

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21945Orig1s000

PHARMACOLOGY REVIEW(S)

Comments on NDA 21-945 Makena Gestiva

From: Abigail Jacobs

Date: Jan 6, 2011

1. I agree that there are no outstanding pharm/tox issues for this NDA.
2. I discussed some possible editorial changes to the carcinogenesis section of the labeling with the Division. The reviewer can address the suggestions as he sees appropriate.

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/s/

ABIGAIL ABBY C C JACOBS
01/06/2011

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: **21-945**
SERIAL NUMBER: **Class 1 Resubmission**
DATE RECEIVED BY CENTER: **July 12, 2010**
PRODUCT: **17 α -Hydroxyprogesterone Caproate**
INTENDED CLINICAL POPULATION: **Pregnant women with recurrent premature labor**
SPONSOR: **Hologic, Inc.**
DOCUMENTS REVIEWED: **Vol. 1**
REVIEW DIVISION: **Division of Reproductive and Urologic Products**
PHARM/TOX REVIEWER: **Alex Jordan, PhD**
PHARM/TOX SUPERVISOR: **Lynnda Reid, PhD**
DIVISION DIRECTOR: **Scott Monroe, MD**
PROJECT MANAGER: **Charlene Williamson**

Date of review submission to Division File System (DFS): November 24, 2010

This NDA was submitted previously and was given a complete response letter dated January 23, 2009 due primarily to clinical deficiencies. There were no nonclinical studies requested or submitted in this Class 1 Resubmission.

Following our recommendations, Sponsor changed the label in section 13.1 Carcinogenicity, Mutagenicity, Impairment of fertility, to reflect the correct exposure multiple of the rat multi-generational study. Also, under 8.1 Pregnancy, Sponsor moved the clinical data to the beginning of the section followed by the animal data.

Recommendation: The label for 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth is satisfactory from the standpoint of pharm/tox.

Alex Jordan, PhD

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/s/

ALEXANDER W JORDAN
11/24/2010

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

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PHARM/TOX REVIEWER: **Alex Jordan, PhD**
PHARM/TOX SUPERVISOR: **Lynnda Reid, PhD**
DIVISION DIRECTOR: **Scott Monroe, MD**
PROJECT MANAGER: **Charlene Williamson**

Date of review submission to Division File System (DFS): August 11, 2010

This NDA was submitted previously and was given a complete response letter dated January 23, 2009 due primarily to clinical deficiencies. There were no nonclinical studies requested or submitted in this Class 1 Resubmission.

The nonclinical sections of the label are identical to those agreed upon previously except for one change that was requested but not made. In section 13.1 Carcinogenicity, Mutagenicity, Impairment of fertility, the exposure multiple of the rat multi-generational study should be changed from (b) (4) to 5.

Recommendation: I recommend approval of 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth.

Alex Jordan, PhD

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	ORIG-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

ALEXANDER W JORDAN
08/11/2010



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: **21-945**
SERIAL NUMBER: **N-000**
DATE RECEIVED BY CENTER: **June 16, 2008**
PRODUCT: **17 α -Hydroxyprogesterone Caproate**
INTENDED CLINICAL POPULATION: **Pregnant women with recurrent premature labor**
SPONSOR: **Cytoc Corp.**
DOCUMENTS REVIEWED: **Vol. 1**
REVIEW DIVISION: **Division of Reproductive and Urologic Products**
PHARM/TOX REVIEWER: **Alex Jordan, PhD**
PHARM/TOX SUPERVISOR: **Lynnda Reid, PhD**
DIVISION DIRECTOR: **Scott Monroe, MD**
PROJECT MANAGER: **Charlene Williamson**

Date of review submission to Division File System (DFS): October 14, 2008

This NDA was submitted previously and was not approved due to, in part, lack of a complete reproductive toxicology study. Sponsor was asked to complete a multigenerational reproductive study.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth.

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling: Under Pregnancy: The pregnancy category should be changed from (b) (4) to B.

The multiples for the mouse and rats studies should be changed from (b) (4) to 95 and 5, respectively. The mouse high dose was 833 mg/kg, converted to 2499 mg/m². The human dose is 250 mg or 5 mg/kg converted to 185 mg/m². The multiple is 13.5 but the mice were injected daily and the humans are injected once a week so I multiplied the multiple by 7 to get 95. The rats were injected every 6 days so I converted the high dose of 150 mg/kg to 900 mg/m² divided by the human dose of 185 mg/m² to get 5.

In the next paragraph, change (b) (4) to "There was embryoletality in rhesus monkeys but not in cynomolgus monkeys injected with 1 and 10 time the human dose equivalent every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either species."

Under Nonclinical Toxicology: Carcinogenesis, Mutagenesis, Impairment of Fertility: The sentence (b) (4) to HPC has not been adequately evaluated for carcinogenicity.

The exposure multiple of the rat multi-generational study should be changed from (b) (4) to 5.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: A multi-generational reproduction study in rats did not show any adverse effects of Gestiva on the health of the dams, fetuses, offspring, or second generation offspring.

B. Pharmacologic activity: 17 α -HPC was shown to help maintain pregnancy in pregnant rabbits but not in the pregnant rat, mare or squirrel monkey. It is not clear how 17 α -HPC exerts its effects on the uterus to prolong gestation but the mechanism does not seem to stem from direct uterine relaxation.

B. Nonclinical safety issues relevant to clinical use: none

Studies reviewed within this submission: multigenerational rat reproductive toxicity study

Studies not reviewed within this submission: none

Study title: An intramuscular multi-generation toxicity study in rats following in-utero exposure

Key study findings: No drug related adverse effects on any reproductive parameter

Study no.: 1409-002

Volume #, and page #: Vol. 1, pg 1

Conducting laboratory and location: (b) (4)

Date of study initiation: June, 2007

GLP compliance: yes

QA reports: yes (x) no ()

Drug, lot #, and % purity: 17 α -hydroxyprogesterone caproate, batch 904306, 99.8% pure

Methods

Doses: 5, 25, 150 mg/kg

Species/strain: CD [CrI:CD (SD)] female rats

Number/sex/group: 25 females/gp

Route, formulation, volume, and infusion rate: intramuscular injection, 0.6 ml/kg

Satellite groups used for toxicokinetics: none

Study design:

The study consisted of three phases, reproductive phases 1 and 2, and a teratology phase. Reproductive Phase 1 and 2: Treatment was to F₀ (first parental generation) only, and vehicle and test article were administered once on gestation day (GD) 8, 14, and 20 by IM injection for reproductive phase 1 and on GD 17 for reproductive phase 2 (presence of sperm or vaginal plug was designated GD 0). In both phases, dams were examined for clinical signs, BW and FC during gestation and lactation, parturition and offspring (F₁ and F₂) litter data, and success in rearing F₁ offspring to weaning. Observations of the F₁ offspring included survival at birth and during lactation, BW and sex at birth and during lactation, gross abnormalities and physical development, including pre-weaning reflex and sensory evaluations (for F₁ offspring, four pups of each sex were randomly selected and evaluated for various behavioral and development indices). After weighing on lactation day (LD) 4, each litter was reduced to the 8 randomly selected pups from LD 0. The pups were weaned on LD 21. On postnatal day (PND) 28, 25 male and 25 female F₁ pups were randomly selected from each group to continue on study for evaluation of sexual maturation (vaginal opening, preputial separation), behavioral (motor activity and learning and memory [step-through passive avoidance]), and reproductive and fertility assessments. The latter was evaluated by assessing sperm quality and quantity and by mating treated animals with naïve animals of similar weight and age (1 male: 1 female).

Mated F₁ females were allowed to deliver; the litters were evaluated, and euthanized on LD 4.

Teratology phase:

Pregnant females were injected on GD 6, 12 and 18 and were sacrificed on GD 20. The total number of implantations, early and late resorptions, viable and nonviable fetuses, sex and individual BW's of the fetuses were recorded. The total number of corpora lutea on each ovary were also recorded. All fetuses were given an external exam and approximately one-half of the fetuses in each litter were processed for visceral exam.

Animal Identification Reference Table						
		Computer Protocol Number 1409-002	Computer Protocol Number 1409-002-F1			
Phase	Group	F ₀ -F	F ₁ -M	F ₁ -F	N-M	N-F
Reproductive Phase 1	1	401-425	101-125	201-225	501-525	601-625
	2	426-450	126-150	226-250	526-550	626-650
	3	451-475	151-175	251-275	551-575	651-675
	4	476-500	176-200	276-300	576-600	676-700
Reproductive Phase 2	9	501-525	301-325	401-425	701-725	801-825
	10	526-550	326-350	426-450	726-750	826-850
	11	551-575	351-375	451-475	751-775	851-875
	12	576-600	376-400	476-500	776-800	876-900
Teratology Phase	5	601-625	NA	NA	NA	NA
	6	626-650	NA	NA	NA	NA
	7	651-675	NA	NA	NA	NA
	8	676-700	NA	NA	NA	NA
F ₀ -F = Parental F ₀ Females; F ₁ -M = F ₁ Offspring Males; F ₁ -F = F ₁ Offspring Females N-M – Naïve Males; N-F = Naïve Females NA = Not Applicable (Teratology Phase did not deliver F ₁ for mating)						

Results Reproductive phase I

Mortality: One LD animal found dead on day 25. Cause of death was not determined.

Clinical signs: None treatment related

Body weight: No differences between groups.

Food consumption: No differences

Toxicokinetics: Not done

Necropsy:

Reproductive Phase 1Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

(b) (4) Study Number 1409-002 Reproductive Phase 1
 17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	N	25	25	25	25
No. Females Pregnant	N	19	23	24	20
Females Delivering Litters ¹	N	19	23	24	20
	%	76.0	92.0	96.0	80.0
With Stillborn Pups ¹	N	1	2	3	0
	%	5.0	9.0	12.5	0.0
With All Stillborn ¹	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Gestation Length (Days)	Mean	21.9	22.0	21.8	22.0
	SD	0.23	0.21	0.38	0.32
	N	19	23	24	20
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	11.1	10.3	11.0	10.4
	SD	2.59	2.01	2.66	2.50
	N	19	23	24	20
Liveborn/Litter	Mean	11.0	10.2	10.9	10.4
	SD	2.56	1.90	2.70	2.52
	N	19	23	24	20
No. of Pups at Day 0 cont. Stillborn/Litter	Mean	0.1	0.2	0.1	0.0
	SD	0.23	0.65	0.34	0.00
	N	19	23	24	20
Gestation Index	%	100.0	100.0	100.0	100.0
	N	19	23	24	20
Stillborn Index	Mean %/Litter	0.40	1.37	1.26	0.00
	SD	1.765	5.041	3.578	0.000
	N	19	23	24	20
Total Implantation Scars/Litter	Mean	12.1	11.3	12.0	11.5
	SD	1.31	1.96	1.87	2.24
	N	19	23	24	20
No. Live Pups/Litter Day 4 (Preculling)	Mean	10.4	9.9	10.9	10.3
	SD	2.61	2.20	2.16	2.47
	N	19	21	23	20
Day 4 (Postculling)	Mean	7.6	7.7	7.9	7.7
	SD	1.43	0.96	0.73	0.98
	N	19	21	23	20
Day 7	Mean	7.6	7.7	7.8	7.7
	SD	1.43	0.97	0.60	0.98
	N	19	21	23	20
Day 14	Mean	7.6	7.6	7.7	7.7
	SD	1.43	0.97	0.62	0.98
	N	19	21	23	20
Day 21	Mean	7.6	7.6	7.7	7.7
	SD	1.43	0.997	0.62	0.98
	N	19	21	23	20

Sex Ratio (% Males per Animal)					
Pups Day 0	Mean %/Litter	57.03	48.23	49.00	47.84
	SD	17.541	17.223	17.006	16.735
	N	19	23	24	20
Pups Day 4 (Preculling)	Mean %/Litter	57.51	49.15	46.61	47.24
	SD	17.561	18.666	13.899	16.655
	N	19	21	23	20
Pups Day 4 (Postculling)	Mean %/Litter	55.26	51.98	48.66	49.38
	SD	14.016	14.045	8.900	13.126
	N	19	21	23	20
Pups Day 21	Mean %/Litter	55.26	51.90	49.79	49.38
	SD	14.016	13.960	9.622	13.126
	N	19	21	23	20
Pup Survival Indices					
Viability Index	Mean %/Litter	95.71	88.07	92.91	99.17
	SD	13.376	28.392	21.659	2.565
	N	19	23	24	20
Lactation Index	Mean %/Litter	100.00	98.81	98.15	100.00
	SD	0.000	3.760	6.666	0.000
	N	19	21	23	20

There were no effects on any fertility parameters.

