

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-778

PHARMACOLOGY REVIEW

03-14-05



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-778
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 6/29/2004
PRODUCT: Megace, Megestrol acetate oral suspension,
mg/kg/mL, NanoCrystal Dispersion (NCD)
INTENDED CLINICAL POPULATION: AIDS patients for anorexia, or cachexia or an
unexplained significant weight loss
SPONSOR: Par Pharmaceutical Inc.
DOCUMENTS REVIEWED: Vol. 1-8
REVIEW DIVISION: Div. of Metabolic and Endocrine Drug Products
(HFD-510)
PHARM/TOX REVIEWER: Herman Rhee
PHARM/TOX SUPERVISOR: Jeri Elhage
DIVISION DIRECTOR: David Orloff
PROJECT MANAGER: Holly Wieland

Date of review submission to Division File System (DFS): 2/26/2005

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW	6
2.6.1 INTRODUCTION AND DRUG HISTORY.....	F6
2.6.2 PHARMACOLOGY.....	9
2.6.2.1 Brief summary	9
2.6.2.2 Primary pharmacodynamics	9
2.6.2.3 Secondary pharmacodynamics	9
2.6.2.4 Safety pharmacology	9
2.6.2.5 Pharmacodynamic drug interactions.....	10
2.6.3 PHARMACOLOGY TABULATED SUMMARY.....	10
2.6.4 PHARMACOKINETICS/TOXICOKINETICS	10
2.6.4.1 Brief summary	10
2.6.4.2 Methods of Analysis	11
2.6.4.3 Absorption	11
2.6.4.4 Distribution.....	11
2.6.4.5 Metabolism.....	12
2.6.4.6 Excretion.....	12
2.6.4.7 Pharmacokinetic drug interactions.....	12
2.6.4.8 Other Pharmacokinetic Studies.....	12
2.6.4.9 Discussion and Conclusions	12
2.6.4.10 Tables and figures to include comparative TK summary	12
2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....	12
2.6.6 TOXICOLOGY	12
2.6.6.1 Overall toxicology summary	12
2.6.6.2 Single-dose toxicity	13
2.6.6.3 Repeat-dose toxicity	14
2.6.6.4 Genetic toxicology.....	31
2.6.6.5 Carcinogenicity.....	31
2.6.6.6 Reproductive and developmental toxicology.....	32
2.6.6.7 Local tolerance	32
2.6.6.8 Special toxicology studies	32
2.6.6.9 Discussion and Conclusions	32
2.6.6.10 Tables and Figures.....	32
2.6.7 TOXICOLOGY TABULATED SUMMARY	33
OVERALL CONCLUSIONS AND RECOMMENDATIONS.....	33
APPENDIX/ATTACHMENTS	34

capability of male offspring of megestrol acetate-treated female rats was impaired. Similar results were obtained in dogs. Pregnant rats treated with Megestrol acetate at doses of 5 and 12.5 mg/kg showed a reduction in fetal weight and number of live births, and feminization of male fetuses. The high dose is approximately 2 times therapeutic exposure based on body surface area comparison. No toxicity data are currently available on male reproduction (spermatogenesis).

Pregnancy:

Pregnancy Category D (see WARNINGS and PRECAUTIONS: Impairment of Fertility sections). No adequate animal teratology information is available at clinically relevant doses.

Teratogenic Effects:

Pregnancy Category D (Megace tablet)

Nursing Mothers:

Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megestrol acetate oral suspension is required.

II. Summary of nonclinical findings**A. Brief overview of nonclinical findings**

Pharmacology of Megace (Megestrol acetate) oral suspension has been well documented in NDA16-979 (BMS Megace) and NDA20-264-(Megace Oral Suspension) as well as in scientific publications. Par's Megestrol acetate oral suspension NanoCrystal Dispersion (NCD) formulation has no novel excipients. The unique feature of this NCD formulation is the fact that the nano-technique was used to improve the bioavailability and subsequent delivery of the active component of the preparation. Pharmacokinetic data support the view that the NCD formulation increased drug bioavailability as shown subsequently. However, the Division requested a 3-month toxicology study of the NCD because of the potential for differential distribution and unexpected toxicity of the NCD preparation. The sponsor complied with the request for a bridging toxicology study. Submitted data were reviewed under Toxicology section (2.6.6.3).

B. Pharmacologic activity

Despite the pharmacokinetic (PK) difference in NCD Megestrol compared to Megace, the pharmacologic activity of Par's Megestrol acetate oral suspension NanoCrystal Dispersion (NCD) formulation is identical to Megace tablets or Megace oral suspension.

C. Nonclinical safety issues relevant to clinical use

There was a slight inhibition of Cyp2A6, 2C9, 2C19, 2D6 and 3A4 by NanoCrystal Dispersion (NCD) formulation of Megace. However, the $IC_{50} > 50 \mu M$ is substantially higher than the expected maximum plasma concentrations based upon the bioavailability study. Thus, the sponsor considered the inhibition potential of Megestrol acetate would not adversely affect human cytochrome activity under normal clinical situation. The glucocorticoid activity of Megace Oral Suspension and NCD formulation has not been fully evaluated.

**Appears This Way
On Original**

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-778

Review number: 1

Sequence number/date/type of submission: 000/June 29, 2004/Commercial

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Par Pharmaceutical Inc.

Manufacturer for drug substance: Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, New York 10977

Reviewer name: Herman Rhee, Ph.D.

Division name: Metabolic and Endocrine Drug Products

HFD #: 510

Review completion date: 3/7/2005

Drug:

Trade name: Megace

Generic name: Megestrol acetate

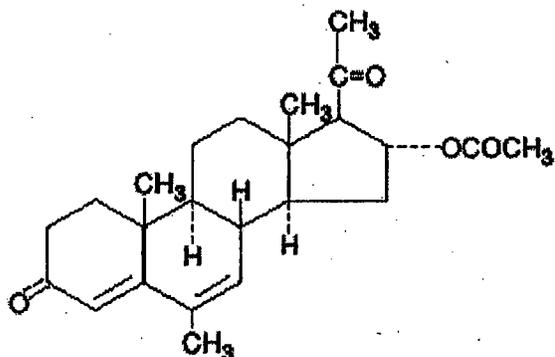
Code name:

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

CAS registry number: 595-33-5

Molecular formula/molecular weight: $C_{24}H_{32}O_4$

Structure:



Relevant INDs/NDAs/DMFs: [redacted] /NDA16-979 (BMS Megace), NDA20-264-(Megace Oral Suspension)

Drug class: Steroid

Intended clinical population: AIDS patients for anorexia, cachexia, or an unexplained significant weight loss

Clinical formulation:

Table 1 Components for Megestrol Acetate Oral Suspension, [redacted]

Ingredient	Function	Reference to Standard
Megestrol Acetate (micronized)	Active Ingredient	USP
[redacted]		
Hydroxypropyl Methylcellulose (Hypromellose)		USP
[redacted]		
Docusate Sodium		USP
Sodium Benzoate		NF
Sodium Citrate (Dihydrate)		USP
Citric Acid (Monohydrate)		USP
Sucrose		NF
Natural and Artificial Lemon Flavor		
Artificial Lime Flavor		
Purified Water		USP

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA21-778 are owned by Par Pharmaceutical Inc. or are data for which Par Pharmaceutical Inc has obtained a written right of reference. Any information or data necessary for approval of NDA21-778 that Par Pharmaceutical Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Par Pharmaceutical Inc. does not own (or from FDA reviews or summaries of a

previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA21-778.

Studies reviewed within this submission: The sponsor was requested to submit a 3-month oral toxicity study with NCD Megestrol Acetate and Megace in rats to evaluate the potential toxicity of NCD formulation. In addition, they submitted two studies on induction of human cytochrome P450 isoforms, which are briefly summarized below.

I. Study 272-1052-01. In this study the sponsor investigated the potential for Megestrol acetate to inhibit the P450 isoforms. Human liver microsomes were incubated in the presence of Megestrol acetate at concentrations of 1, 3.3, 10, 33.3 and 50 μM with various substrates as shown below. The concentrations of respective substrates are listed in the table below.

