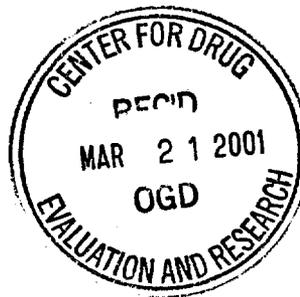
P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Attached is the hard copy of the amendment that was faxed to you today.

Correspondence concerning this request should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. I can be reached at (614) 241-4131.

Respectfully,

Virginia J. Fojas for
Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.





Boehringer Ingelheim
Roxane Laboratories

NEW CORRESP

Lina Nwaba
OGD, CDER, FDA
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Roxane Laboratories, Inc.

Patent Amendment
ANDA 75-997, Megestrol Acetate Oral Suspension, 40 mg/mL

March 1, 2001

Dear Ms. Nwaba,

We would like to amend the above referenced ANDA. Attached, please find a copy of the certification in accordance with § 314.95. This is in response to the November 21, 2000 comments concerning Roxane's Paragraph IV patent certification.

As indicated in the attached, Bristol-Myers Squibb Company has not responded to the patent certification notice within the 45 day period. This indicates that no legal action against Roxane Laboratories is being instituted.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

We have also submitted a copy of the amendment contained in the archival and review copies of this application to Mr. Steven Eastham, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this request should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. I can be reached at (440) 232-3320, ext. 3333.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.





Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Dale P. Conner, Pharm. D
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

February 20, 2001

AB
VIA ORG AMENDMENT

Subject: ANDA 75-997
Megestrol Acetate Oral Suspension, 40 mg/mL
Bioequivalency Amendment

ATTN: Krista Scardina, Pharm. D.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Dr. Conner:

We wish to amend ANDA 75-997. Enclosed please find a point-by-point response to the questions in the deficiency letter dated January 31, 2001.

Correspondence concerning this request should be directed to Elizabeth Ernst, Associate Director of Regulatory Affairs, Roxane Laboratories, Inc. Elizabeth can be reached by telephone at (614) 272-4785 and by telefax at (614)276-2470. I can be reached at (440) 232-3320, ext. 3333.

Sincerely,

Shahid Ahmed
Vice President, Regulatory Affairs
Roxane Laboratories, Inc.





Boehringer Ingelheim
Roxane Laboratories

Michelle Dillahunt
OGD, CDER, FDA
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Roxane Laboratories, Inc.

NEW CORRESP

re *1/19/01*
2/7/01
NAT

January 19, 2001

Patent Amendment
ANDA 75-997 Megestrol Acetate Oral Suspension, 40 mg/mL

Dear Ms. Dillahunt:

We would like to amend our unapproved ANDA for Megestrol Acetate Oral Suspension, 40 mg/mL, ANDA # 75-997. Attached please find a copy of the Patent Certification Notice to Bristol-Myers Squibb Company for Megestrol Acetate Oral Suspension, 40 mg/mL, in accordance with 21 CFR 314.95(b). Also attached is a letter from Bristol-Myers Squibb Company, in lieu of a Return Receipt which could not be located at the U.S. Post Office, confirming the receipt of Roxane's Patent Certification Notice, in accordance with 21 CFR 314.95(e) and Section 505(j)(2)(B)(ii) of the Act.

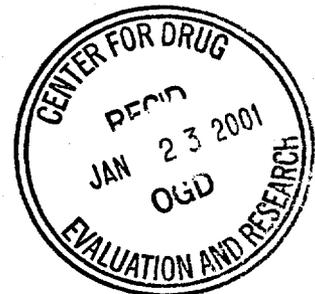
P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

We have also submitted a copy of this amendment to Mr. Steven Eastham, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director of Regulatory Affairs, Roxane Laboratories, Inc., who can be reached at (614) 272-4785, or I can be reached at (440) 232-3320 x 3333.

Respectfully,

Shahid Akmed
Vice President, Regulatory Affairs
Roxane Laboratories, Inc.



SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

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

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

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5862

Sincerely yours,


Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Boehringer Ingelheim
Roxane Laboratories

Martin Shimer
OGD, CDER, FDA
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Roxane Laboratories, Inc.

November 10, 2000

NEW CORRESP

NC

Telephone Amendment
ANDA 75-997 Megestrol Acetate Oral Suspension, 40 mg/mL

Dear Mr. Shimer:

We would like to amend our unapproved ANDA for Megestrol Acetate Oral Suspension, 40 mg/mL, ANDA # 75-997 in response to the 11/09/00 telephone call from Martin Shimer of OGD to Shahid Ahmed of Roxane Laboratories, Inc.

Included in this amendment are three additional copies of the draft labeling, a field copy certification for Megestrol Acetate Oral Suspension, 40 mg/mL, and copies of sections 1 through 5 section 7 for the Division of Bioequivalence.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Correspondence concerning this application should be directed to Elizabeth Ernst, Regulatory Affairs and Clinical Research Manager, Roxane Laboratories, Inc., who can be reached at (614) 272-4785, or I can be reached at (440) 232-3320 x 3333.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
Roxane Laboratories, Inc.





Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Roxane Laboratories, Inc.

September 27, 2000

505 (U) (2) (A) OK
(S) - 21-NOV-2000
M
(S) -

**Abbreviated New Drug Application
Megestrol Acetate Oral Suspension, 40 mg/mL**

Dear Madam/Sir:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Megestrol Acetate Oral Suspension, 40 mg/mL. This ANDA was formatted in accordance with the Guidance for Industry, Organization of an ANDA, February 1999.

The reference listed drug is Megace® (megestrol acetate) Oral Suspension, manufactured by Bristol-Myers Squibb. The product will be tested according to the enclosed specifications and will be labeled and marketed as Megestrol Acetate Oral Suspension, 40 mg/mL. Draft labeling is contained in this application. The product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. Furthermore, an *in vivo* bioequivalence study report is also included with this application.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Drug product samples will be submitted at the request and direction of the Office of Generic Drugs.

We have also submitted a copy of this application to Mr. Steven Eastham (Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Shahid Ahmed or Elizabeth Ernst, Regulatory Affairs and Clinical Research Manager, Roxane Laboratories, Inc. I can be reached at (614) 241-4131 or Elizabeth can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-8061.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
Roxane Laboratories, Inc.