(b) (4) Study Number 1409-002 Reproductive Phase 1
 17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Summary of F₁ Prewaning Pup Clinical Findings*

Observation	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Number of Animals Alive at Start of Interval	209	233	259	207
Animals with No Abnormalities Detected	205	226	245	202
Behavior/Activity				
Activity decreased	1/1	1/1	5/5	0/0
External Appearance				
Abdomen distended	1/1	0/0	0/0	0/0
Ear/portion of ear missing, Ear/right	0/0	0/0	1/1	0/0
Emaciated	1/1	0/0	0/0	0/0
Limb function impaired, Hind limb/left	0/0	0/0	1/1	0/0
Material around mouth, Red	0/0	0/0	1/1	0/0
Swelling, Entire body	0/0	0/0	2/2	0/0
Swelling, Hind limb/left	0/0	0/0	1/1	0/0
Pelage/Skin				
Abrasion(s), Cervical region	0/0	0/0	1/1	0/0
Abrasion(s), Cranial region	0/0	0/0	1/1	0/0
Abrasion(s), Dorsal surface	1/1	0/0	0/0	0/0
Abrasion(s), Hind foot/right	0/0	0/0	1/1	0/0
Abrasion(s), Hind limb/right	0/0	0/0	4/1	0/0
Abrasion(s), Thoracic region	0/0	0/0	1/1	0/0
Nodule, 1-5 mm, Abdominal region	1/1	0/0	0/0	0/0
Scabbed area, Abdominal region	0/0	1/1	0/0	0/0
Scabbed area, Cervical region	0/0	0/0	1/1	0/0
Scabbed area, Cranial region	0/0	0/0	2/2	0/0
Scabbed area, Dorsal surface	2/1	1/1	0/0	0/0
Scabbed area, Hind limb/left	0/0	0/0	2/1	0/0
Pelage/Skin				
Scabbed area, Nose/muzzle	0/0	2/1	0/0	0/0
Skin cold to touch	1/1	0/0	5/5	0/0
Skin discolored, Black, Hind limb/right	0/0	0/0	4/1	0/0
Skin discolored, Blue, Abdominal region	0/0	1/1	2/2	0/0
Skin discolored, Blue, Cervical region	0/0	1/1	0/0	1/1
Skin discolored, Blue, Cranial region	0/0	0/0	2/2	3/3
Skin discolored, Blue, Dorsal surface	0/0	1/1	0/0	0/0
Skin discolored, Blue, Hind foot/left	0/0	0/0	1/1	0/0
Skin discolored, Blue, Hind foot/right	0/0	0/0	1/1	0/0
Skin discolored, Blue, Nose/muzzle	0/0	0/0	1/1	0/0
Skin discolored, Gray, Entire body	0/0	0/0	1/1	0/0
Skin discolored, Gray, Thoracic region	1/1	0/0	0/0	0/0
Skin discolored, Pale, Entire body	0/0	1/1	0/0	1/1
Skin discolored, Red, Forelimb/left	0/0	0/0	2/2	0/0
Skin discolored, Red, Forelimb/right	0/0	0/0	2/2	0/0
Skin discolored, Red, Hind foot/right	0/0	0/0	1/1	0/0
Skin discolored, Red, Hind limb/left	0/0	0/0	3/3	0/0
Skin discolored, Red, Hind limb/right	0/0	0/0	1/1	0/0
Respiration				
Breathing difficult	1/1	0/0	4/4	0/0
Breathing slow	0/0	0/0	2/2	0/0

* - Number of times observed/Total number of animals affected

Physical development of F₁

(b) (4) Study Number 1409-002 Reproductive Phase 1
17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Static Righting Reflex (Days)	Mean	2.2	2.3	2.3	2.3
	SD	0.19	0.37	0.35	0.27
	N	19	22	23	20
Pinna Detachment (Days)	Mean	2.2	2.3	2.4	2.2
	SD	0.33	0.39	0.51	0.30
	N	19	21	23	20
Cliff Aversion (Days)	Mean	11.0	11.0	11.0	11.0
	SD	0.00	0.00	0.00	0.06
	N	19	21	23	20
Eye Opening (Days)	Mean	14.3	14.4	14.4	14.1
	SD	0.55	0.48	0.50	0.50
	N	19	21	23	20
Air Drop Righting Reflex (Days)	Mean	16.0	16.2	16.0	16.0
	SD	0.07	0.26	0.00	0.06
	N	19	21	23	20
Auditory Response Percent Pups Passing/Dam	Mean	100.0	100.0	98.8	100.0
	SD	0.00	0.00	5.21	0.00
	N	19	21	23	20

Sexual maturation of F₁

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Vaginal Opening (Days)	Mean	33.6	32.6	33.5	33.0
	SD	1.41	1.26	2.20	1.58
	No. of Pups Passing	25	25	25	25
Body Weight on Day Passed Vaginal Opening, g	Mean	128.3	118.2 ^a	124.1	129.0
	SD	11.93	11.04	19.13	14.39
	No. of Pups	25	25	25	25
Preputial Separation (Days)	Mean	43.3	43.9	44.8 ^a	43.9
	SD	1.97	2.31	2.12	2.28
	No. of Pups Passing	25	25	25	25
Body Weight on Day Passed Preputial Separation, g	Mean	241.3	241.9	248.0	253.2
	SD	21.28	25.18	21.79	26.74
	No. of Pups	25	25	25	25

No. - Number
SD - Standard Deviation

^aSignificantly different from control; (p<0.05)

Behavioral observations of F₁

Table 18 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Basic Movement (count)	0-5	1234.4	248.49	25	1217.4	235.73	25	1311.5	220.06	25	1224.3	163.54	25
	5-10	955.4	296.15	25	867.2	258.67	25	984.7	194.28	25	955.2	173.67	25
	10-15	774.9	216.06	25	643.1	202.86	25	794.0	235.98	25	760.4	175.36	25
	15-20	574.5	259.05	25	546.6	286.36	25	697.1	216.60	25	705.5	378.85	25
	0-20	3539.2	901.67	25	3274.3	868.41	25	3787.2	743.98	25	3645.4	690.84	25

Table 19 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Basic Movement (count)	0-5	1376.4	182.14	25	1333.5	162.05	25	1356.2	223.83	25	1392.8	221.12	25
	5-10	1058.8	160.11	25	1075.2	199.90	25	1188.7	227.67	25	1175.3	297.24	25
	10-15	840.7	235.93	25	837.0	262.47	25	935.8	196.46	25	936.1	264.61	25
	15-20	696.6	268.94	25	689.9	245.10	25	754.4	247.64	25	761.8	315.00	25
	0-20	3972.5	704.34	25	3935.6	673.88	25	4235.1	778.12	25	4265.9	964.51	25

(b) (4) Study Number 1409-002 Reproductive Phase 1
 17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Table 18 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fine Movement (count)	0-5	895.0	168.46	25	884.5	165.72	25	949.5	151.39	25	882.6	115.80	25
	5-10	741.8	215.54	25	671.0	184.19	25	756.9	138.66	25	732.4	116.46	25
	10-15	625.6	167.13	25	522.0	152.10	25	643.8	174.56	25	606.3	129.80	25
	15-20	481.5	201.62	25	452.8	217.91	25	570.1	159.36	25	566.6	278.86	25
	0-20	2743.9	664.56	25	2530.3	639.11	25	2920.2	532.73	25	2787.9	506.64	25

Table 19 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fine Movement (count)	0-5	976.6	132.21	25	934.0	116.29	25	960.0	162.60	25	987.3	155.65	25
	5-10	789.9	115.25	25	805.5	135.24	25	876.9	159.71	25	864.0	198.72	25
	10-15	651.3	165.55	25	647.3	179.88	25	714.4	135.80	25	715.2	178.43	25
	15-20	540.2	188.10	25	552.6	173.52	25	592.4	165.31	25	593.6	215.65	25
	0-20	2966.9	496.15	25	2939.3	462.86	25	3143.8	538.81	25	3160.2	652.79	25

(b) (4) Study Number 1409-002 Reproductive Phase 1
 17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Table 18 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Rearing (count)	0-5	30.4	8.47	25	30.0	9.37	25	35.4	10.69	25	32.8	10.72	25
	5-10	24.5	9.08	25	21.4	12.46	25	25.0	9.50	25	25.2	10.38	25
	10-15	15.2	6.98	25	11.3	7.53	25	15.1	7.77	25	17.0	7.18	25
	15-20	8.7	6.38	25	8.3	6.64	25	14.4 ^a	7.85	25	14.8 ^a	10.85	25
	0-20	78.8	22.50	25	71.3	28.75	25	89.8	28.59	25	89.7	32.70	25

Table 19 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Rearing (count)	0-5	40.7	9.67	25	39.2	12.60	25	41.2	14.35	25	41.6	11.02	25
	5-10	30.8	8.11	25	32.6	11.10	25	38.8	15.01	25	37.6	14.91	25
	10-15	21.9	11.24	25	22.6	12.32	25	28.1	11.61	25	27.1	12.90	25
	15-20	18.8	13.36	25	16.3	9.71	25	18.9	9.13	25	21.8	11.61	25
	0-20	112.2	36.42	25	110.8	38.17	25	127.0	43.04	25	128.1	43.13	25

(b) (4) Study Number 1409-002 Reproductive Phase 1
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Table 18 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Distance (cm)	0-5	2229.4	381.24	25	2224.0	371.68	25	2394.7	355.82	25	2227.5	270.28	25
	5-10	1688.2	481.08	25	1561.4	425.34	25	1757.0	315.71	25	1714.8	291.08	25
	10-15	1365.4	348.12	25	1153.2	354.52	25	1408.9	410.60	25	1347.2	303.06	25
	15-20	1009.6	444.32	25	964.1	502.96	25	1231.7	359.60	25	1239.9	655.34	25
	0-20	6292.6	1449.05	25	5902.8	1445.10	25	6792.3	1221.78	25	6529.4	1153.70	25

Table 19 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Distance (cm)	0-5	2458.5	274.52	25	2423.0	235.84	25	2441.7	347.48	25	2496.5	349.72	25
	5-10	1868.0	260.53	25	1919.7	315.39	25	2096.0	371.18	25	2077.2	510.86	25
	10-15	1476.6	394.79	25	1487.3	448.83	25	1643.8	317.18	25	1639.2	430.15	25
	15-20	1221.5	471.22	25	1217.8	415.97	25	1317.2	414.83	25	1334.3	534.28	25
	0-20	7024.6	1168.32	25	7047.8	1092.88	25	7498.7	1252.81	25	7547.1	1588.77	25

(b) (4) Study Number 1409-002 Reproductive Phase 1
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Table 20 Summary of F₁ Behavioral Observations (Passive Avoidance) - MALE

Endpoint	0 mg/kg/dose Frequency	5 mg/kg/dose Frequency	25 mg/kg/dose Frequency	150 mg/kg/dose Frequency
Number of animals tested ^a	25	25	25	25
Non-responsive animals	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Passive or non-passive				
Passive	15 (60.0%)	17 (68.0%)	15 (60.0%)	19 (76.0%)
Non-passive	10 (40.0%)	8 (32.0%)	10 (40.0%)	6 (24.0%)
Number of trials(passive animals only)				
3	6 (40.0%)	5 (29.4%)	7 (46.7%)	7 (36.8%)
4	5 (33.3%)	7 (41.2%)	6 (40.0%)	10 (52.6%)
5	4 (26.7%)	5 (29.4%)	2 (13.3%)	2 (10.5%)

Table 21 Summary of F₁ Behavioral Observations (Passive Avoidance) - FEMALE

Endpoint	0 mg/kg/dose Frequency	5 mg/kg/dose Frequency	25 mg/kg/dose Frequency	150 mg/kg/dose Frequency
Number of animals tested ^a	25	25	25	25
Non-responsive animals	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Passive or non-passive				
Passive	16 (64.0%)	16 (64.0%)	18 (72.0%)	20 (80.0%)
Non-passive	9 (36.0%)	9 (36.0%)	7 (28.0%)	5 (20.0%)
Number of trials(passive animals only)				
3	7 (43.8%)	7 (43.8%)	6 (33.3%)	3 (15.0%)
4	8 (50.0%)	5 (31.3%)	11 (61.1%)	10 (50.0%)
5	1 (6.3%)	4 (25.0%)	1 (5.6%)	7 (35.0%)

Sperm evaluation of F₁

(b) (4) Study Number 1409-002 Reproductive Phase 1
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Endpoint	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sperm Motility												
Percent Motility	91.5	7.00	25	90.6	5.97	25	88.6	12.53	24	89.8	6.90	25
Total Sperm Concentration per Cauda Epididymis x 10 ⁹	3.072	0.4697	25	3.238	0.5877	25	3.010	0.8522	25	3.084	0.4083	25
Sperm Concentration per gram Cauda Epididymis x 10 ⁵	10.262	1.4472	25	10.086	1.4801	25	9.592	2.6022	25	9.506	1.1735	25
Percent Abnormal	2.18	0.912	25	2.82	1.471	25	10.22	27.046	25	2.84	1.657	25

There were no adverse effects on sperm percent motility, count or concentration or percent abnormal.