Isoform	Substrate	Concentration (μM)
CYP1A2	Phenacetin	150
CYP2A6	Coumarin	8
CYP2C9	Tolbutamide	250
CYP2C19	S-Mephenytoin	50
CYP2D6	Dextromethorphan	72
CYP2E1	Chlorzoxazone	50
CYP3A4	Testosterone	100

Megestrol acetate had no effect on Cyp1A2 or Cyp2E1. There was a slight inhibition of Cyp2A6, 2C9, 2C19, 2D6 and 3A4. However, the $\text{IC}_{50} > 50 \mu\text{M}$, which is substantially higher than the maximum plasma concentrations observed in the PK bioavailability study. Thus, the sponsor considered that the inhibition potential of Megestrol acetate would not adversely affect in human cytochrome enzymes under normal clinical situation.

II. Study 272-1053-02.

In this study the sponsor investigated the potential for Megestrol acetate to induce the activities of cytochrome P450 isoforms in cryopreserved human hepatocytes from three human donors. The hepatocytes were incubated in the presence of Megestrol acetate for two days at concentrations of 0.25, 2.5, and 25 μM . The three isoforms and their respective substrates and tested concentrations are summarized in a table below. The

study demonstrated that there was no induction of human Cyp 1A2, 2C9 and 3A4 by Megestrol acetate at the concentrations tested.

Isoform	Substrate	Concentration (µM)
CYP1A2	Ethoxyresorufin	2
CYP2C9	Tolbutamide	50
CYP3A4	Testosterone	125

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Pharmacology of Megace (Megestrol acetate) oral suspension has been well documented. Par's Megestrol acetate oral suspension NanoCrystal Dispersion (NCD) formulation has no novel excipients. The unique feature of this NCD formulation is the fact that a nanotechnology was used to improve the bioavailability of the effective component of the preparation. Pharmacokinetic data support the view that the NCD formulation increased drug bioavailability as shown subsequently. However, the Division requested a 3-month bridging toxicology study of the NCD because of the potential for differential distribution and unexpected toxicity of NCD preparation. The sponsor complied with the request of this office and the toxicology study data are reviewed under Toxicology section (2.6.6.3).

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

The precise mechanism by which Megestrol acetate produces effects in anorexia and cachexia is unknown at this time.

2.6.2.3 Secondary pharmacodynamics

NA

2.6.2.4 Safety pharmacology:

Safety pharmacology of Megace NCD formulation was not performed by the sponsor.

2.6.2.5 Pharmacodynamic drug interactions

There are potential pharmacodynamic drug interactions with Megace with some drugs that are metabolized by Cyp2A6, 2C9, 2C19, 2D6 and 3A4 because Megace inhibits the enzyme isoforms slightly. However, the IC₅₀ (> 50 µM) value is substantially higher than the expected maximum plasma concentrations under common clinical Megace usage.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

NA.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The sponsor compared pharmacokinetic parameters after oral administration of 575 mg of NCD Megestrol acetate oral suspension and 800 mg of Megace suspension to healthy volunteers under fed conditions. The two doses produced comparable C_{max} and T_{max}, although the Megace 800 mg increased AUC value approximately 20% over the NCD Megestrol preparation as shown below. AUC values were based on AUC₀₋₇₂ in this study, although the sponsor indicated as "?" in the table below. The effects of food on some pharmacokinetic parameters were also investigated as shown below (Table 4).

Comparison of pharmacokinetic parameters after oral administration of 575 mg of megestrol acetate oral suspension NCD and 800 mg of Megace® suspension to healthy volunteers under fed conditions			
Parameter ¹	NCD 575 mg (5 mL × 115 mg/mL)	Megace® 800 mg (20 mL × 40 mg/mL)	Geometric Mean Ratio (90% Confidence Interval)
C _{max} (ng/mL)	1,421 ± 421	1,401 ± 351	100.62 (94.10 → 107.60)
T _{max} (h)	3.75 ± 1.57	3.88 ± 1.02	²
AUC ₀₋₇₂ (h·ng/mL)	14,743 ± 4,451	18,274 ± 5,623	80.92 (77.95 → 84.00)

¹Mean ± standard deviation.
²Not applicable.

Table 4 Pharmacokinetic parameters for megestrol acetate after oral administration of 10 mg/kg of prototype PAR NCD suspensions, Megace[®], and PAR Megestrol Acetate Suspension to Beagle dogs

Parameter ¹	NCD #1		NCD #2		Megace [®]		PAR	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
C _{max} (ng/mL)	3,777 ± 2,489	2,210 ± 352	2,876 ± 1,334	1,563 ± 787	2,578 ± 665	340 ± 176	2,181 ± 406	485 ± 322
T _{max} (h)	1.7 ± 2.0	0.8 ± 0.3	3.0 ± 4.3	0.5 ± 0.0	0.8 ± 0.3	2.7 ± 0.6	1 ± 0.0	18.7 ± 9.2
AUC _{0-t} (h·ng/mL)	48,544 ± 11,609	37,774 ± 11,685	36,688 ± 12,016	21,858 ± 10,738	31,397 ± 5,824	10,094 ± 1,991	27,332 ± 6,489	17,395 ± 10,429
AUC _∞ (h·ng/mL)	61,735 ± 4,919	49,409 ± 3,393	42,788 ± 14,631	27,864 ± 15,279	40,219 ± 8,649	12,007 ± 1,924	31,721 ± 5,580	6,948 †

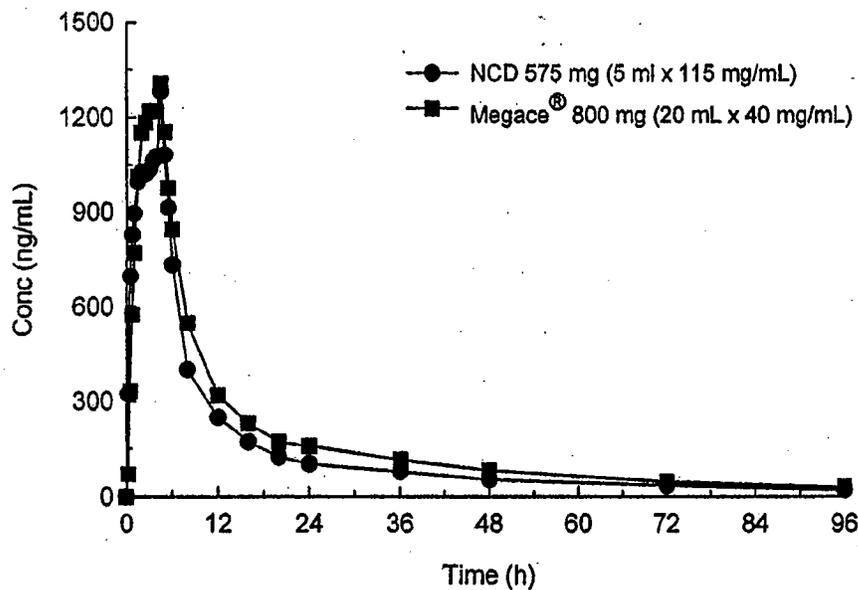
¹Mean value.
† n=1

2.6.4.2 Methods of Analysis

NA

2.6.4.3 Absorption

A 575 mg NCD formulation and megestrol acetate (800 mg) provided equivalent C_{max}, AUC and T_{max} values in healthy volume volunteers under fed conditions as shown in a figure below.



2.6.4.4 Distribution

NA

2.6.4.5 Metabolism

Megestrol acetate metabolites were 5 to 8 % of the dose administered, which were eliminated via urine. Respiratory excretion was demonstrated as labeled carbon dioxide.

2.6.4.6 Excretion

The major route of drug elimination in human is urine. Fecal excretion of the drug is approximately 20% and the total recovered radio-labeled drug ranged from 83 to 95% in human.

2.6.4.7 Pharmacokinetic drug interactions

There was a slight inhibition of Cyp2A6, 2C9, 2C19, 2D6 and 3A4 in human hepatocytes with an $IC_{50} > 50 \mu M$, which is substantially higher than the expected maximum plasma concentrations observed in the bioavailability study. Thus, the possibility to interaction with other drugs that are metabolized by the same P450 isoforms is minimal to slight.

2.6.4.8 Other Pharmacokinetic Studies

NA

2.6.4.9 Discussion and Conclusions

Pharmacokinetic data indicate that Megestrol Acetate NanoCrystal Dispersion (NCD) Oral Suspension provides an improved bioavailability of Megace in human, although there are limited preclinical data. The fact that there was a slight inhibition of Cyp2A6, 2C9, 2C19, 2D6 and 3A4 in human hepatocytes suggests potential interactions with drugs that are metabolized by the respective P450 isoform. However, it will not likely occur in clinical setting because of the $IC_{50} > 50 \mu M$, which is substantially higher than the expected maximum plasma concentrations observed in the bioavailability study.

2.6.4.10 Tables and figures to include comparative TK summary

NA

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NA

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

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 Neutrophils counts was observed in a two-year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

Genetic toxicology:

No mutagenesis data are currently available.

Carcinogenicity:

Carcinogenesis Data on carcinogenesis were obtained from studies conducted in rats, dogs, and monkeys treated with Megestrol acetate. No males were used in the dog and monkey studies. In 2-year carcinogenicity study Sprague Dawley rats received Megestrol acetate with food at doses of 1.5, 3.9 and 10 mg/kg/day. Pituitary tumors were observed in female rats treated with the mid and high dose groups (approximately 0.05 and 0.1 times therapeutic exposures based on body surface area comparison).

In female beagles, Megestrol acetate at doses of 0.01, 0.1 or 0.25 mg/kg/day was administered for up to 7 years. Megestrol acetate induced both benign and malignant tumors of the breast of the mid and high dose groups. The mid and high doses represent approximately 0.04 and 0.1 times therapeutic exposure based on body surface area comparison. 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. The high dose is approximately 0.1 times therapeutic exposure based on body surface area comparison. 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 section)

Reproductive toxicology:

Perinatal/postnatal (segment III) toxicity studies were performed in rats with doses of 0.05 to 12.5 mg/kg/day. The high dose is approximately 2 times therapeutic exposure based on body surface area comparison. In these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated female rats was impaired. Similar results were obtained in dogs. Pregnant rats treated with Megestrol acetate at doses of 5 and 12.5 mg/kg showed a reduction in fetal weight and number of live births, and feminization of male fetuses. The high dose is approximately 2 times therapeutic exposure based on body surface area comparison. No toxicity data are currently available on male reproduction (spermatogenesis).

Special toxicology:

NA

2.6.6.2 Single-dose toxicity

NA

2.6.6.3 Repeat-dose toxicity

Study title: 3-Month oral dose toxicity study with toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley rats.

Key study findings:

According to the preclinical data that were observed in 3-month toxicology study, the toxicology profiles of Megace NCD formulation is equivalent to those of Megestrol acetate except an increased bioavailability.

Study no.: 04-S12-VL

Volume #1, and page #1-2647

Conducting laboratory and location: _____

Date of study initiation: 7/19/04

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, and % purity: Par NCD megestrol acetate, 042056; _____

Methods

Doses: 0, 13.3, 40, and 66.5 mg/kg/day Megace or NCD

Species/strain: Rat/Sprague Dawley, _____ CD(SD)BR)

Number/sex/group or time point (main study): 10 rats/sex/group of 7 groups

Route, formulation, volume, and infusion rate: Oral, 10 ml/kg

Satellite groups used for toxicokinetics: 15 rats/sex/group, for recovery group: 10 rats/sex/group of 1 control and 2 high dose groups.

Age: 6 weeks old

Weight: 125-175 g

Unique study design or methodology (if any): NA

Mortality: Once daily

Clinical signs: Once daily

Body weights: Animals body weights were determined prior to the first dose and then weekly thereafter.

Food consumption: Weekly

Ophthalmoscopy: All animals were examined prior to randomization and only those rats free of ocular abnormalities were used. All surviving main and recovery animals were evaluated during weeks 3 and 12. The conjunctiva, cornea, and lens were evaluated using a slit lamp microscope _____

EKG: NA

Hematology: During week four and prior to necropsy, fasted main and recovery rats were anesthetized and blood samples were collected from the orbital sinus. Approximately 0.5 ml of whole blood was obtained for hematology study.

Clinical chemistry: Approximately 1 ml of whole blood from each animal was obtained for serum chemistry study.

Urinalysis: Urine was collected overnight from the overnight fasted animals

Gross pathology: All main or recovery group animals found or moribund were used for gross necropsy. Animals were fasted overnight prior to tissue samplings.

Tissues were examined from all animals in the control and high dose main study groups.

Organ weights (specify organs weighed if not in histopath table):

Histopathology: All tissues were stained with hematoxylin and eosin. Recuts and special stains were requested to deem necessary by the veterinary pathologist (PAI).

Adequate Battery: yes (x), no ()—explain

Peer review: yes (x), no ()

Toxicokinetics: Two anesthetized rats/sex/group/time point were used to collect blood samples for TK studies. After the first dose: blood samples were taken at 0.5, 1, 3, 6, 12, and 24 hours after dosing (the first 12/sex/group) and 48 and 72 hours after the first dose (the remaining 2/sex/group). After dose 30 and 90: blood samples were taken at 0.5, 1, 3, 6, 12, and 24 hours after dosing and at 0.5, 1, 3, 6, 12, 24, 48 and 72 hours after dosing.

Statistical analysis: All data were collected via DATATOX software and analyzed by Bartlett's or Dunnett's tests. For the Bartlett test, $p \leq 0.001$ was considered significant while $p \leq 0.05$ was considered significant for all other tests.

Results:

Mortality: There were 5 and 2 deaths in Megace treated and MCD Megestrol treated animals, respectively. In Megace group, 4 (3 males and 1 female) in the HD and 1 in the MD group animals died from 2 to 86 days after treatment. In NCD Megestrol group, one HD female and one MD male died on 24 and 90 days after the treatment, respectively. The sponsor considered that all the deaths were not related to the treatment since the deaths appeared to be due to gavage accidents.

Clinical signs: There were increases in the incidence of alopecia in all females treated with NCD Megestrol. The incidences were 50%, 100%, 100% and 80% in the control, LD, MD, and HD groups, respectively, which appeared to drug-related. The recovery animals did not show any increases in alopecia as compared to concurrent control recovery animals. There were no other treatment related clinical signs in all animals.

Body weights:

In the 3-month toxicology study with Megace and NCD Megestrol, the two formulations had no effects on mean body weights in both males and females in the LD groups except a point on Day 63 in males with NCD Megestrol as shown in two tables below. Megace decreased mean body weight gain by approximately 35% in the MD and HD males. NCD Megestrol acetate decreased body weight gain by 30-40% in the MD and HD male rats.

Effects of Megace on Body Weight in 3-Month Toxicity Study in Rat(Study#04-S12-VL)@					
Day	Sex	Control	Low Dose	Mid-Dose	High Dose
0	M	277	279	277	277
7	M	320	310	267	297
14	M	356	341	328	324*
20	M	381	363	349*	346*
28	M	401	383	360*	357*
35	M	425	403	382*	374*
42	M	444	422	395*	389*
50	M	473	441	413*	403*
56	M	484	453	423*	414*
63	M	506	467	428*	422*
70	M	517	473	432*	429*
77	M	530	488	442*	440*
84	M	534	484	437*	444*
0	F	203	198	199	202
7	F	215	219	216	219
14	F	229	234	234	233
20	F	238	245	248	247
28	F	249	253	254	256
35	F	256	263	267	270
42	F	264	270	277	279
50	F	273	283	288	293
56	F	279	290	296	299
63	F	282	296	304	305
70	F	288	304	311	314
77	F	297	311	318	320
84	F	298	315	323	321

@Indicate mean body weight in grams. *P ≤ 0.05. M and F indicate male and female, respectively.