F₁ delivery and litter data

In utero treated females mated to naïve males

Endpoint	0 mg/kg/dose		5 mg/kg/dose		25 mg/kg/dose		150 mg/kg/dose	
No. Females on Study	N	25		25		25		25
No. Females Pregnant	N	25		23		23		24
Female Fertility Index	%	100.0		92.0		92.0		96.0
Females Delivering Litters ¹	N	25		23		23		24
%	%							
With Stillborn Pups ¹	N	2		0		2		1
%	%	8.0		0.0		8.7		4.2
With All Stillborn ¹	N	0		0		0		0
%	%	0.0		0.0		0.0		0.0
Gestation Length (Days)	Mean	21.8		22.0		21.9		21.8
SD	SD	0.78		0.22		0.66		0.56
N	N	24		21		19		17
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	14.7		14.9		14.0		14.1
SD	SD	2.61		2.01		4.49		2.61
N	N	25		23		23		24
Liveborn/Litter	Mean	14.4		14.9		13.9		14.1
SD	SD	2.60		2.01		4.42		2.64
N	N	25		23		23		24
Gestation Index	%	100.0		100.0		100.0		100.0
N	N	25		23		23		24
Stillborn Index	Mean %/Litter	1.71		0.00		0.77		0.32
SD	SD	5.999		0.000		2.647		1.570
N	N	25		23		23		24
Total Implantation Scars/Litter	Mean	15.8		15.7		15.7		15.1
SD	SD	1.88		1.58		3.51		2.06
N	N	25		23		23		24
No. Live Pups/Litter Day 4	Mean	13.5		14.0		13.0		13.6
SD	SD	3.28		3.34		4.45		2.90
N	N	25		23		22		24

Sex Ratio (% Males per Animal)						
Pups Day 0	Mean %/Litter	48.59	50.14	52.47	47.34	
	SD	15.804	14.665	14.820	17.143	
	N	25	23	23	24	
Pups Day 4	Mean %/Litter	48.85	50.66	53.63	47.11	
	SD	16.162	15.231	18.018	17.590	
	N	25	23	22	24	
Pup Survival Indices						
Viability Index	Mean %/Litter	94.00	94.23	89.90	96.53	
	SD	16.207	17.822	22.174	8.882	
	N	25	23	23	24	

F₁ delivery and litter data

In utero treated males mated with naïve females

(b) (4) Study Number 1409-002 Reproductive Phase 1
17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	N	25	25	25	25
No. Females Pregnant	N	25	23	23	24
Female Fertility Index	%	100.0	92.0	92.0	96.0
Females Delivering Litters ¹	N	25	23	23	24
	%				
With Stillborn Pups ¹	N	2	0	2	1
	%	8.0	0.0	8.7	4.2
With All Stillborn ¹	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Gestation Length (Days)	Mean	21.8	22.0	21.9	21.8
	SD	0.78	0.22	0.66	0.56
	N	24	21	19	17
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	14.7	14.9	14.0	14.1
	SD	2.61	2.01	4.49	2.61
	N	25	23	23	24
Liveborn/Litter	Mean	14.4	14.9	13.9	14.1
	SD	2.60	2.01	4.42	2.64
	N	25	23	23	24
No. of Pups at Day 0 cont. Stillborn/Litter	Mean	0.3	0.0	0.1	0.0
	SD	0.98	0.00	0.46	0.20
	N	25	23	23	24
Gestation Index	%	100.0	100.0	100.0	100.0
	N	25	23	23	24
Stillborn Index	Mean %/Litter	1.71	0.00	0.77	0.32
	SD	5.999	0.000	2.647	1.570
	N	25	23	23	24
Total Implantation Scars/Litter	Mean	15.8	15.7	15.7	15.1
	SD	1.88	1.58	3.51	2.06
	N	25	23	23	24
No. Live Pups/Litter Day 4	Mean	13.5	14.0	13.0	13.6
	SD	3.28	3.34	4.45	2.90
	N	25	23	22	24

Sex Ratio (% Males per Animal)					
Pups Day 0	Mean %/Litter	48.59	50.14	52.47	47.34
	SD	15.804	14.665	14.820	17.143
	N	25	23	23	24
Pups Day 4	Mean %/Litter	48.85	50.66	53.63	47.11
	SD	16.162	15.231	18.018	17.590
	N	25	23	22	24
Pup Survival Indices					
Viability Index	Mean %/Litter	94.00	94.23	89.90	96.53
	SD	16.207	17.822	22.174	8.882
	N	25	23	23	24

There were no adverse effects on any F₁ fertility parameters or on the F₂ sex ratio or viability index

Reproductive phase 2: delivery and litter data

(b) (4) Study Number 1409-002 Reproductive Phase 2
17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	N	25	25	25	25
No. Females Pregnant	N	25	25	25	25
Females Delivering Litters ¹	N	25	25	25	25
	%	100.0	100.0	100.0	100.0
With Stillborn Pups ¹	N	2	1	0	0
	%	8.0	4.0	0.0	0.0
With All Stillborn ¹	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Gestation Length (Days)	Mean	21.8	22.0	21.9	21.8
	SD	0.50	0.35	0.40	0.47
	N	25	25	25	25
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	12.6	12.3	13.3	12.7
	SD	1.44	2.39	1.93	1.46
	N	25	25	25	25
Liveborn/Litter	Mean	12.5	12.2	13.3	12.7
	SD	1.42	2.35	1.93	1.46
	N	25	25	25	25
No. of Pups at Day 0 cont. Stillborn/Litter	Mean	0.1	0.0	0.0	0.0
	SD	0.44	0.20	0.00	0.00
	N	25	25	25	25
Gestation Index	%	100.0	100.0	100.0	100.0
	N	25	25	25	25
Stillborn Index	Mean %/Litter	0.88	0.27	0.00	0.00
	SD	3.188	1.333	0.000	0.000
	N	25	25	25	25
Total Implantation Scars/Litter	Mean	13.3	13.2	13.8	13.2
	SD	1.57	2.02	1.85	1.67
	N	25	25	25	25

No. Live Pups/Litter Day 4 (Preculling)	Mean	12.4	11.8	13.1	12.5
	SD	1.50	3.11	1.91	1.48
	N	25	24	25	25
Day 4 (Postculling)	Mean	8.0	7.7	8.1	8.0
	SD	0.00	1.43	0.60	0.00
	N	25	24	25	25
Day 7	Mean	8.0	7.6	8.0	8.0
	SD	0.00	1.44	0.20	0.20
	N	25	24	25	25
Day 14	Mean	8.0	7.6	8.0	8.0
	SD	0.00	1.44	0.20	0.20
	N	25	24	25	25
Day 21	Mean	8.0	7.6	8.0	7.9
	SD	0.00	1.44	0.20	0.28
	N	25	24	25	25
Sex Ratio (% Males per Animal) Pups Day 0	Mean %/Litter	48.69	47.98	50.93	52.07
	SD	17.062	15.983	13.652	14.770
	N	25	25	25	25
Pups Day 4 (Preculling)	Mean %/Litter	49.14	46.05	50.60	52.49
	SD	17.139	18.807	13.865	14.302
	N	25	24	25	25
Pups Day 4 (Postculling)	Mean %/Litter	48.50	48.51	49.32	50.50
	SD	7.500	14.234	5.738	4.390
	N	25	24	25	25
Pups Day 21	Mean %/Litter	48.21	48.81	49.21	51.07
	SD	7.576	14.341	5.834	4.753
	N	25	24	25	25
Pup Survival Indices Viability Index	Mean %/Litter	99.00	91.05	98.53	98.42
	SD	2.764	26.597	3.024	3.266
	N	25	25	25	25
Lactation Index	Mean %/Litter	99.50	99.48	98.41	99.00
	SD	2.500	2.552	5.905	3.461
	N	25	24	25	25

No adverse effects.

Reproductive Phase 2: Prewaning F₁ pup clinical findings

(b) (4) Study Number 1409-002 Reproductive Phase 2
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Summary of F₁ Prewaning Pup Clinical Findings*

Table 66	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Observation				
Number of Animals Alive at Start of Interval	313	292	329	317
Animals with No Abnormalities Detected	299	268	275	274
Behavior/Activity				
Activity decreased	0/0	2/2	0/0	1/1
External Appearance				
Digit(s) missing, Forefoot/left	0/0	0/0	12/8	0/0
Digit(s) missing, Forefoot/right	0/0	0/0	15/7	0/0
Digit(s) missing, Hind foot/left	0/0	1/1	22/8	6/3
Digit(s) missing, Hind foot/right	0/0	0/0	13/5	3/1
Emaciated	3/2	0/0	0/0	2/2
Limb function impaired, Forelimb/left	1/1	1/1	18/10	18/9
Limb function impaired, Forelimb/right	0/0	3/3	20/11	23/10
Limb function impaired, Hind limb/left	1/1	4/2	36/19	30/15
Limb function impaired, Hind limb/right	0/0	5/2	15/11	21/9
Limb function lost, Hind limb/right	0/0	0/0	0/0	1/1
Swelling, Digit	0/0	1/1	3/3	0/0
Swelling, Forefoot/left	6/3	14/8	12/9	27/10
Swelling, Forefoot/right	5/3	12/5	13/9	24/9
Swelling, Forelimb/left	0/0	0/0	1/1	2/2
Swelling, Forelimb/right	0/0	2/1	0/0	10/6
Swelling, Hind foot/left	2/1	0/0	6/4	12/3
Swelling, Hind foot/right	0/0	0/0	0/0	10/3
Swelling, Hind limb/left	0/0	0/0	1/1	19/10
Swelling, Hind limb/right	0/0	0/0	0/0	6/3
Thin	1/1	1/1	0/0	0/0

There was a dose related increase in what the sponsor called traumatic lesions of the feet (and infrequently limbs) in the MD and HD gps for reproductive phase 2. Sponsor considers these effects unrelated to treatment but were considered to be caused by traumatic injury as the pups were being tattooed for postnatal identification. Why this trauma occurred primarily in the mid and high dose gps was not explained. This effect was not seen in the reproductive phase 1 gps which received two more injections than the repro phase 2 gps so I am willing to accept sponsors argument that the findings were unrelated to treatment.

Summary of F₁ Postweaning Pup Clinical Findings*

Table 67	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Observation				
Number of Animals Alive at Start of Interval	199	183	199	198
Animals with No Abnormalities Detected	199	180	191	196
External Appearance				
Digit(s) missing, Forefoot/left	0/0	0/0	1/1	0/0
Digit(s) missing, Forefoot/right	0/0	0/0	3/3	0/0
Digit(s) missing, Hind foot/left	0/0	1/1	5/5	2/2
Eye/Ocular				
Eye not evident, Eye/right	0/0	1/1	0/0	0/0
Pelage/Skin				
Hair sparse, Forefoot/left	0/0	1/1	0/0	0/0
Hair sparse, Forefoot/right	0/0	1/1	0/0	0/0

Table 71 **Summary of F₁ Physical Development**

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Static Righting Reflex (Days)	Mean	2.4	2.4	2.3	2.3
	SD	0.31	0.34	0.30	0.36
	N	25	24	25	25
Pinna Detachment (Days)	Mean	2.5	2.3	2.2 ^a	2.4
	SD	0.49	0.33	0.45	0.46
	N	25	24	25	25
Cliff Aversion (Days)	Mean	11.0	11.0	11.0	11.0
	SD	0.07	0.03	0.08	0.10
	N	25	24	25	25
Eye Opening (Days)	Mean	14.5	14.4	14.8	14.6
	SD	0.72	0.89	0.48	0.55
	N	25	24	25	25
Air Drop Righting Reflex (Days)	Mean	16.0	16.0	16.0	16.0
	SD	0.05	0.09	0.05	0.11
	N	25	24	25	25
Auditory Response Percent Pups Passing/Dam	Mean	100.0	100.0	100.0	100.0
	SD	0.00	0.00	0.00	0.00
	N	25	24	25	25

Table 72 **Summary of F₁ Sexual Maturation**

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Vaginal Opening (Days)	Mean	33.2	33.4	33.6	34.3
	SD	2.53	1.71	1.80	1.97
	No. of Pups Passing	25	25	25	25
Body Weight on Day Passed Vaginal Opening, g	Mean	123.0	124.6	125.3	131.6
	SD	20.22	15.59	12.54	13.94
	No. of Pups	25	25	25	25
Preputial Separation (Days)	Mean	45.0	44.8	44.8	44.9
	SD	2.92	2.56	3.27	4.20
	No. of Pups Passing	25	25	25	25
Body Weight on Day Passed Preputial Separation, g	Mean	254.1	264.0	250.2	253.8
	SD	28.10	29.43	31.49	37.71
	No. of Pups	23	22	24	25

Table 73 **Summary of F₁ Behavioral Observations (Motor Activity) - MALE**

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Basic Movement (count)	0-5	1300.1	163.17	25	1221.4	227.87	25	1298.9	208.49	25	1298.4	166.56	25
	5-10	934.1	237.68	25	988.7	230.41	25	1096.0 ^a	221.34	25	1048.4	197.52	25
	10-15	784.0	228.99	25	799.0	156.05	25	916.6 ^a	155.53	25	863.7	220.27	25
	15-20	659.2	242.62	25	703.5	188.14	25	827.0 ^a	239.77	25	697.5	225.19	25
	0-20	3677.5	705.52	25	3712.6	604.84	25	4138.4 ^a	635.27	25	3907.9	551.21	25

Table 74 **Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE**

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Basic Movement (count)	0-5	1366.4	210.50	25	1439.3	202.26	25	1426.8	236.70	25	1417.4	175.04	25
	5-10	1076.2	201.85	25	1184.1	193.61	25	1211.2	240.64	25	1259.9 ^a	258.20	25
	10-15	842.4	251.03	25	1024.9 ^b	221.03	25	988.8	208.34	25	995.7 ^a	204.94	25
	15-20	734.2	256.84	25	796.4	216.87	25	870.7	139.49	25	805.1	231.57	25
	0-20	4019.2	714.47	25	4444.7	703.27	25	4497.6 ^a	668.32	25	4478.2	689.77	25

Table 73 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fine Movement (count)	0-5	949.6	110.38	25	912.0	154.00	25	958.8	153.33	25	953.5	114.86	25
	5-10	736.2	170.08	25	763.2	166.37	25	835.4	158.82	25	797.2	135.32	25
	10-15	626.4	162.19	25	645.5	114.01	25	731.4 ^a	110.58	25	681.7	163.35	25
	15-20	525.6	168.92	25	574.3	128.98	25	663.5 ^b	166.75	25	570.1	169.19	25
	0-20	2837.8	502.24	25	2895.0	428.34	25	3189.1 ^a	449.72	25	3002.6	404.37	25

Table 74 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fine Movement (count)	0-5	984.8	160.37	25	1032.5	144.88	25	1032.0	171.90	25	1015.9	136.19	25
	5-10	813.0	148.15	25	887.8	138.08	25	907.6	160.29	25	927.8 ^a	178.92	25
	10-15	664.5	176.49	25	780.6 ^a	151.77	25	757.2	154.10	25	755.2	144.53	25
	15-20	575.1	185.10	25	621.0	154.39	25	680.7 ^a	95.50	25	636.6	168.89	25
	0-20	3037.5	522.60	25	3321.9	496.30	25	3377.6 ^a	477.84	25	3335.6	502.16	25

Table 73 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Rearing (count)	0-5	36.5	10.48	25	34.8	11.03	25	35.2	10.97	25	35.4	12.49	25
	5-10	23.4	9.17	25	26.4	11.98	25	29.5	11.28	25	30.6	10.12	25
	10-15	17.2	8.91	25	18.1	8.37	25	18.8	6.38	25	23.0 ^a	10.24	25
	15-20	14.8	7.98	25	14.9	9.61	25	17.0	7.79	25	16.8	8.83	25
	0-20	91.9	27.93	25	94.2	32.13	25	100.6	27.83	25	105.8	23.23	25

Table 74 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Rearing (count)	0-5	41.4	11.77	25	46.8	11.57	25	44.2	10.74	25	42.4	10.54	25
	5-10	32.6	10.26	25	38.0	12.16	25	36.2	10.62	25	41.6 ^a	12.23	25
	10-15	21.8	9.47	25	28.8 ^a	9.69	25	29.0 ^a	8.99	25	30.6 ^b	11.39	25
	15-20	20.0	7.78	25	22.2	7.82	25	24.1	11.71	25	19.4	8.78	25
	0-20	115.9	29.14	25	135.8	33.84	25	133.5	31.05	25	134.0	34.55	25

Table 73 Summary of F₁ Behavioral Observations (Motor Activity) - MALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Distance (cm)	0-5	2332.0	268.96	25	2159.5	369.70	25	2296.5	333.24	25	2293.3	259.84	25
	5-10	1654.8	398.86	25	1722.7	364.21	25	1904.4 ^a	335.27	25	1829.4	334.48	25
	10-15	1376.4	401.61	25	1393.2	270.50	25	1585.6	255.79	25	1499.0	372.06	25
	15-20	1160.8	426.95	25	1212.8	337.00	25	1422.3	408.05	25	1206.3	375.21	25
	0-20	6524.0	1201.60	25	6488.1	979.21	25	7208.8	1020.36	25	6828.0	902.75	25

Table 74 Summary of F₁ Behavioral Observations (Motor Activity) - FEMALE

Endpoint	Study Interval (Minutes)	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Distance (cm)	0-5	2427.7	320.21	25	2523.9	293.54	25	2494.1	332.43	25	2488.0	268.24	25
	5-10	1881.9	300.12	25	2050.0	303.04	25	2077.2	358.47	25	2173.2 ^b	398.02	25
	10-15	1462.4	411.94	25	1778.0 ^b	355.46	25	1710.2 ^a	328.39	25	1741.3 ^a	337.74	25
	15-20	1270.2	428.00	25	1397.7	354.01	25	1500.3	227.03	25	1388.8	378.37	25
	0-20	7042.1	1074.07	25	7749.7	1084.63	25	7781.9 ^a	961.30	25	7791.3 ^a	1079.71	25

Table 75 Summary of F₁ Behavioral Observations (Passive Avoidance) - MALE

Endpoint	0 mg/kg/dose Frequency	5 mg/kg/dose Frequency	25 mg/kg/dose Frequency	150 mg/kg/dose Frequency
Number of animals tested ^a	25	25	25	25
Non-responsive animals	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Passive or non-passive				
Passive	19 (76.0%)	18 (72.0%)	17 (68.0%)	16 (64.0%)
Non-passive	6 (24.0%)	7 (28.0%)	8 (32.0%)	9 (36.0%)
Number of trials(passive animals only)				
3	9 (47.4%)	6 (33.3%)	8 (47.1%)	8 (50.0%)
4	9 (47.4%)	6 (33.3%)	6 (35.3%)	5 (31.3%)
5	1 (5.3%)	6 (33.3%)	3 (17.6%)	3 (18.8%)

Table 76 Summary of F₁ Behavioral Observations (Passive Avoidance) - FEMALE

Endpoint	0 mg/kg/dose Frequency	5 mg/kg/dose Frequency	25 mg/kg/dose Frequency	150 mg/kg/dose Frequency
Number of animals tested ^a	25	25	25	25
Non-responsive animals	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Passive or non-passive				
Passive	15 (60.0%)	16 (64.0%)	17 (68.0%)	18 (72.0%)
Non-passive	10 (40.0%)	9 (36.0%)	8 (32.0%)	7 (28.0%)
Number of trials(passive animals only)				
3	5 (33.3%)	7 (43.8%)	3 (17.6%)	9 (50.0%)
4	4 (26.7%)	6 (37.5%)	8 (47.1%)	6 (33.3%)
5	6 (40.0%)	3 (18.8%)	6 (35.3%)	3 (16.7%)

Sperm evaluation of F₁

Table 89 Summary of F₁ Sperm Evaluations

Endpoint	0 mg/kg/dose			5 mg/kg/dose			25 mg/kg/dose			150 mg/kg/dose		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sperm Motility												
Percent Motility	90.4	4.61	24	92.2	5.86	25	89.5	6.04	25	89.8	7.26	25
Total Sperm Concentration per Cauda Epididymis x 10 ³	2.895	0.7060	24	2.863	0.8288	25	2.570	0.6408	25	2.745	0.7424	25
Sperm Concentration per gram Cauda Epididymis x 10 ³	8.986	2.2657	24	8.759	2.2084	25	7.892	1.7618	25	8.251	2.1731	25
Percent Abnormal	2.71	1.188	24	2.84	1.784	25	2.44	1.074	25	3.06	1.911	25

No adverse effects on sperm motility, concentration or percent abnormal

Reproductive phase 2
in utero treated females mated with naïve males

Table 90		Summary of F ₁ Natural Delivery and Litter Data			
Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	N	25	25	25	25
No. Females Pregnant	N	24	25	24	24
Female Fertility Index	%	96.0	100.0	96.0	96.0
Females Delivering Litters ¹	N	24	25	24	24
	%	100.0	100.0	100.0	100.0
With Stillborn Pups ¹	N	1	2	3	0
	%	4.2	8.0	12.5	0.0
With All Stillborn ¹	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Gestation Length (Days)	Mean	22.4	22.1	22.0	21.9 ^a
	SD	0.59	0.46	0.38	0.64
	N	21	23	21	18
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	13.9	13.8	14.6	14.6
	SD	1.90	2.45	1.95	2.55
	N	24	25	24	24
Liveborn/Litter	Mean	13.8	13.6	14.5	14.6
	SD	1.90	2.48	1.89	2.55
	N	24	25	24	24
No. of Pups at Day 0 cont. Stillborn/Litter	Mean	0.0	0.2	0.1	0.0
	SD	0.20	0.62	0.34	0.00
	N	24	25	24	24
Gestation Index	%	100.0	100.0	100.0	100.0
	N	24	25	24	24
Stillborn Index	Mean %/Litter	0.30	1.11	0.78	0.00
	SD	1.458	4.225	2.111	0.000
	N	24	25	24	24
Total Implantation Scars/Litter	Mean	15.3	15.0	15.5	15.6
	SD	1.71	2.03	1.74	2.34
	N	24	25	24	24
No. Live Pups/Litter Day 4	Mean	13.4	13.4	14.1	14.1
	SD	1.64	2.38	1.64	2.33
	N	24	25	24	24
Sex Ratio (% Males per Animal) Pups Day 0	Mean %/Litter	46.69	44.01	50.99	50.19
	SD	11.563	12.469	12.452	13.165
	N	24	25	24	24
Pups Day 4	Mean %/Litter	45.98	43.70	51.44	50.68
	SD	12.937	12.301	12.342	12.571
	N	24	25	24	24
Pup Survival Indices Viability Index	Mean %/Litter	97.31	98.95	97.67	97.40
	SD	5.205	2.500	4.616	3.954
	N	24	25	24	24

In utero treated males mated with naïve females

Endpoint		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	N	25	25	25	25
No. Females Pregnant	N	25	24	25	25
Female Fertility Index	%	100.0	96.0	100.0	100.0
Females Delivering Litters ¹	N	25	24	25	25
	%	100.0	100.0	100.0	100.0
With Stillborn Pups ¹	N	0	3	3	2
	%	0.0	12.5	12.0	8.0
With All Stillborn ¹	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Gestation Length (Days)	Mean	22.4	22.2	22.1	22.0 ^a
	SD	0.50	0.50	0.43	0.32
	N	23	22	22	20
No. of Pups at Day 0 (Total Pups Born/Litter)	Mean	14.1	14.3	14.3	14.6
	SD	2.56	2.09	2.23	2.68
	N	25	24	25	25
Liveborn/Litter	Mean	14.1	14.0	14.2	14.5
	SD	2.56	2.14	2.24	2.68
	N	25	24	25	25
No. of Pups at Day 0 cont. Stillborn/Litter	Mean	0.0	0.3	0.1	0.1
	SD	0.00	1.04	0.33	0.28
	N	25	24	25	25
Gestation Index	%	100.0	100.0	100.0	100.0
	N	25	24	25	25
Stillborn Index	Mean %/Litter	0.00	1.87	0.82	0.53
	SD	0.000	6.550	2.265	1.846
	N	25	24	25	25
Total Implantation Scars/Litter	Mean	15.2	15.2	15.5	15.6
	SD	2.32	2.08	2.02	1.87
	N	25	24	25	25
No. Live Pups/Litter Day 4	Mean	13.8	13.6	13.6	14.2
	SD	2.53	2.06	3.26	2.72
	N	25	24	25	25
Sex Ratio (% Males per Animal) Pups Day 0	Mean %/Litter	49.20	47.86	51.57	50.73
	SD	12.079	15.079	11.314	15.177
	N	25	24	25	25
Pups Day 4	Mean %/Litter	49.12	47.90	53.43	50.36
	SD	11.991	14.877	14.321	14.596
	N	25	24	25	25
Pup Survival Indices Viability Index	Mean %/Litter	97.98	97.70	95.29	97.48
	SD	3.452	3.859	16.334	3.948
	N	25	24	25	25

Teratology phase

(b) (4) Study Number 1409-002 Teratology Phase
 17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following *In-Utero* Exposure

Endpoint	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Females on Study	25	25	25	25
No. Not Pregnant	1	0	0	1
No. Pregnant	24	25	25	24
Pregnancy Index Percent	96.0	100.0	100.0	96.0
No. Died Pregnant	0	0	0	0
No. Abortions	0	0	0	0
No. Early Deliveries	0	0	0	0
No. Females with All Resorptions	0	0	0	0
No. Females with Viable Fetuses	24	25	25	24

		0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
Fetal Weight					
Males	Mean	4.10 (4.10)	3.99 (3.99)	4.04 (4.05)	4.12 (4.12)
	SD	0.186	0.203	0.292	0.246
	N	24	25	25	24
Females	Mean	3.91 (3.90)	3.76 (3.76)	3.84 (3.86)	3.86 (3.85)
	SD	0.221	0.246	0.322	0.184
	N	24	24	25	24
Males + Females	Mean	4.01 (4.00)	3.91 (3.90)	3.94 (3.96)	3.98 (3.98)
	SD	0.186	0.188	0.304	0.213
	N	24	25	25	24