Effects of NCD Megestrol on Body Weight in 3-Month Toxicity Study in Rat(Study#04-S12-VL)@					
Day	Sex	Control	Low Dose	Mid-Dose	High Dose
0	M	277	275	278	276
7	M	320	308	298	294
14	M	356	335	325*	320*
20	M	381	358	345*	340*
28	M	401	371	360*	349*
35	M	425	395	380*	359*
42	M	444	410	397*	383*
50	M	473	431	414*	398*
56	M	484	442	422*	407*
63	M	506	454*	434*	417*
70	M	517	463	444*	424*
77	M	530	475	452*	435*
84	M	534	472	453*	431*
0	F	203	196	197	201
7	F	215	215	214	218

14	F	228	232	232	241
20	F	238	247	247	258
28	F	249	259	252	264
35	F	256	270	266	277
42	F	264	278	276	287
50	F	273	292	286	300
56	F	279	297	290	305
63	F	282	306	297	312
70	F	288	316	306	320
77	F	297	322	312	327
84	F	298	320	314	327
@Indicate mean body weight in grams. *P ≤ 0.05. M and F indicate male and female, respectively.					

Food consumption: There was no effect on food consumption after Megace treatment in males or females except the recovery group males and females, which produced variable responses in several points of time. It appears that the changes in the recovery group were due to small group size rather than representing the treatment action. NCD Megestrol treatment did not have significant effects on food consumption, although there were increases in food consumption in males during Weeks 6-12 of treatment in the MD and HD groups.

Ophthalmoscopy: On Day 80 the effects of Megace and NCD Megestrol acetate were evaluated in male and female rats as shown below. In males, there were one animal with uveitis and one rat with phthisis bulbi in the control group. There were rats with retinal degeneration in MD Megace group.

In females, two rats had retinal degeneration in the control group while two rats (one from the LD and another from the HD group) had the retinal degeneration. Two rats from the MD Megestrol group had uveitis and phthisis bulbi, respectively. It appears that ophthalmologic effects were not drug dose dependent and NCD formulation had slightly higher ophthalmologic incidences in female, although such incidences were also observed in male control group. It appears that the retinal degeneration may not be related to the drug since a few control- and treated-animals had the problem and there was no dose-related pattern of incidence.

Appears This Way
On Original

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley
 Study : 04-812-VL - Toxicology TABLE OP2K-SUM OPTHALMOLOGY Date : 13-JAN-05
 Species: Rat OPTHALMOLOGY Time : 15:02
 Sex : Male PRE-TERMINAL/MAIN GROUPS Page : 1
 Clinical Summary Incidence Report (Brief report)

Day 80
With reference to nominal day zero

Dose Group	A	B	C	D	E	F	G
Dose	CONTROL	13.3 MEGACE	40 MEGACE	66.5 MEGACE	13.3 NCD	40 NCD	66.5 NCD
Total animals	10	10	10	10	10	10	10
OPHTHALMIC EXAMINATION							
NORMAL Incidence (%)	9 (90)	10 (100)	8 (80)	10 (100)	9 (90)	10 (100)	10 (100)
DEGENERATION, RETINAL Incidence (%)	0 (0)	0 (0)	2 (20)	0 (0)	1 (10)	0 (0)	0 (0)
UVEITIS Incidence (%)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PHTHISIS BULBI Incidence (%)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley
 Study : 04-812-VL - Toxicology TABLE OP2K-SUM OPTHALMOLOGY Date : 13-JAN-05
 Species: Rat OPTHALMOLOGY Time : 15:03
 Sex : Female PRE-TERMINAL/MAIN GROUPS Page : 1
 Clinical Summary Incidence Report (Brief report)

Day 80
With reference to nominal day zero

Dose Group	A	B	C	D	E	F	G
Dose	CONTROL	13.3 MEGACE	40 MEGACE	66.5 MEGACE	13.3 NCD	40 NCD	66.5 NCD
Total animals	10	10	10	10	10	10	9
OPHTHALMIC EXAMINATION							
NORMAL Incidence (%)	8 (80)	10 (100)	10 (100)	10 (100)	9 (90)	9 (90)	8 (88)
DEGENERATION, RETINAL Incidence (%)	2 (20)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (11)
UVEITIS Incidence (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)
PHTHISIS BULBI Incidence (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)

EKG: Not performed.

Hematology:

Megace and NCD Megestrol acetate decreased WBC in all treated groups, which appeared to be test article-dose dependent, although the NCD formulation decreased RBC in the male HD group only. Both MCH and RDW increased in males after Megace and the NCD formulation. In females, the two formulation decreased platelet and WBC in all treated groups. Hemoglobin, hematocrit, MCV, MCH and RDW were increased by the two formulations similarly without clear dose-dependent pattern as shown below. Thus, it is safe to say that the two formulations produced qualitatively similar hematologic effects in male and female rats.

Comparison of Megace and NCD on Hematologic Parameters in Male Rats in 3-Month Toxicity Study on Day 84								
	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
Platelet	1003	985	891	852	1003	988	1009	915
Wbc	10.5	6.8*	5.5*	4.9*	10.5	7.6*	5.3*	4.2*
Rbc	9.1	9.5	9.2	8.8	9.1	9.2	9.2	8.3*
Hgb	16.5	17.2	17.1	16.5	16.5	16.3	16.6	15.9
Hct	47.6	49.6	48.6	47.4	47.6	47.5	47.7	45.4
MCV	52.2	52.2	52.6	54.2	52.2	51.4	51.9	54.7*
MCH	18.1	18.1	18.6	18.9*	18.1	17.6	18.0	19.1*
MCHC	34.6	34.7	35.2	34.9	34.6	34.3	34.8	35.0
RDW	11.8	11.6	12.5	13.3*	11.8	12.1	12.6*	13.9*
HDW	2.37	2.29	2.39	2.51	2.37	2.35	2.44	2.52

*p<0.05.

Comparison of Megace and NCD on Hematologic Parameters in Female Rats in 3-Month Toxicity Study on Day 84								
	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
Platelet	1122	917*	855*	891*	1122	953*	901*	833*
Wbc	7.7	5.3*	5.1*	6.2*	7.7	5.6*	5.3*	5.1*
RBC	8.5	8.6	8.6	8.3	8.5	8.8	8.7	8.2
Hgb	15.7	16.8*	16.7*	16.2	15.7	16.9*	16.7*	16.5
Hct	45.0	47.8*	47.3*	46.2	45.0	48.0*	47.4*	47.0*
MCV	53.1	55.4*	55.0	56.0*	53.1	54.8	54.6	57.3*
MCH	18.6	19.5*	19.4*	19.6*	18.6	19.3	19.2	20.0*
MCHC	35.0	35.1	35.3	35.0	35.0	35.1	35.2	35.0
RDW	11.6	11.4	12.2	12.7*	11.6	11.9	12.1	12.5*
HDW	2.26	2.22	2.31	2.28	2.26	2.26	2.28	2.31

*p<0.05.

Clinical chemistry:

Both Megace and NCD Megestrol randomly increased glucose, TG, total proteins, and albumin in male rats without clear dose dependency. The elevation of ALT was significant in all treated groups after Megace and NCD Megestrol treatment. In females, chloride, urea nitrogen, and bilirubin were reduced without dose dependency after treatment with Megace and NCD Megestrol, which was quite different from the observation in males. Glucose, TG, and ALT were elevated in females after the drug treatment similar to the observations in males. Thus, it is concluded that both Megace and Megestrol had qualitatively similar effects on clinical chemistry, although there were some differences in males and females as shown below.