Observation	Classification	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Litters Evaluated		24	25	25	24
No. Fetuses Evaluated		239	247	272	237
Tail					
Entire, Absent	M				
No. Litters (%)		0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)
No. Fetuses (%) ¹		0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

Observation	Classification	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Litters Evaluated		24	24	25	24
No. Fetuses Evaluated		117	124	133	118
Abdominal cavity					
Kidney, Increased renal pelvic cavitation	V				
No. Litters (%)		0 (0.0)	0 (0.0)	1 (4.0)	1 (4.2)
No. Fetuses (%) ¹		0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Ureter, Dilated	V				
No. Litters (%)		0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
No. Fetuses (%) ¹		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Thoracic cavity					
Thyroid, Smaller than normal	V				
No. Litters (%)		0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)
No. Fetuses (%) ¹		0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)

	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Litters Evaluated	24	25	25	24
No. Fetuses Evaluated	239	247	272	237
Total Malformations				
No. Litters (%)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)
No. Fetuses (%) ¹	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Total Variations				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. Fetuses (%) ¹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	0 mg/kg/dose	5 mg/kg/dose	25 mg/kg/dose	150 mg/kg/dose
No. Litters Evaluated	24	24	25	24
No. Fetuses Evaluated	117	124	133	118
Total Malformations				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. Fetuses (%) ¹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Variations				
No. Litters (%)	0 (0.0)	0 (0.0)	3 (12.0)	1 (4.2)
No. Fetuses (%) ¹	0 (0.0)	0 (0.0)	3 (2.3)	1 (0.8)

No adverse effects

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This study was conducted to evaluate the possible adverse effects of 17 alpha hydroxyprogesterone caproate on the pregnant female and on the development of the conceptus and the offspring. The multi-generational study was conducted in three phases. Each phase was comprised of three treatment groups of 25 time-mated female rats per gp. Two reproductive phases were conducted by administering the drug to the F₀ females using two different dosing regimens during gestation. Rats in the first phase (reproductive phase 1) received the test article by IM injection on GD 8, 14, and 20, and rats in the second phase (reproductive phase 2) received the test article on GD 17. Rats in the third phase (teratology phase) received the drug on GD 6, 12, and 18. Dose levels in each were 0 (vehicle control) 5, 25 and 150 mg/kg/dose.

These phases were selected to examine exposure to hydroxyprogesterone caproate before (phase 1) and after (phase 2) gametogenesis which occurs around GD 12 in the female and GD 15 in the male. In an earlier study published by Pushpalatha, et.al. *Naturwissenschaften* 91: 242-244, 2004; *Naturwissenschaften* 92: 385-388, 2005, pregnant rats were injected with hydroxyprogesterone caproate on days 1, 7, and 14 of gestation at doses of 10 and 25 mg/kg. In the male F₁ offspring, there was a reduction in serum testosterone, and a decrease in sperm motility, viability and count. Furthermore, when the F₁ males were mated to naïve females, the number of implantation sites and viable fetuses was significantly reduced. In the Pushpalatha study, Wistar rats (not Sprague-Dawley as used in the present study) were injected IP and not IM. But the most significant difference between the two studies was drug administration on GD 1 in the Pushpalatha study. Waiting until GD 8 as in reproductive phase 1 or GD 17 as in reproductive phase 2 more closely resembled clinical administration during the later weeks of pregnancy (weeks 16-37). In humans, sexual differentiation starts around week 7.

In the reproductive phases, there were no drug related effects on the dams which had normal delivery and produced viable offspring (F₁). The pups showed comparable survival rates between the gps and controls for each phase. Physical, developmental and behavioral evaluations of the F₁ for both phases did not reveal any test article related effects during lactation or the maturation phase.

The in utero exposed males and females for each reproductive phase were then mated to naïve animals. The mating and fertility indices for the two phases did not reveal any treatment related effects. The F₂ generation was born to these animals without showing any drug related effects on growth and survival up to LD 4.

Sperm evaluation of the F₁ in utero treated males revealed comparable results to the controls in all the tested parameters.

In the teratology phase, there were no drug related effects on the dams. There were also no adverse effects on the number of corpora lutea, implantations, viable fetuses, litter size and mean fetal wts per litter. Fetal evaluations revealed only a single external

malformation at the LD (absent tail). There were no other external or visceral malformations at any dose. There were no treatment related increases in fetal variations. For some reason, sponsor did not do an alizarin red dye skeletal examination, only visceral. Not sure why.

The no adverse effect level in this study is the high dose of 150 mg/kg. The recommended human dose is 250 mg IM weekly.

The stark differences between the results of the study by Pushpalatha and this study are not easily resolved. The most obvious difference is the lack of an injection on GD 1. The rat blastocyst normally implants on GD 6 and the differentiation of males from females begins around day 11. Possibly some perturbation of sexual development could occur between days 1 and day 8 although it is difficult to imagine a hormone affecting males and not females if it occurred before sexual differentiation. However, the Pushpalatha study, as far as I can tell, did not look at the effect of the drug on females. The difference between IP and IM injection could result in higher fetal exposures with the IP injection but the current study used a high dose of 150 mg/kg, 6 times higher than the high dose used by Pushpalatha. Also, different strains of rats were used.

Regardless of the reason for the different results, the end result showed that hydroxyprogesterone caproate under the conditions of the study (which more closely resembled the clinical situation than the Pushpalatha study) produced no adverse effect on either male or female offspring or their offspring.

In a related study, Sponsor did a pharmacokinetic study using the same rat strain injected IM with 5 or 150 mg/kg hydroxyprogesterone caproate on day 5 of gestation. Plasma analysis showed a maximum concentration at 24 hrs following exposure and the half-life was calculated to be approximately 6 days under the conditions of the study. The PK data were used to determine the spacing of the injections in the toxicity study.

Because of the different results between this study and the Pushpalatha study, I have requested an FDA inspection of the study.

A preliminary report of the GLP inspection of the study 1409-002 by (b) (4), (b) (4) found some minor deviations but in general the data were deemed acceptable. The differences between this study and the Pushpalatha study were ascribed to strain differences (Sprague-Dawley at (b) (4) Wistar at Pushpalatha) and the date of first dosing (GD8 at (b) (4) GD1 at Pushpalatha).

Unresolved toxicology issues (if any): none

Recommendations: I recommend approval of 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm birth.

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

/s/

Alexander W. Jordan
10/14/2008 02:06:36 PM
PHARMACOLOGIST

Lynnda Reid
10/14/2008 02:38:55 PM
PHARMACOLOGIST

Pharm/tox filing memo

There are no labeling issues at this time.

Sponsor submitted the unaudited results of a pharmacokinetic study and a multigenerational reproductive toxicology study.

The Pk study determined that the half-life of 17-hydroxyprogesterone in rats is 6 days and this was used in the final design of the repro study.

The repro study used 25 females/gp with doses of 5, 25 and 150 mg/kg
For Phase I the drug was given IM on gestation days 8, 14 and 20
For Phase II the drug was given on gestation day 17.

Endpoints included maternal toxicity and ability to produce viable offspring (F₁), F₁ was evaluated for development and behavioral changes and when sexually mature, they were mated to naïve animals to evaluate the ability to produce F₂. F₂ was evaluated and necropsied on lactation day 4.

Teratology Phase

F₀ dosed on GD 6, 12 and 18

Examined for maternal, developmental and fetal toxicity during gestation.

The study protocol was approved by us.

There was essentially no toxicity to dams or offspring.

In the Pushpalatha study, rats were given 10 and 25 mg/kg OHP on GD 1, 7 and 14 and the fertility of males from treated dams was assessed on day 90 by analyzing sperm quality and quantity and by mating with control females. The number of implantation sites and viable fetuses were significantly reduced in the control females and the F₁ males had a decrease in sperm function as assessed by sperm motility, viability and counts.

In the present study, all these parameters were normal at all doses. The only difference in the two studies was the present study did not include drug administration on GD1.

There are no indications from the present study that OHP has any negative effect on the offspring.

Sponsor proposes to submit the final audited study report on June 30. I should finish the review within a week of receipt.

Alex Jordan, PhD

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

/s/

Alexander W. Jordan
6/13/2008 10:51:23 AM
PHARMACOLOGIST

Lynnda Reid
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PHARMACOLOGIST

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: September 21, 2006
Reviewer: Lynnda Reid, Ph.D.
Supervisory Pharmacologist
NDA #/SS#/date: 21-945 / N000 / April 20, 2006
Sponsor: Adeza Biomedical
Drug Product: 17 alpha-hydroxyprogesterone caproate
Indication: Prevention of recurrent preterm birth

Drug History: The subject of this NDA is 17 Alpha-Hydroxyprogesterone Caproate Injection, 250 mg/mL for the proposed indication of prevention of recurrent preterm birth. The use of 17 alpha-hydroxyprogesterone caproate will be limited to pregnant women with a history of at least one spontaneous preterm birth at less than 37 weeks of gestation.

17 alpha-hydroxyprogesterone caproate, hereafter referred to as 17-HPC, was first approved and marketed as Delalutin (NDA 10-347) in 1956 for the treatment of habitual and recurrent abortion, threatened abortion and post-partum after pains. In 1972 it was also approved for the treatment of endometrial cancer, management of amenorrhea and abnormal uterine bleeding, and for the production of secretory endometrium and desquamation (NDA 16-911). After notification by Bristol-Myers Squibb Co. that Delalutin was no longer marketed, NDAs 10-347 and 16-911 were withdrawn without prejudice by the FDA (Federal Register 2000). 17-HPC continues to be used in women at high risk for recurrent preterm birth and is available through compounding pharmacies in the U.S.

Meetings were held between Adeza Biomedical and DRUP on 30 January 2004, 5 April 2004 and 16 July 2004 under IND 68,108 to discuss the overall drug development program leading to a submission of a 505(b)(2) NDA. A Pre-NDA meeting with the applicant was held on 27 June 2005. At these meetings Adeza was told that no additional nonclinical studies would be needed to file a NDA. At that time, it was thought that there was sufficient clinical and nonclinical safety data to support the safety of 17-HPC.

After a review of the published nonclinical data it was found that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies were old and did not comply with either Good Laboratory Practices or

conform to current CDER and ICH guidances. The primary deficiencies in the nonclinical studies included insufficient numbers of animals, use of unconventional species, lack of any PK/ADME data, correlation between gestational timing of exposures and pregnancy outcome, and lack of developmental studies in offspring exposed in utero. In addition there were conflicting findings in the studies, regarding 17-HPC embryoletality and potential differences in species sensitivity, which have not been adequately addressed and remain safety concerns.

Teratogenicity: There were no published reports of teratogenic effects in any species studied including non-human primates. However, potential adverse effects on learning and behavior have not evaluated in any of the reviewed nonclinical literature.

Supranormal doses of 17-HPC (100 to 200 times the MRHD), delivered by various routes of administration, have been associated with impairment of reproductive performance in male rats exposed to 17-HPC in utero, maternal and fetal deaths in mice and rats, retarded fetal growth in rats, and fetal deaths in monkeys.

Impairment of reproductive performance in adult male rats exposed in utero may be associated with decreased enzyme activity levels (3 β -hydroxysteroid dehydrogenase and 17 β -hydroxysteroid dehydrogenase) of the testis. Decreases in cauda epididymal sperm counts and motility were observed, as well as decreased serum testosterone levels. Serum FSH and LH levels were increased.

There was no reported evidence of androgenic or glucocorticoid activity at supranormal doses in rats or rabbits.

Non-human primate Studies:

- 1) In a retrospective study performed by Courtney and Valerio (1968) in breeding colonies of Rhesus monkeys routinely treated with 17-HPC for threatened abortions, there were no findings of adverse effects on development. The results of treatment with 17-HPC were reported for a total of 15 monkeys: 14 dosed at 125 mg/day and 1 at 250 mg/day for 1-10 days during various stages of gestation.

Dose*	Treatment Days	No. of Females	Outcome
125 mg/day	GD 7, 13, 57, 55, 77	1	aborted
	GD 13-53	5	4 normal births 1 aborted
	GD 19, 21, 22, 27, 30 or 31	6	4 normal births 2 aborted
	GD 24, 25, 29, 31, 62, 87, 111	1	aborted
	GD 32-41	1	normal birth
250 mg/day	GD 132	1	aborted

*Note: The proposed human dose for the treatment of recurrent preterm delivery is 250 mg/day. Based on body surface area, the doses used to prevent preterm delivery in the monkeys were approximately 3 to 7 times higher than the proposed human dose.

The nine normal births all resulted in viable neonates which survived for at least seven months. There were no signs of masculinization in the four female offspring,

and the mean weight of the nine offspring at birth was 458g, comparable to historical control birth weights. The mean gestation length, 160 days, was also comparable to controls.

2) In a prospective study by Hendrickx et al. (1987), pregnant Rhesus (*Macacca mulatta*) and Cynomologous (*Macacca fascicularis*) monkeys (n=?/group) were administered 17-HPC (i.m.) alone or combined with estradiol valerate (EV) at 7-day intervals between 20 and 146 days of gestation. Fetuses were examined after Caesarean delivery at 150±2 days. The 17-HPC dose administered was only given in relationship to the human dose as 0.01 to 10 times the human equivalent dose (HED). The pregnant animals were observed regularly for adverse clinical signs, food intake and vaginal bleeding. Immediately after delivery all fetuses were weighed, morphometrically measure, and examined for malformations. All visceral organs were examined in situ prior to removal, then weighed and preserved in 10% formalin.