Comparison of Megace and NCD on Clinical Chemistry Parameters in Male Rats in 3-Month Toxicity Study on Day 84								
	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
Na	144	142	143	143	144	144	143	145
K	5.3	5.3	5.5	5.0	5.3	4.7	4.9	4.8
Cl	104	103	103	102	104	103	103	103
UN	13	12	12	13	13	13	11	12
Glucose	109	115	122*	117	109	122*	126*	109
Creatine	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Uric A	0	0	0	0	0	0	0	0
TG	77	168*	129*	139*	77	150*	320*	489*
Chol	44	51	118*	132*	44	57	126*	132*
AST	84	81	80	90	84	74	75	86
ALT	33	45*	91*	104*	33	47*	99*	98*
ALP	91	97	103	117	91	105	84	95
T-Bili	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
D-Bili	0	0	0	0	0	0	0	0
T-Prot	6.8	7.3*	8.0*	8.0*	6.8	7.3	7.9*	7.8*
Alb	3.9	4.3*	4.8*	4.8*	3.9	4.3*	4.8*	4.6*
Phos	6.1	6.5	6.6	6.4	6.1	6.7	6.4	7.2*
Calc	9.8	10.4*	10.8*	10.9*	9.8	10.5*	10.8*	10.8*
Glob	2.9	3.1	3.2*	3.2*	2.9	2.9	3.2*	3.1*
A:G	1.4	1.4	1.5*	1.5*	1.4	1.5*	1.5*	1.5*

Comparison of Megace and NCD on Clinical Chemistry Parameters in Female Rats in 3-Month Toxicity Study on Day 84								
	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
Na	143	143	142	143	143	143	143	143
K	5.0	5.0	5.2	4.8	5.0	5.0	4.9	5.1
Cl	103	102	101	101*	103	103	101	102
UN	15	12*	11*	130*	15	12*	11*	11*
Glucose	102	111	119*	110	102	117*	121*	112*
Creatine	0.9	0.9	0.8	0.8	0.9	0.8	0.8	0.8
Uric A	0	0	0	0	0	0	0	0
TG	85	143*	275*	292*	85	157*	153*	356*
Chol	63	91*	114*	119*	63	84	104*	135*
AST	94	89	97	118	94	110	82	127
ALT	40	60*	85*	110*	40	83*	78*	131*
ALP	40	60	66*	82*	40	66	62	71*
T-Bili	0.3	0.2*	0.2*	0.2*	0.2	0.3*	0.2*	0.2*
D-Bili	0	0	0	0	0	0	0	0
T-Prot	7.5	7.4	7.5	7.6	7.5	7.3	7.7	7.8
Alb	4.5	4.4	4.5	4.5	4.5	4.4	4.6	4.7
Phos	5.6	6.3*	6.6*	6.8*	5.6	6.9*	6.6*	7.0*
Calc	10.3	10.2	10.4	10.5	10.3	10.4	10.6	10.6
Glob	3.0	3.0	3.0	3.1	3.0	2.9	3.1	3.1
A:G	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Urinalysis:

In males, Both Megace and NCD increased pH at all doses with decreases in ketones on Day 29 as shown below. Bld significantly increased in the HD NCD formulation. On Day 78 ketones were still reduced by Megace and by the LD and MD of NCD formulation. Both Megace and NCD Megestrol acetate increased protein in the MD and HD groups, which indicated drug related changes.

In females, there were significant decreases in pH in LD Megace and MD NCD Megestrol acetate groups with a significant decrease in bilirubin in all treated females. No ketones were affected by neither Megace nor NCD Megestrol acetate on Day 29. On Day 78 there were changes in any parameters except specific gravity which was reduced by Megace (MD and HD) and Megestrol acetate (MD group) as shown below.

**Appears This Way
On Original**

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley Date : 13-DEC-04
 Study : 04-613-VL - Toxicology TABLE URI-SUM Time : 13:53
 Species: Rat 3 WEEK INTERVAL Page : 1
 Sex : Male

Group Means
 Nominal days in study 29

M A L E S		pH	Pro mg/dL	Glu mg/dL	Ket mg/dL	Bil	Bld	Uro Eu/dL	Sp.Gr.	Nit
CONTROL	Mean	8.1	99	0	11	0	0.3	0.2	1.038	0
	SD	0.4	78	0	5	0	0.5	0.0	0.011	0
	n	10	10	10	10	10	10	10	10	10
13.3 MEGACE	Mean	8.6*	65	0	3*	0	0.3	0.2	1.038	0
	SD	0.4	37	0	3	0	0.6	0.0	0.013	0
	n	10	10	10	10	10	10	10	10	10
40 MEGACE	Mean	8.7*	99	0	2*	0	0.4	0.2	1.028	0
	SD	0.3	78	0	3	0	0.7	0.0	0.005	0
	n	10	10	10	10	10	10	10	10	10
66.5 MEGACE	Mean	8.8*	106	0	4*	0	0.9	0.2	1.033	0
	SD	0.3	74	0	2	0	0.7	0.0	0.008	0
	n	10	10	10	10	10	10	10	10	10
13.3 NCD	Mean	8.8*	113	0	6*	0	0.5	0.3	1.038	0
	SD	0.4	69	0	6	1	0.6	0.3	0.010	0
	n	10	10	10	10	10	10	10	10	10
40 NCD	Mean	8.8*	133	0	2*	0	0.2	0.3	1.040	0
	SD	0.3	91	0	3	0	0.3	0.3	0.008	0
	n	10	10	10	10	10	10	10	10	10
66.5 NCD	Mean	8.6*	192	0	3*	0	1.6*	0.4	1.035	0
	SD	0.4	117	0	3	0	1.0	0.3	0.015	0
	n	10	10	10	10	10	10	10	10	10

Statistics: Anova + Dunnett's tests. (Two-Sided) * P<5% ; Exp.Unit = Animal

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley Date : 13-DEC-04
 Study : 04-613-VL - Toxicology TABLE URI-SUM Time : 13:54
 Species: Rat 3 WEEK INTERVAL Page : 1
 Sex : Female

Group Means
 Nominal days in study 29

F E M A L E S		pH	Pro mg/dL	Glu mg/dL	Ket mg/dL	Bil	Bld	Uro Eu/dL	Sp.Gr.	Nit
CONTROL	Mean	7.6	58	0	2	1	0.0	0.3	1.040	0
	SD	0.4	46	0	2	1	0.0	0.3	0.028	0
	n	10	10	10	10	10	10	10	10	10
13.3 MEGACE	Mean	8.4*	28	0	2	0*	0.0	0.2	1.028	0
	SD	0.4	26	0	3	0	0.0	0.0	0.013	0
	n	10	10	10	10	10	10	10	10	10
40 MEGACE	Mean	8.0	23	0	2	0*	0.1	0.2	1.024	0
	SD	0.2	11	0	3	0	0.3	0.0	0.009	0
	n	10	10	10	10	10	10	10	10	10
66.5 MEGACE	Mean	8.0	28	0	1	0*	0.1	0.2	1.023	1
	SD	0.2	27	0	2	0	0.2	0.0	0.007	1
	n	10	10	10	10	10	10	10	10	10
13.3 NCD	Mean	7.9	42	0	2	0*	0.2	0.0	0.013	0
	SD	0.6	42	0	3	0	0.3	0.0	0.013	0
	n	10	10	10	10	10	10	10	10	10
40 NCD	Mean	8.3*	15	0	2	0*	0.0	0.2	1.024	0
	SD	0.3	10	0	2	0	0.0	0.0	0.007	0
	n	10	10	10	10	10	10	10	10	10
66.5 NCD	Mean	8.0	57	0	2	0*	0.0	0.2	1.029	1
	SD	0.5	91	0	3	0	0.0	0.0	0.005	1
	n	10	10	10	10	10	10	10	10	10

Appears This Way
 On Original

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley Date : 13-DEC-04
 Study : U1-S12-VL Toxicology TABLE UR1-SUM Time : 13:54
 Species: Rat TERMINATION INTERVAL Page : 1
 Sex : Male
 Group Means
 Nominal days in study 78

M A L E S		pH	Pro mg/dL	Glu mg/dL	Ket mg/dL	Bil	Bld	Uro Bu/dL	Sp.Gr.	Nit
CONTROL	Mean	8.1	65	0	8	0	0.4	0.2	1.034	1
	SD	0.3	37	0	5	0	0.9	0.0	0.012	1
	n	10	10	10	10	10	10	10	10	10
13.3 MEGACE	Mean	8.6*	112	0	2*	0	0.4	0.2	1.034	1
	SD	0.3	104	0	3	0	0.9	0.0	0.010	0
	n	10	10	10	10	10	10	10	10	10
40 MEGACE	Mean	8.4	193*	0	3*	0	0.8	0.2	1.033	1
	SD	0.4	115	0	3	0	0.9	0.0	0.008	0
	n	10	10	10	10	10	10	10	10	10
66.5 MEGACE	Mean	8.1	273*	0	2*	0	1.4	0.2	1.026	1
	SD	0.3	85	0	3	0	1.2	0.0	0.008	0
	n	10	10	10	10	10	10	10	10	10
13.3 NCD	Mean	8.7*	173	0	3*	0	0.2	0.2	1.037	1
	SD	0.4	111	0	3	0	0.3	0.0	0.009	0
	n	10	10	10	10	10	10	10	10	10
40 NCD	Mean	8.4	260*	0	3*	0	0.8	0.2	1.035	0
	SD	0.3	84	0	3	0	1.0	0.0	0.011	1
	n	10	10	10	10	10	10	10	10	10
66.5 NCD	Mean	8.2	253*	0	4	0	1.1	0.2	1.034	1
	SD	0.3	100	0	2	0	1.1	0.0	0.014	0
	n	10	10	10	10	10	10	10	10	10

Statistics: Anova + Dunnett's tests. (Two-Sided) * P<=5% ; Exp.Unit = Animal

Three Month Oral Dose Toxicity Study with Toxicokinetics of Megace and PAR NCD Megestrol Acetate in Sprague Dawley Date : 13-DEC-04
 Study : U1-S12-VL Toxicology TABLE UR1-SUM Time : 13:54
 Species: Rat TERMINATION INTERVAL Page : 1
 Sex : Female
 Group Means
 Nominal days in study 78

F E M A L E S		pH	Pro mg/dL	Glu mg/dL	Ket mg/dL	Bil	Bld	Uro Bu/dL	Sp.Gr.	Nit
CONTROL	Mean	7.5	23	0	1	0	0.2	0.3	1.034	1
	SD	0.3	11	0	1	0	0.3	0.3	0.014	1
	n	10	10	10	10	10	10	10	10	10
13.3 MEGACE	Mean	7.6	30	0	2	0	0.0	0.2	1.028	1
	SD	0.4	27	0	1	0	0.0	0.0	0.008	0
	n	10	10	10	10	10	10	10	10	10
40 MEGACE	Mean	7.4	44	0	1	0	0.3	0.2	1.021*	1
	SD	0.5	40	0	2	0	0.4	0.0	0.009	0
	n	10	10	10	10	10	10	10	10	10
66.5 MEGACE	Mean	7.6	46	0	2	0	0.2	0.2	1.018*	1
	SD	0.4	47	0	2	0	0.3	0.0	0.005	0
	n	10	10	10	10	10	10	10	10	10
13.3 NCD	Mean	7.6	28	0	2	0	0.2	0.2	1.025	1
	SD	0.5	27	0	3	0	0.3	0.0	0.013	0
	n	10	10	10	10	10	10	10	10	10
40 NCD	Mean	7.8	31	0	1	0	0.0	0.2	1.020*	1
	SD	0.3	38	0	2	0	0.0	0.0	0.008	0
	n	10	10	10	10	10	10	10	10	10
66.5 NCD	Mean	7.5	83	0	3	0	0.2	0.2	1.025	1
	SD	0.3	123	0	3	0	0.7	0.0	0.007	0

Appears This Way
On Original

Gross pathology: Megace reduced the size of the adrenal glands, which was consistent with the decreased organ weights of all doses in both sexes. There was decreased size of testes, epididymides, prostate glands and seminal vesicles in the MD and HD group males. A few animals in the LD group did not show the symptoms. There was similar reduction in adrenal gland at all doses and in both sexes after NCD Megestrol treatment. As the case with Megace, NCD also decreased the size of reproductive organs. Both Megace and NCD Megestrol acetate did not produce gross abnormalities in other tissues in both sexes.

Organ weights (specify organs weighed if not in histopath table):

In male rats both Megace and NCD Megestrol acetate decreased the weights of adrenal gland, testes, and prostate glands in the test articles dose-dose dependent manner. The weights of spleen were also affected, although the magnitude was slight as shown below. In female rats, the two substances decreased the weights of adrenal gland, ovary and uterus. The weights of spleen were also reduced slightly while the weight of liver was slightly increased, which is different from the males.

	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
B. Wt.	515	496	419	420	515	459	437	415
Adrenal	0.064	0.026	0.015	0.014	0.064	0.029	0.016	0.016
Brain	2.2	2.1	2.1	2.0	2.2	2.1	2.1	2.0
Heart	1.6	1.5	1.4	1.4	1.6	1.5	1.4	1.4
Kidney	3.9	3.2	3.3	2.9	3.9	3.3	3.1	3.0
Liver	16.6	14.4	14.5	15.5	16.6	14.1	15.3	15.3
Lung	1.8	1.8	1.5	1.5	1.8	1.7	1.6	1.4
Spleen	0.86	0.68	0.54	0.49	0.86	0.61	0.54	0.52
Testes	3.6	3.2	1.7	1.0	3.6	3.0	1.4	1.0
Pituitary	0.013	0.013	0.010	0.012	0.013	0.015	0.012	0.010
Thymus	0.387	0.392	0.366	0.473	0.387	0.373	0.475	0.504
Prostate	1.356	0.627	0.263	0.225	1.356	0.693	0.264	0.247
@Dose in mg/kg/day.								

Comparison of Megace and NCD on Organ Weight in Female Rats in 3-Month Toxicology Study								
	Megace				NCD Megestrol acetate			
Dose@	0	13.3	40	66.5	0	13.3	40	66.5
B. Wt.	276	292	299	299	276	297	291	306
Adrenal	0.072	0.024	0.021	0.022	0.072	0.023	0.021	0.019
Brain	2.0	1.9	1.9	1.9	2.0	1.9	1.9	1.9
Heart	1.0	1.1	1.1	1.1	1.0	1.0	1.1	1.2
Kidney	2.2	2.1	2.1	2.3	2.2	2.1	2.2	2.4
Liver	9.6	8.8	10.4	11.6	9.6	9.9	10.9	12.8
Lung	1.4	1.3	2.1	1.2	1.4	1.3	1.2	1.3
Ovary	0.137	0.097	0.087	0.082	0.137	0.086	0.081	0.076
Spleen	0.597	0.493	0.484	0.484	0.597	0.531	0.503	0.464
Pituitary	0.016	0.016	0.012	0.011	0.016	0.012	0.013	0.012
Thymus	0.263	0.318	0.389	0.498	0.263	0.334	0.315	0.368
Uterus	0.720	0.461	0.388	0.302	0.720	0.389	0.355	0.346

@Dose in mg/kg/day.

Histopathology: Adequate Battery: yes (x), no ()—explain
Peer review: yes (x), no ()

Both Megace and NCD megestrol acetate induced significant histopathological changes in both male and female rats. Atrophy in adrenal glands, hypocellularity in femur and sternum bone, renal hyperplasia, hyperplasia in mammary gland, hepatic hypertrophy and fatty infiltration in liver are some of many examples as shown in two tables below. Spermatid depletion in epididymis and atrophy in prostate, pituitary glands, testis and seminal vesicle, and thymus atrophy were observed in males after the treatment with Megace or NCD formulation. In females, sex organ-related changes such as corpus luteum depletion in ovary, uterus atrophy, cervix and vaginal mucification were observed after both the two drugs.

The two formulations produced qualitatively similar responses in many histopathological parameters both in males and females. However, the incidences of sinus hemorrhage in mesenteric lymph node were slightly higher in NCD formulation in males, although the observation was not dose dependent. In females, the incidences of retinal degeneration and atrophy, fibrosis in eye were observed only after NCD formulation, not after Megace or in the control groups. However, the severity was minimal to mild and the effects were not test article dose dependent. Thus, it is safe to say that the histopathological effects of Megace and NCD formulation were similar both in male and female rats.