Embryo lethality was observed in all groups including controls, but was significantly increased (100% lethality) only in the Rhesus monkeys treated at 1X and 10X 17-HPC.

Species	Treatment	17-HPC HDE*	No. of Pregnancies	Embryo lethality (%)	Fetal Weight (g)
Rhesus	17-HPC + EV	Control	15	2 (13%)	348 ± 57
		0.01	8	3 (38%)	348 ± 64
		0.1	9	3 (33%)	353 ± 75
		0.33	10	3 (30%)	360 ± 51
		1	10	10 (100%)	-
		10	10	10 (100%)	-
Rhesus	17-HPC	Control	8	0 (0%)	339 ± 63
		1	10	10 (100%)	-
		10	10	10 (100%)	-
Cynomologous	17-HPC	Control	10	3 (30%)	319 ± 32
		0.1	10	2 (20%)	291 ± 31
		0.33	10	4 (40%)	305 ± 30
		1	10	4 (40%)	308 ± 30

*Note: As defined by the authors, HDE = human dose equivalent based on approximate human dose of 10.0 mg/kg 17-HPC and 0.2 mg/kg EV. This would equal a 17-HPC dose of approximately 600 mg/day in a 60 kg female, a dose 2 to 3 times higher than the proposed dose of 250 mg/day for the treatment of preterm delivery.

Abortions/resorptions occurred between gestational days 20 and 146. No anomalies were found in any of the surviving fetuses examined at Caesarean-section. All fetal weights and measurements were within the normal range for control fetuses. There were no dose-related malformations noted.

There was no discussion by the authors regarding the apparent increase in sensitivity to 17-HPC in the Rhesus monkeys. Since PK/ADME parameters were not measured,

it is not possible to determine which strain of monkeys may be more relevant to human exposures.

Unresolved Toxicology Issues:

- Based on the information available in the published literature, it appears that high doses of 17-HPC are associated with increased embryoletality in several species. The nonclinical data provided is insufficient to calculate a no adverse effect level (NOAEL) in animals.
- There is insufficient nonclinical information on potential adverse effects on postnatal development including learning, behavior, and reproduction.

Conclusions and Recommendations: From a Pharmacology/Toxicology standpoint, this NDA is approvable. There is insufficient nonclinical data on which to base the safety of 17-HPC, especially in regards to long-term effects in offspring exposed in utero. We recommend that a thorough reproductive and developmental study be performed in accordance with ICH S5A “Guideline for Industry: Detection of toxicity to Reproduction for Medicinal Products”. A multigenerational study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed in utero.

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/s/

Lynnda Reid
10/5/2006 03:16:54 PM
PHARMACOLOGIST



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: **21-945**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **04/20/06**
PRODUCT: **17 α -hydroxyprogesterone caproate (17-HPC)**
INTENDED CLINICAL POPULATION: **Prevention of recurrent preterm birth**
SPONSOR: **Adeza Biomedical**
DOCUMENTS REVIEWED: **Vol. 1-3**
REVIEW DIVISION: **Division of Reproductive & Urologic Products (HFD-580)**
PHARM/TOX REVIEWER: **Wafa A. Harrouk**
PHARM/TOX SUPERVISOR: **Lynnda Reid**
DIVISION DIRECTOR: **Scott Monroe**
PROJECT MANAGER: **Eufrecina Deguia**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Approvable
- B. Recommendation for nonclinical studies: A state of the art, GLP-compliant, multigenerational reproductive toxicology study which covers the stages of pregnancy covered in the clinic, is recommended to evaluate the safety of 17-HPC on maternal and fetal health.
- C. Recommendations on labeling: Although no teratogenicity was seen in mice or monkeys (Rhesus & Cynomolgus), it should be stated that fetal deaths were seen in the Rhesus reproductive toxicity study. No well-controlled nonclinical toxicity studies have been conducted with 17-HPC to support the indication of preterm labor.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings: No new nonclinical information has been submitted to assess whether 17-HPC confers a potential risk to the developing fetus or to the mother.
- B. Pharmacologic activity: 17-HPC was shown to help maintain pregnancy in pregnant rabbits but not in the pregnant rat, mare or squirrel monkey. It is not clear how 17-HPC exerts its effects on the uterus to prolong gestation but the mechanism does not seem to stem from direct uterine relaxation. Sponsor suggests that progesterone involvement in controlling labor may be due to genomic changes in the expression of the progesterone receptor isoforms but no data is available to support this hypothesis (Sexton et al, 2004)¹.
- C. Nonclinical safety issues relevant to clinical use: New evidence in an inflammation-induced preterm mouse model showed an increase in maternal mortality (n=3/4) at 4 mg/kg (human equivalent dose of 8 mg/kg) within 24 hrs of dosing and in maternal mortalities (n=11/24) at 2 mg/kg (HED of 4 mg/kg). In a separate study, dams (n=10) treated with 17-HPC at 1hr prior to LPS treatment (to induce inflammation) on GD 15 delivered between GD16-18, none of whose pups were alive. This finding is interesting in light of the increase in mortality finding in the rhesus, but not in the Cynomolgus monkey study. The significance of the study findings is not known but raises some concerns regarding the assumed safety of the use of 17- β -Progesterone for the preterm indication. In addition, no information exists on the potential breakdown of 17-HPC to hydroxyprogesterone and caproate once in the circulation.

¹ Sexton et al., 2004. *Reprod. Biol. Endocrinol.* Functional effects of 17 alpha-hydroxyprogesterone caproate on human myometrial contractility in vitro.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-945

Review number: 1

Sequence number/date/type of submission: 000, April 20, 2006, Original NDA submission

Information to sponsor: Yes () No ()

Sponsor and/or agent: Adeza Biomedical Corp., Sunnyvale, CA 94080

Manufacturer for drug substance: Adeza Biomedical Corp., Sunnyvale, CA 94080

Reviewer name: Wafa A. Harrouk

Division name: DRUP

HFD #: HFD-580

Review completion date: September 19, 2006

Drug:

Trade name: Gestiva

Generic name: 17 α -hydroxyprogesterone caproate (17-HPC)

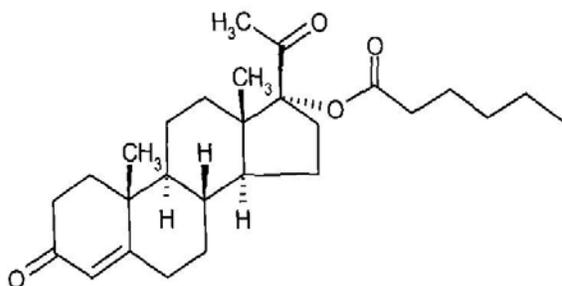
Code name: None

Chemical name: 17[(1-oxohexyl)oxy] pregn-4-ene-3, 20-dione hexanoate

CAS registry number: 630-56-8

Molecular formula/molecular weight: C₂₇H₄₀O₄, MW 428.60Da

Structure:



Relevant INDs/NDAs/DMFs: Delalutin (NDA 10-347) was approved in March 1956 for the treatment of habitual and recurrent spontaneous abortion, threatened abortion and post-partum pains. Another Delalutin application, NDA 16-911, was approved on February 24, 1972 for the treatment of endometrial cancer, management of amenorrhea and abnormal uterine bleeding, as a test for endogenous estrogen production, and for the production of secretory endometrium and desquamation. FDA approval for NDAs 16-911 and 10-347 was withdrawn without prejudice after the sponsor (Bristol Myers Squibb) notified the FDA that Delalutin was no longer marketed. Delalutin is currently available in the USA from compounding pharmacies.

17-HPC is listed under the following DMF numbers:

DMF No.	Date Issued	Manufacturer
(b) (4)		
[Redacted]		

* DMF covering 17-HPC used in Adeza product, 17P.

FDA-approved products containing 17-HPC:

Manufacturer	Trade Name	NDA/ANDA	Marketing Status	Source of Information
Bristol-Myers Squibb, formerly E.R. Squibb and Sons	Delalutin, 125 and 250 mg/mL	NDA 10-347 NDA 16-911	Discontinued	Federal Register, 2000
Akorn	None, 125 mg/mL	ANDA 18-004	Discontinued	Orange Book, 2005
Watson Labs, previously Steris	None, 125 and 250 mg/mL	ANDA 17-439	Discontinued	Orange Book, 2002 and 2005
Unknown	Duralutin	Unknown	Discontinued	Martindale, 1999
Unknown	Hylutin	Unknown	Discontinued	Martindale, 1999
Unknown	Hyprogest	Unknown	Discontinued	Martindale, 1999
Unknown	Prodrox 250	Unknown	Discontinued	Martindale, 1999

Products containing 17-HPC without FDA approval (NDA or ANDA):

Website	Product	Manufacturer
www.WedgewoodPharmacy.com	Compounded product requested by physician	Wedgewood Pharmacy
www.USAmesonline.com	Proluton Depot	None listed
www.DrugListing.com	Proluton Depot	None listed
www.ClickDrugStore.com	Proluton Depot	Schering AG (Germany) or Schering/Medipharma (India)
www.Endlessmeds.com	Proluton Depot	Schering/Medipharma (India)

Drug class: Progestational agents such as 17- α -hydroxyprogesterone (17-HP) have many functions including decreasing the frequency of the hypothalamic pulse generator and increasing the amplitude of LH pulses released from the pituitary, decreasing estrogen-driven endometrium proliferation, leading to development of secretory endometrium and in concert with estrogen cause proliferation of the acini of the mammary glands. 17 α -hydroxyprogesterone is a naturally occurring progestin which was originally isolated from the adrenal gland of animals in 1941 and shown to have weak progestational activity, slight mineralcorticoid action, no corticoid activity and weak androgenic activity. 17-HPC is a synthetic progestin hormone, which is an esterified derivative of 17- α -hydroxyprogesterone with caproate. It has been shown to have an increased degree of progesterone activity and a longer duration of action when compared to 17-HP.

Intended clinical population: Pregnant women at risk of recurrent preterm labor with a history of at least one spontaneous preterm birth at less than 37 weeks of gestation.

Clinical formulation: Delalutin HPC is prepared as white crystals or powder with a melting point of 120-124°C. Each 5 ml vial of 17-HPC for injection USP, 250 mg/ml (25% w/v) (b) (4) previously marketed Delalutin formulation. The inactive ingredients include Castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v). The diluent (b) (4) benzyl benzoate but with the same concentration of benzyl alcohol (tables 3.1.5-2 & 3.1.4.1-1).

Table 3.1.5-2. Composition of Injectable Formulations of 17-HPC

Component	Adeza Product	Study 17P-CT-002	Delalutin, 250 mg/mL	Delalutin, 125 mg/mL
17-HPC	250 mg/mL	250 mg/mL		(b) (4)
Benzyl benzoate	46%	46%		
Benzyl alcohol	2%	2%		
Castor oil	q.s. to volume	q.s. to volume		

Table 3.1.4.1-1. Composition of 17P Drug Product Formulations

Component	Adeza 17 Drug Product 250 mg/mL	Study 17P-CT-002 250 mg/mL	Delalutin ² 250 mg/mL
17 α -Hydroxyprogesterone Caproate USP ¹	250 mg/mL 25% (v/v)	250 mg/mL 25% (v/v)	(b) (4)
Benzyl Benzoate USP ¹	(b) (4) 46% (v/v)	(b) (4) 46% (v/v)	(b) (4)
Benzyl Alcohol NF ¹	(b) (4) 2% (v/v)	(b) (4) 2% (v/v)	(b) (4)
Castor Oil USP ¹	(b) (4) 28.6% (v/v)	(b) (4) 28.6% (v/v)	(b) (4)

¹ Formulary designations are for the Adeza 17P Drug Product and 17P Drug Product for Study 17P-CT-002 only.

² Delalutin Package Insert (1979). The type of percentage is not reported for excipients, but assumed to be v/v according to the FDA Chemist Review (1970).

3 (b) (4)
4

Route of administration: A single dose of 250 mg will be administered by intramuscular injection once weekly from week 16 day 0 (referred to as 16^{0/7}) until week 20 day 6 (referred to as 20⁶), week 37 or until birth.

Background: No well-controlled animal studies have been conducted to evaluate the safety of 17-HPC since the first approval for 17-HPC which was granted in 1956 for Delalutin (NDA 10-347). As per the Division request at the pre-NDA meeting held with Adeza representatives on Dec. 2004, the Sponsor has submitted relevant non-clinical literature articles. However, these articles suffer from a number of shortcomings including: 1) none of the studies conform to the current reproductive toxicity guidance (S3) or the Good laboratories Practices (GLP). 2) study designs are not deemed adequate from the drug safety evaluation stand and lack from such deficiencies such as the use of insufficient number of animals, insufficient historical controls for strains used, unknown route of administration, unknown actual dose administered or actual drug systemic exposure and 3) unknown safety profile of the drug during the fetal development since these studies were conducted to resolve the issue of whether 17-HPC was a potential teratogen.

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

Data reliance: As a 505(b)(2) application, except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-945 are owned by Adeza Biomedical or are data for which Adeza Biomedical has obtained a written right of reference. Any information or data necessary for approval of NDA 21-945 that Adeza Biomedical 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 Adeza Biomedical 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 NDA 21-945.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: 17-HPC was shown to help maintain pregnancy in pregnant rabbits but not in the pregnant rat, mare or squirrel monkey.

2.6.2.2 Primary pharmacodynamics: Dose-dependent progestational changes were seen in the uterus of a rabbit model pretreated with 5 µg of estradiol for 6 days, after 4 daily treatments ranging from 0.06 up to 1 g of 17-HPC. The potency of 17-HPC was twice that of progesterone, and its activity increased when used in combination with (b)(4) and benzyl benzoate (effects were still evident on day 20 compared to only day 8 for Progesterone). No effect was noted in the horse or squirrel monkey (Table 5.1.1).

Table 5.1.1 Primary Pharmacodynamic Studies

Species	No. Animals	Dose of 17-HPC	Surgery	Results	Reference
Rabbit	3/group	100 mg/kg, single dose 3 days before surgery	Ovariectomy on Day 7, 14 or 21 of gestation	Pregnancy was maintained to term.	Suchowsky 1958
Horse	5 5 5	500 mg q 7 days 500 mg q 2 days altrenogest qd	Unilateral ovariectomy after 2 days	Pregnancy was not maintained by 17-HPC.	McKinnon 1993
Squirrel monkey	31 29	25 mg q 6 days saline q 6 days	None	No difference observed in duration of pregnancy.	Aksel 1991

Note: q 2, q 6 or q 7 indicates dosing every 2, 6 or 7 days.

Mechanism of action: The mechanism of action through which 17-HPC prevents recurrent preterm labor is not well known. While progesterone can act directly by reducing uterine contractions, the mechanism by which it controls the onset of labor is not well understood but is hypothesized to be due to indirect or genomic changes in the expression of progesterone receptor isoforms. The caproate group helps increase the metabolic stability of the 17-HPC entity and thus increases its half-life and its progestational activity.

In a rat study², the mRNA expression of the long (but not the short) form of prolactin in the rat brain was induced for several weeks post partum following treatment with 17-HPC.

Drug activity related to proposed indication: In a rat study, the expression of the long form, but not the short form, of the prolactin receptor, was shown to be induced by 17-HPC. In a separate rat study, calmodulin concentrations in the uterus increased as pregnancy progressed. Whereas estrogen treatments increased the production of calmodulin, treatment with 17-HPC did not alter the profile of calmodulin levels during pregnancy.

2.6.2.3 Secondary pharmacodynamics

The effects of 17-HPC on estrus and fertility have been conducted in the rat, rabbit, pig and water buffalo. Rats treated with 17-HPC (s.c., 3x daily for a week) showed a consistent variation in the length of the estrus cycle compared to rats treated with progesterone or (b) (4) alone. The effect lasted for 2 cycles following the end of the treatment period. This study suggested that 17-HPC stabilized the estrus cycle and prolonged the pregestational activity.

2.6.2.4 Safety pharmacology: 17-HPC did not activate any receptors in the non-reproductive tissues of fetal mice and monkeys. A summary of safety pharmacology studies found in the literature is summarized in Table 3.1.5-11.

Table 3.1.5-11. Safety Pharmacology

Organ Systems Evaluated	Species/Strain	Route, Duration	Doses of 17-HPC or Comparator	Gender and No. per Group	Noteworthy Findings	GLP	Reference*
Fetal receptors in uterus, lungs, liver, kidney, heart, brain, adrenal, limbs	Mouse/CD-1 Monkey/cynomolgus	In vitro	Not applicable	Mouse: 20 uteri, 3 hearts, 4 limbs, 1 each of other tissues Monkey: 3 male, 2 female	Estrogen receptors, but not progesterone receptors were found in fetal monkey and mouse uteri. No estrogen or progesterone receptors were found in the lungs, liver, kidney, heart, brain, adrenal gland, or limbs.	No	Hochner-Celnikier 1986
Neonatal uterus	Hamster/Golden	Subcutaneous Single dose	0, 250 µg 17-HPC 10 µg oestrol Tamoxifen, amount not specified Control: no treatment	Females, 134 total, No. per group not specified	Higher proliferation on Day 1 with oestrol. Decrease of proliferation over 20 days in untreated controls. 17-HPC accelerated decrease in proliferation. No effect of tamoxifen.	No	Loktionov 1981
Cartilage during bone growth	Rabbit/strain not specified	Intramuscular Every 3 rd day for 15 days	10 mg/kg 17-HPC Control: no treatment	5 male, 5 female total for both groups	17-HPC may cause noticeable changes in articular and conjugation cartilage during growth due to endocrine effects.	No	Tato 1981a & b
Renal function	Rat/Sprague Dawley	Not specified 12 - 14 days	12.5 mg 17-HPC + 0.25 mg estradiol valerate q 3 d Vehicle q 3 d	5 female/group	17-HPC + estradiol had no effect on urinary flow after vasopressin or oxytocin challenges. The hormones lowered the sodium and chloride excretion after oxytocin challenge and delayed peak electrolyte excretion after vasopressin challenge.	No	Eckert 1999
Renal function	Rat/strain not specified	Subcutaneous 3 days	0, 0.5, 2, 4 mg 17-HPC for 3 days Adrenalectomy	5 male/group	17-HPC for 3 days increased sodium excretion above untreated control to levels for adrenalectomized rats.	No	Kessler 1958

² Sugiyama et al., 1994. *J. Endocrinology*. Preferential expression of long form prolactin receptor mRNA in the rat brain during the estrous cycle, pregnancy and lactation: Hormones involved in its gene expression. 141:325-33

Organ Systems Evaluated	Species/Strain	Route, Duration	Doses of 17-HPC or Comparator	Gender and No. per Group	Noteworthy Findings	GLP	Reference*
Androgenic and glucocorticoid	Rat/strain not specified	Subcutaneous 20 days	0, 1, 5, 10 mg 17-HPC 1, 5, 10 mg 17 α -hydroxyprogesterone 0.1, 0.5, 1 mg testosterone	10 immature castrated males/group	17-HPC had no effect on body weight or weights of seminal vesicles, ventral prostate, or thymus. Non dose-dependent slight increase in adrenal weight. No effect on liver glycogen.	No	Kessler 1958
Monoamine synthesis and metabolism	Rat	Subcutaneous for 17-HPC, estradiol valerate, testosterone and vehicle. Not specified for ACTH 7 days	80 mg/kg 17-HPC for 7 days 12 mg/kg estradiol valerate for 7 days 20 mg/kg testosterone for 7 days Control: peanut oil for 7 days 40 IU/kg ACTH for 7 days	12 males/group	Compared to vehicle, 17-HPC lowered amount of dopamine, but not norepinephrine or epinephrine in adrenal. 17-HPC group had lower activity for monoamine oxidase measured using kynuramine, but no lowering of monoamine oxidase activity if measured using [¹⁴ C]-tryptamine. 17-HPC did not affect phenylethanolamine N-methyl transferase or catechol-O-methyl transferase. Effects for 17-HPC less pronounced than effects for estradiol or testosterone.	No	Bukhari 1981

Neurological effects: No relevant data could be mined from the literature.

Cardiovascular effects: No relevant data could be mined from the literature.

Pulmonary effects: No relevant data could be mined from the literature.

Renal effects: Pretreatment of ovariectomized rats with 12.5 mg 17-HPC plus 0.25 mg estradiol valerate every 3rd day for 12-14 days did not affect the urinary flow or sodium excretion compared to vehicle-treated rats. A similar pattern was seen for chloride excretion and no consistent pattern was noted for potassium excretion profile.

Gastrointestinal effects: No relevant data could be mined from the literature.

Abuse liability: No relevant data could be mined from the literature.

Other: Treatment of female rabbits aged 30-40 days with 17-HPC resulted in an increase in articular and conjugation cartilage during growth possibly due to endocrine effects. However, 17-HPC showed no androgenic or glucocorticoid activities in the immature castrated male rats³.

2.6.2.5 Pharmacodynamic drug interactions

While no effect on uterine weights was seen after treatment of ovariectomized rats with 17-HPC plus estradiol, ovariectomized rabbits treated with 17-HPC alone (8.3 mg/kg, s.c. once a week) and fed high cholesterol diets showed reduced endometrial area compared to controls. The opposite finding was seen when estradiol valerate was administered alone (0.3 mg/kg/week). No change in endometrial area was noted when 17-HPC (2.8 mg/kg/week) was administered with estradiol valerate (1 mg/kg/week) (Table 5.2.5).

³ Kessler & Berman, 1958 Jul 30. Ann N Y Acad Sci. Some biological activities of certain progestogens. I. 17 alpha-Hydroxyprogesterone 17-n-caproate; 71(5):486-93.

Table 5.2.5 Pharmacodynamic Drug Interactions

Species	No. Animals	Dose of 17-HPC or Comparitor	Route	Pre or Post Treatment or Precondition	Results
Mouse	10 F per group	0.01 - 0.160 mg 17-HPC + 0.03 µg estradiol 0.015 - 0.06 µg estradiol 0.01 - 0.160 mg 17 α-hydroxyprogesterone + 0.03 µg estradiol 0.01 - 0.05 mg progesterone + 0.03 µg estradiol 0.1 mL sesame oil	Intramuscular, 3 days	Immature female mice	Estradiol produced a dose-dependent substantial increase in the uterine weights. Neither 17-HPC nor 17 α-hydroxyprogesterone inhibited the weight increase caused by 0.03 µg estradiol. Progesterone produced a dose-dependent inhibition.
Rat	5 - 8 F per dose	0.5 - 4.0 mg 17-HPC 0.5 - 4.0 mg 17-HPC + 0.1 µg estradiol 0.1 µg estradiol 0.5 - 4.0 mg progesterone + 0.1 µg estradiol 0.5 - 4.0 mg progesterone 0.3 mL sesame oil	Subcutaneous, 3 days	Bi-lateral ovariectomy 7 days prior to dosing	17-HPC plus estradiol had minimal or no effect on the increase in uterine weights produced by estradiol. 17-HPC administered alone caused a minor increase in uterine weight. The effects of progesterone were similar, but more pronounced than those for 17-HPC.

Species	No. Animals	Dose of 17-HPC or Comparitor	Route	Pretreatment or Precondition	Results
Rabbit	8 F per group	8.3 mg/kg/week 17-HPC 8.3 mg/kg/week 17-HPC + 0.3 mg/kg/week estradiol valerate 8.3 mg/kg/week 17-HPC + 1 mg/kg/week estradiol valerate 2.8 mg/kg/week 17-HPC + 1 mg/kg/week estradiol valerate 1 mg/kg/week estradiol valerate for 12 weeks + 25 mg/kg 17-HPC at weeks 3, 4, 7, 8, 11 and 12 0.3 mg/kg/week estradiol valerate Control: no treatment	Intramuscular, 12 weeks	Bi-lateral ovariectomy Diet containing 0.5% cholesterol	17-HPC significantly reduced endometrial area and estradiol valerate significantly increased endometrial area compared to controls. 17-HPC completely inhibited the estradiol valerate-induced increase in endometrial area. Some inflammatory histological changes were seen in the endometria of the treated animals, but the effects were less with the lower dose of 17-HPC. 17-HPC did not affect the development of aortic plaque. Estradiol valerate reduced plaque size significantly, and high doses of estradiol valerate reduced plasma cholesterol levels. Addition of 17-HPC did not change the response to estradiol.
Rat	6 F, 6M per treatment 3F, 3 M for control	2.5 mg/week 17-HPC + 0.1 mL CCl ₄ twice weekly 0.1 mL CCl ₄ twice weekly 2.5 mg/week medroxyprogesterone acetate + 0.1 mL CCl ₄ twice weekly 2.5 mg/week medroxyprogesterone acetate + 0.1 mL CCl ₄ twice weekly for 2 months 2.5 mg/week medroxyprogesterone acetate Control: no treatment	Subcutaneous, 1 month except second group with medroxyprogesterone acetate, which was treated for 2 months	7% ethanol in drinking water for 10 days before treatment	Histologically, rats treated with 17-HPC + CCl ₄ had a more severe degree of cirrhosis compared to the rats treated with CCl ₄ alone. Addition of 17-HPC to carbon tetrachloride produced a slight increase in the collagen content of the liver. Animals receiving CCl ₄ with and without medroxyprogesterone acetate did not show any histological differences. Without CCl ₄ , neither 17-HPC nor medroxyprogesterone acetate had any effect on collagen content of the liver compared to controls.