Histopathologic Effects of Megace and NCD Megestrol Acetate in 3-Month Toxicology Study in Male Rats@							
Observations	Drug	Megace			NCD Megestrol acetate		
	C	13.3	40.0	66.5	13.3	40.0	66.5
Adrenal, atrophy	0	3",7*	10*	9*	5",5*	10*	8*
Adrenal, cortex congestion	0	0	2	0	0	0	0
Bone, femur hypocellularity	0	6, 4'	1,5',3",1*	6",4*	5,3',1",1*	1',8",1*	2',6",2*
Bone, Sternum, hypocellularity	0	1,2'	5,3',2*	1,3',6"	1,2'	1,3',6"	5',5"
Epididymis, Spermatid depl.	0	0	1,3",5*	10"	0	1,1',8"	1,9"
Sperm granulose	0	0	0	1	0	0	0
Eye, hemorrhage	1'	0	1*	0	0	0	0
Eye, inflammation	1'	0	0	1'	0	0	0
Eye, fibrosis	1',1"	0	1"	1"	0	0	0
Fat, acinar cell degeneration	6	0	0	2	0	0	2
Cardiomyopathy	3	0	0	2	0	0	4
Kidney, nephropathy	5	3	6,1',1"	6,4"	5	6,3'	5,5'
Kidney, hydronephrosis	0	0	1'	0	0	1"	0
Kidney, hyperplasia	0	0	2	2	0	5	2
Kidney, inflammation	0	1'	0	0	0	1'	0
Kidney, mineralization	0	0	2	3	0	5	3
Liver, hypertrophy	0	0	3	3	1	2	3
Liver, inflammation	6,3'	7	3	3	4	1	0
Liver, fatty infiltration	0	1	3,3'	2', 4"	1	1, 5'	6,1*
Lung, inflammation	1	0	0	0	0	0	2
Lung, artery, hypertrophy	3	0	0	4,1"	0	0	4
LN, mesenteric, lymphocytic depl	2	3	4,1',1"	2,4'	1	5,2'	5,5'
Lymph node, sinus hemorrhage	0	0	0	0	1, 1'	1'	0
LN, mast cell infiltration	2,1	7	3,2	9	4	7,3	4,4
LN, mandibular lymphocytic dep	1	1	2',2",2*	5',2",1*	2	2,5',3"	2',8"
LN, mandibular medulla hemor	2	0	0	1,1'	0	2	1
LN, mandibular, plasmacytic inf	2,6'	2,3',3"	2,1',1"	3,3',1"	4,2',1"	5'	4,6'
Mammary gland, atrophy	1	3,2',2"	5,3',1"	2',1"	3,1',3"	2,6',2"	4,1',1"
Nerve, optic, degeneration	2*	0	0	1	0	0	0
Pituitary gland,	0	0	5	9	2	8	8,2'

atrophy							
Prostate, atrophy	0	4,1*	2',3'',5*	1'',8*	2,1',2*	1',5'',4*	10*
Seminal vesicle, atrophy	0	1,2'1*	9*	9*	4,2*	1'',9*	10*
Spleen, lymphocytic dep	2	7	7,2'	3,2',3''	2	5,5'	7,2',1''
Spleen, hematopoiesis	0	3	4,1'	7	2	6,3'	6
Testis, atrophy	0	0	2,5'',2*	10*	2'	1,1'',8*	1,9*
Testis, seminifer- ous tubule, deg	0	1	0	0	0	1'	0
Thymus, atrophy	0	0	3,2',5''	1,6',3''	3	3,4',3''	1,2',5'',1*

@In all groups, 10 rats were examined except a few HD groups of Megace and NCD. Dep., Inf., and Deg. indicate depletion, inflammation and degeneration, respectively. Severity score: ', '', and * indicate mild, moderate, and marked, respectively. No sign means minimal.

Histopathologic Effects of Megace and NCD Megestrol Acetate in 3-Month Toxicology Study in Female Rats@							
Observations	Drug	Megace			NCD Megestrol acetate		
		C	13.3	40.0	66.5	13.3	40.0
Adrenal, atrophy	0	10*	10*	10*	10*	9*	9*
Adrenal, cortex congestion	0	2	0	0	0	0	0
Bone, femur hypocellularity	0	5, 3'	4, 5', 1''	2, 7', 1''	7	5, 4'	2, 6' 1''
Bone, Sternum, hypocellularity	0	4, 2'	3, 4', 2''	1, 7', 2''	6	7, 2', 1''	4, 5'
Bone, vertebra, anomaly	0	0	0	0	1	0	0
Cervix, mucification	0	1,1',4'',4*	2',6'',2*	1,1',3'',5*	4',5'',1*	5'', 5*	1,5',1'',2*
Eye, retina deg.	0	0	0	0	0	1	1'
Eye, retinal, atrophy	0	0	0	0	0	0	1
Eye, fibrosis	0	0	0	0	0	1	0
Fat, fibrosis	0	0	0	0	1	0	0
Fat, hemorrhage	0	0	0	0	1	0	0
Cardiomyopathy	0	0	0	2	0	0	4
Intestine, rectum, edema	0	0	0	0	0	0	1'
Kidney, nephropathy	0	0	0	2, 1'	0	1	4
Kidney, hydronephrosis	0	0	0	1	0	0	0
Kidney, hyperplasia	0	8	3	2, 1'	4	4	1
Kidney, pelvis inflammation	0	0	0	1, 1''	0	0	0
Kidney, mineralization	2	7, 1'	3	5, 1'	5	2	5, 1'
Liver, hypertrophy	0	3	3	6	0	4	7
Liver, inflammation	3, 1'	0	4	2	3	2	0

Liver, fatty infiltration	0	3	6, 1'	3,2',1'',1*	5	1, 3'	2,5',1'',1*
Lung, artery mineralization	5	0	0	1	0	0	3
Lung, artery, hypertrophy	3	0	0	1'	0	0	1
Lung, alveolar histiocytosis	0	0	0	1,1'	0	0	4
LN, mesenteric lymphocytic dep	0	2,2'	1,1'	3,3',2''	2	2,1'	2, 4',1''
LN, mast cell infiltration	3	9	10	8,2'	8	9	6,2'
LN, mandibular lymphocytic dep	0	5', 4''	1, 6', 3''	1', 6'', 2*	8', 2''	1, 2', 7''	3', 3'', 1*
LN, mandibular medulla hemor	0	0	1'	0	0	0	1, 1'
LN,mandibular, plasmacytic inf	4, 4', 1''	6,2'	6, 2'	3, 4' 1''	4, 5'	5, 4'	5, 3', 1''
Mammary gland, hyperplas	0	1,5',4''	2', 5''	1, 6', 3''	3', 7''	2', 8''	2, 3', 4''
Nerve, optic, degeneration	1'	0	0	0	0	0	1
Ovary, corpus luteum, dep.	0	1,2',7''	1',1'',8*	10*	1', 9*	1'', 9*	9*
Pancreas, sinusoid dilation	0	0	0	0	0	0	1
Pituitary gland, cyst, pars distali	0	0	0	0	0	0	1
Stomach, gland, Dilation	0	0	0	0	0	0	1
Spleen, lymphocytic dep	4,2'	4, 6'	3, 7'	1, 6' 3''	3, 4'	3, 5', 2''	2, 4', 2''
Spleen, hematopoiesis	4	6, 4'	5, 5'	5	2, 5'	3, 7'	9
Thymus, atrophy	0	7	6, 2', 1''	2,3', 3''	4, 5	3,3',3''	1,7'
Thyroid gland, cyst	2	0	0	1	0	0	4
Uterus, lumen, dilation	1, 1', 2''	1''	0	0	0	0	0
Uterus, atrophy	0	9, 1'	10	9, 1'	9, 1'	9, 1'	9
Vagina, mucification	0	10*	1'', 9*	10*	10*	1'', 9*	1, 8*

@In all groups, 10 rats were examined except a few HD groups of Megace and NCD. Dep., Inf., and Deg. indicate depletion, inflammation and degeneration, respectively. Severity score: ', ', and * indicate mild, moderate, and marked, respectively. No sign means minimal.

Toxicokinetics:

In the fasted animals, mean plasma concentrations of Megace were smaller than those of NCD Megestrol acetate after 90-day in both sexes at 0.5- and 1 hour sampling time. The differences were disappeared after 3 hours and longer, which may indicate that the rate of NCD preparation absorption is faster than that of Megace as shown below. It appears that the rate of drug absorption in females was slightly faster than the males in the LD group.

Tmax, Cmax and AUC₀₋₇₂ were comparable 90 days after the treatment, although both Cmax and AUC values were quite variable as shown below.

Mean Plasma Concentrations (ng/ml) of Megace after 90-Day Treatment in Rats									
Dose*	Sex	0.5#	1	3	6	12	24	48	72
13.3	M	44	94	279	492	62	68	2	0
	F	262	601	748	462	214	81	11	14
40	M	282	1097	1340	922	307	106	18	13
	F	367	1089	1378	841	401	73	25	18
66.5	M	437	894	2199	1650	771	216	25	21
	F	384	696	2673	1440	726	194	27	16
Mean Plasma Concentrations (ng/ml) of NCD Megestrol acetate after 90-Day Treatment in Rats									
13.3	M	560	697	412	282	79	4	27	0
	F	1052	881	413	318	265	59	16	14
40	M	1499	2552	1662	1436	396	147	54	8
	F	1026	980	1248	1099	478	102	34	8
66.5	M	1629	2613	2541	1812	613	277	80	19
	F	1505	2287	2828	1908	961	218	55	14

* Dose in mg/kg/day. #Indicates time (hour) after test-article treatment

Mean TK Values of Megace after 1-, 30-, 90-Day Treatment in Rats										
Dose*	Sex	Day 1			Day 30			Day 90		
		Tmax	Cmax	AUC	Tmax	Cmax	AUC	Tmax	Cmax	AUC
13.3	M	3	196	1221	3	384	2112	6	492	4836
40	M	3	675	5040	3	971	6089	3	1340	14254
66.5	M	3	1077	7516	3	1433	12360	3	2199	25026
13.3	F	3	995	6805	3	889	6654	3	748	8758
40	F	6	1498	14639	3	1986	11546	3	1578	14504
66.5	F	3	2168	23470	3	2539	16762	3	2673	25079
Mean TK Values of NCD Megestrol acetate after 1-, 30-, 90-Day Treatment in Rats										
13.3	M	0.5	266	1232	0.5	633	2772	1	697	4555
40	M	3	1546	9809	3	2276	11657	1	2552	22131
66.5	M	3	3328	38835	3	3981	25541	1	2613	31232
13.3	F	1	1055	7033	3	962	7624	0.5	1052	8075
40	F	6	2373	23489	3	2128	15433	3	1248	16812
66.5	F	3	3429	37813	3	3404	26674	3	2828	31540

*Dose was in mg/kg/day. Units of Tmax, Cmax and AUC₀₋₇₂ were hour, mg/kg/day and ng.h/ml, respectively.

Other: The pharmacology and toxicology profiles of two formulations of Megace and NCD Megestrol acetate are quite similar as presented above with a few exceptions. The active component in both formulations is steroid, which produced signs of immunosuppression with significant decreases in bone marrow cellularity with lymphocytic depletion. The two formulations also produced atrophy in several organs such as adrenal glands in both sexes, mammary and pituitary glands, and seminal vesicle and testis in males. In females, retinal atrophy, fibrosis, and degeneration were observed in NCD Megestrol acetate treated MD and HD groups. Thus, therapeutic exposure ratios were compared in rats and human based on AUC₀₋₇₂ values at a clinical human dose of

NCD Megestrol acetate (585 mg/day). The AUC ratios were also calculated for Megace for male and female rats as shown below. NOAELs for Megace as well as NCD Megestrol acetate were ≤ 13.3 mg/kg/day, based on histopathology findings in the 3-month toxicology study in rats. The AUC exposure multiples at the NOAEL dose are approximately 0.3 and 0.6, respectively in male and female rats for Megace and NCD Megestrol acetate. The HD doses provides exposure multiples of approximately 2 for both drug products in males and females as shown below.

Human Multiples of Megace and NCD Megestrol Acetate in 3-Month Toxicology Study in Rat@				
Drug dose in rats(mg/kg/day)	Megace (800 mg/day)		NCD Megestrol acetate(585 mg/day)	
	Male	Female	Male	Female
13.3	0.3	0.6	0.3	0.6
40.0	0.9	1.0	1.5	1.1
66.5	1.6	1.7	2.1	2.1

@Based on human AUC₀₋₇₂ values of 18,274 and 14,743 h.ng/ml, respectively after indicated doses of two formulations in healthy volunteers under fed conditions.

Histopathology inventory (optional)

Study	04-S12-VL		
Species	Rat		
Adrenals	X*		
Aorta	X		
Bone Marrow smear	X		
Bone (femur)	X		
Brain	X*		
Cecum	X		
Cervix	X		
Colon	X		
Duodenum	X		
Epididymis	X		
Esophagus	X		
Eye	X		
Fallopian tube			
Gall bladder			
Gross lesions	X		
Harderian gland	X		
Heart	X*		
Ileum	X		
Injection site			
Jejunum	X		
Kidneys	X*		

Lachrymal gland				
Larynx				
Liver	X*			
Lungs	X*			
Lymph nodes, cervical				
Lymph nodes mandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity				
Optic nerves	X			
Ovaries	X*			
Pancreas				
Parathyroid	X			
Peripheral nerve	X			
Pharynx				
Pituitary	X*			
Prostate	X*			
Rectum	X			
Salivary gland	X			
Sciatic nerve				
Seminal vesicles	X			
Skeletal muscle	X			
Skin	X			
Spinal cord	X			
Spleen	X*			
Sternum	X			
Stomach	X			
Testes	X*			
Thymus	X*			
Thyroid	X			
Tongue	X			
Trachea	X			
Urinary bladder	X			
Uterus	X*			
Vagina	X			
Zymbal gland				

X, histopathology performed

*, organ weight obtained

2.6.6.4 Genetic toxicology

No mutagenesis data are currently available.

2.6.6.5 Carcinogenicity

Carcinogenesis Data on carcinogenesis were obtained from studies conducted in rats, dogs, and monkeys treated with Megestrol acetate. No males were used in the dog and monkey studies. In 2-year carcinogenicity study Sprague Dawley rats received Megestrol acetate with food at doses of 1.5, 3.9 and 10 mg/kg/day. Pituitary tumors were observed

in female rats treated with the mid and high dose groups (approximately 0.05 and 0.1 times therapeutic exposures based on body surface area comparison).

In female beagles, Megestrol acetate at doses of 0.01, 0.1 or 0.25 mg/kg/day was administered for up to 7 years. Megestrol acetate induced both benign and malignant tumors of the breast of the mid and high dose groups. The mid and high doses represent approximately 0.04 and 0.1 times therapeutic exposure based on body surface area comparison. 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. The high dose is approximately 0.1 times therapeutic exposure based on body surface area comparison. 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 section)

2.6.6.6 Reproductive and developmental toxicology

Perinatal/postnatal (segment III) toxicity studies were performed in rats with doses of 0.05 to 12.5 mg/kg/day. The high dose is approximately 2 times therapeutic exposure based on body surface area comparison. In these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated female rats was impaired. Similar results were obtained in dogs. Pregnant rats treated with Megestrol acetate at doses of 5 and 12.5 mg/kg showed a reduction in fetal weight and number of live births, and feminization of male fetuses. The high dose is approximately 2 times therapeutic exposure based on body surface area comparison. No toxicity data are currently available on male reproduction (spermatogenesis).

2.6.6.7 Local tolerance

NA

2.6.6.8 Special toxicology studies

NA

2.6.6.9 Discussion and Conclusions

Pharmacology and toxicology profiles of Megace is equivalent to those of NCD Megestrol acetate formulation in the 3-month bridging toxicology study except for increased incidences of retinal degeneration and fibrosis in female rats after NCD Megestrol acetate treatment.

2.6.6.10 Tables and Figures

NA

2.6.7 TOXICOLOGY TABULATED SUMMARY

NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Pharmacology and toxicology profiles of Megace is equivalent to those of NCD Megestrol acetate formulation in the 3-month bridging toxicology study except for increased incidences of retinal degeneration and fibrosis in female rats after NCD Megestrol acetate treatment. Since the incidence in females was low and comparable findings were not observed in the retina of male rats. The significance of the findings is unclear.

Unresolved toxicology issues (if any): None

Recommendations:

Preclinical pharmacology and toxicology recommends approval of NDA 21-778, based on the preclinical findings for Megestrol Acetate NanoCrystal Dispersion (NCD) Oral Suspension as reviewed in this document.

Suggested labeling: Recommendations on labeling

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Mutagenesis:

No mutagenesis data are currently available.

Impairment of Fertility:



Pregnancy:



Nursing Mothers:

Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megestrol acetate oral suspension is required.

Signatures (optional):

Reviewer Signature Herman Rhee, Ph.D.

Supervisor Signature _____ Concurrence Yes No

APPENDIX/ATTACHMENTS : NONE.

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

/s/

Herman Rhee
3/14/05 10:06:35 AM
PHARMACOLOGIST

Jeri El Hage
3/15/05 11:00:22 AM
PHARMACOLOGIST