Species	No. Animals	Dose of 17-HPC or Comparitor	Route, Duration	Pre or Post Treatment or Precondition	Results
Rat	5 F per group	38.5 mg/kg/week 17-HPC 38.5 mg/kg/week 17-HPC + 1.2 g/kg CCl ₄ twice weekly 38.5 mg/kg/week medroxyprogesterone acetate 38.5 mg/kg/week medroxyprogesterone acetate + 1.2 g/kg CCl ₄ twice weekly 19.5 mg/kg/week progesterone 19.5 mg/kg/week progesterone + 1.2 g/kg CCl ₄ twice weekly 1.2 g/kg/week CCl ₄ Control: not specified	Subcutaneous, 45 days	Ovariectomized 20 days prior to treatment	17-HPC, progesterone or medroxyprogesterone alone did not produce any histological evidence of fibrosis or fatty change in the liver. CCl ₄ produced fibrosis, fatty change and fibronectin staining. Medroxyprogesterone acetate plus CCl ₄ produced prominent hepatic steatosis. 17-HPC and progesterone accelerated the liver damage caused by carbon tetrachloride. Biochemical changes produced by 17-HPC in CCl ₄ treated animals were increased fibronectin and decreased triglycerides.
Rat	5 F per group	5.0 mg/week 17-HPC for 1 month 5.0 mg/week medroxyprogesterone acetate for 1 month 2.5 mg/week progesterone for 1 month Control: untreated	Subcutaneous, 1 month	-	17-HPC and progesterone produced increases in collagen formation of 63% and 43%, respectively. Medroxyprogesterone acetate had no effect. 17-HPC and progesterone increased the beta fraction significantly.
Rabbit	10 F, 6 M	1.5 mg/kg 17-HPC for 3 days 1 mg/kg testosterone propionate for 3 days 0.5 mg progesterone + 0.3 mg/kg estradiol benzoate for 3 days No treatment All treatments in same animals with 7-day washout periods	Not specified, 3 days	Anesthesia induced after treatment with 16 mg/kg thiopentone sodium, iv	All treatments, including 17-HPC, increased the time to onset of anesthesia and decreased the duration of anesthesia.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table 5.2.2 Primary Pharmacodynamics

Species	No. Animals	Dose of 17-HPC or Comparitor	Route, Duration	Pretreatment	Results	Reference*
Rabbit	2 - 4 animals per sacrifice time	0.16 - 20 mg/animal 17-HPC progesterone and 37 other analogs	Subcutaneous Subcutaneous Single dose	0.5 µg estradiol subcutaneously for 6 days plus daily after 17-HPC or comparitor until sacrifice	17-HPC showed potent and long-lasting progestational changes. At 2.5 mg, changes were observed up to 13 days after injection, and at 5 mg or more, the changes were observed up to 17 days.	Junkmann 1954
Rabbit	4 - 6 per group	0.06 - 1.0 mg 17-HPC	Subcutaneous 4 days	5 µg estradiol for 6 days then 0.5 µg daily during 17-HPC treatment	17-HPC showed dose-dependent (0.06 - 1.0 mg) progestational effects.	Kessler 1958
Rabbit	3/group	100 mg/kg 17-HPC 3 days before surgery	Not specified Single dose	Ovariectomy on Day 7, 14 or 21 of gestation	Pregnancy maintained to term.	Suchowsky 1958
Horse	5 5 5	500 mg q 7 days 500 mg q 2 days altrenogest q d	Intramuscular Day 15 to end of pregnancy	Unilateral ovariectomy after 2 days	Pregnancy not maintained by 17-HPC.	McKinnon 1993
Squirrel monkey	31 29	25 mg q 6 days saline q 6 days	Intramuscular 60 - 70 days	-	No difference in duration of pregnancy.	Aksel 1991
Rat	15/group	25 mg 17-HPC 0.5 mg estradiol valerate	Not specified 7 days	Ovariectomy	0.5 mg estradiol valerate or 25 mg 17-HPC increased the long form of prolactin receptors in the brain, but not the short form.	Sugiyama 1994
Rat	36 36 64	2.5 mg 17-HPC q 3 days 0.1 mg estradiol valerate q 3 days Pregnancy	Subcutaneous 18 days	-	Estrogen increased calmodulin in the uterus similarly to pregnancy. 17-HPC treatment had no apparent effect on uterine calmodulin.	Yoshida 1985

* References are included in Section 5.8 of the NDA
Note: q 2, q 3, q 6 or q 7 indicates dosing every 2, 3, 6 or 7 days.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Following subcutaneous injection of 17-HPC in rats, the drug is distributed slowly from the injection site and is widely distributed to various tissues such as the liver. Excretion is mainly by the fecal route and elimination is slow since a single dose of 17-HPC was still available 7 days post-injection. 17-HPC is thought to be metabolized to 17 α -hydroxyprogesterone, progesterone and related compounds.

2.6.4.2 Methods of Analysis: N/A

2.6.4.3 Absorption: Since 17-HPC is intended to be administered intramuscularly, no oral distribution data are required.

2.6.4.4 Distribution: Studies conducted in the rat showed that 17-HPC is absorbed and distributed to the tissues with the highest concentration seen in the liver, kidney, muscle and uterus (Table 5.3.1).

Table 5.3.1 Tissue Distribution of [14 C]-17-HPC

Tissue	Mean % of Dose in Tissue (Mean % of dose/g dry tissue)				
	0.5 Day	1 Day	2 Days	4 Days	8 Days
Blood	0.0	0.0	4.55	0.0	1.96
Liver	4.17 (2.78)	1.89 (1.30)	7.25 (6.71)	0.89 (0.86)	0.0
Kidney	0.27 (1.25)	1.69 (7.05)	0.0	0.72 (3.28)	0.0
Brain**	0.0	0.0	0.0	0.23	0.21
Uterus	0.11 (1.25)	0.14 (1.84)	0.50 (6.25)	0.60 (14.0)	0.04 (2.5)
Pituitary**	0.0	0.0	0.0	0.0	0.02
Muscle**	0.61	1.85	0.50	7.34*	0.0
Bone**	0.0	0.18	0.0	0.0	0.11
Injection site	21.01	59.0	30.0	0.47	0.32

* Kimbel et al. (1958) consider this a questionable value.

** Kimbel et al. (1958) consider the results for these values questionable because of wide variation.

2.6.4.5 Metabolism: HPC is metabolized by human hepatocytes (both phase I & II) by undergoing reductive reactions of the double bond at C4-C5 and ketone groups at C-3, hydroxylation and conjugation. The conjugated products include sulfated, glucuronidated and acetylated products.

2.6.4.6 Excretion: [14 C]-17-HPC administered at 100 mg/kg to white rats was excreted by day 8 (~ 85%) in the urine (12.5%) and in the feces (72%). The excretion half-life for HPC in the plasma is ~ 7.8 \pm 3days.

2.6.4.7 Pharmacokinetic drug interactions: 17-HPC is predominantly bound to albumin in the blood.

2.6.4.8 Other Pharmacokinetic Studies: None

2.6.4.9 Discussion and Conclusions: 17-HPC is slowly distributed after sc injection in rats, widely distributed, excreted mainly by the fecal route and elimination is slow. 17-HPC is thought to be metabolized to 17 α -hydroxyprogesterone, progesterone and related compounds.

2.6.4.10 Tables and figures to include comparative TK summary: None

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Type of Study	Test System	Method of Administration	GLP
Absorption None	-	-	-
Distribution Single-dose study	Rat	Subcutaneous	No
Metabolism Multi-dose study	Squirrel monkey	Intramuscular	No
Multi-dose study	Water buffalo	Intramuscular	No
Single and multi-dose studies	Human	Intramuscular	No
Excretion Single-dose study	Rat	Subcutaneous	No
Drug Interaction None	-	-	-
Other None	-	-	-

Table 5.4.2 Pharmacokinetics: Organ Distribution

Reference: Kimbel KH, Willenbrink J, Junkmann K. *Acta Endocrinologica*. 28:502-506, 1958.

Species: Rat

Gender/Number of animals: 25 Female

Feeding condition: Fed daily

Vehicle/Formulation: 20% solution in castor oil:benzyl benzoate 2:3

Method of Administration: Subcutaneous

Dose (mg/kg): 100

Radionuclide: Carbon-14

Specific activity: 215 $\mu\text{Ci}/\text{mmol}$

Sampling times: 0.5, 1, 2, 4 and 8 days

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* Kimbel et al. (1958) consider this a questionable value.

** Kimbel et al. (1958) consider the results for these values questionable because of wide variation.

Table 5.4.3 Pharmacokinetics: Excretion

Reference: Kimbel KH, Willenbrink J, Junkmann K. *Acta Endocrinologica*. 28:502-506, 1958.

Species: Rat

Gender/Number of animals: 25 Female

Feeding condition: Fed daily

Vehicle/Formulation: 20% solution in castor oil:benzyl benzoate 2:3

Method of Administration: Subcutaneous

Dose (mg/kg): 100

Analyte: Radioactivity from [¹⁴C]-17-HPC

Assay: Amount of [¹⁴C]-CO₂ after combustion

Excretion route: Urine and feces

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2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary: No well-controlled animal studies have been conducted to evaluate the safety of 17-HPC since the first approval for 17-HPC which was granted in 1956 for Delalutin (NDA 10-347). As per the Division request at the pre-NDA meeting held with Adeza representatives on Dec. 2004, the Sponsor has submitted relevant nonclinical literature articles. However, these articles suffer from a number of shortcomings including: 1) none of the studies conform to the current reproductive toxicity guidance (S3) or the Good laboratories Practices (GLP). 2) study designs are not deemed adequate from the drug safety evaluation stand and lack from such deficiencies including the use of insufficient number of animals, insufficient historical controls for strains used, unknown route of administration, unknown actual dose administered or actual drug systemic exposure and 3) unknown safety profile of the drug during the fetal development since these studies were conducted to resolve the issue of whether 17-HPC was a potential teratogen. Based on the lack of new nonclinical data for 17-HPC, it is not known whether exposure to 17-HPC pauses a potential risk to the mother or the fetus.

General toxicology: No new data were submitted.

2.6.6.2 Single-dose toxicity: None

2.6.6.3 Repeat-dose toxicity: None

2.6.6.4 Genetic toxicology: No new data were submitted.

2.6.6.5 Carcinogenicity⁴: In the female Wistar rat (=15/group) administered weekly subcutaneous injections of 20 mg/kg 17-HPC in sesame oil alone or in combination with N-nitrosodiethylamine in drinking water for life at 3 mg/kg body weight, liver carcinomas occurred in 78% of combination treated rats and in 100% of animals treated with the nitrosamine alone. 17-HPC has not been shown to be carcinogenic. Mean survival time was 145 days. This reviewer cannot reach any significant conclusions from this study regarding the carcinogenic potential for 17-HPC. However, since Gestiva will not be prescribed for chronic use (presumably less than 6 months of total use), it is unlikely that carcinogenicity will be a potential concern for this product.

2.6.6.6 Reproductive toxicology: Based on published animal and human studies, 17-HPC carries a pregnancy category A due to the absence of congenital anomalies in infants born to mothers treated with progesterone or hydroxyprogesterone during pregnancy.

Relevant articles in the literature:

- 1) Hendrickx et al., 1987⁵: No teratogenic effects were noted in the mouse when tested up to 10 mg/kg (160 times the human dose equivalent, HED). No teratogenic effect was noted in the rhesus monkey when exposed once weekly to HED of 0.1x-10x 17-HPC starting from the early fetal life (gestational day GD 20) until GD 146 to mimic a supportive hormonal therapy of weekly injections throughout the period of pregnancy. A similar result was seen in Cynomolgus monkeys exposed to 0.1-10x HED of 17-HPC when exposed during the same embryonic stages. In the Rhesus monkey, complete embryo-lethality (n=10/10 litters) was seen at 1x and 10x the HED. However, no embryo-lethality was seen in the Cynomolgus monkey exposed to the same dose during the same gestational period.
- 2) Seegmiller et.al, 1983⁶: Female Swiss Webster mice were injected daily with Delalutin on GD 6-15 at 42-833 mg/kg (corresponding to 10, 100 or 200x the HED) of 17-HPC. All doses resulted in a higher incidence of resorptions (4-12%). Maternal death was seen at the 2 highest doses where the incidence of death was 8% and 13%, respectively, compared to controls. Treatment with Delalutin did

⁴ IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex Hormones (II), International Agency for Research on Cancer, Volume 21, December 1979.

⁵ Hendrickx et al. Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. *Teratology* 35:129-136 (1987).

⁶ Seegmiller et al. Evaluation of the teratogenic potential of Delalutin (17- α -Hydroxyprogesterone) in mice. *Teratology* 28:201-208 (1983).

- not result in adverse events on uterine growth rate, sex ratios, malformation rates or altered development of reproductive organs in either sex.
- 3) Elovitz & Mrinalini, 2006⁷. In this abstract, the authors provided new evidence in an inflammation-induced preterm mouse model where a dose-dependent increase in maternal mortality was seen: Deaths (n=3/4) were seen at 4 mg/kg (human equivalent dose of 8 mg/kg) and at 2 mg/kg (HED of 4 mg/kg; n=11/24) within 24 hrs of dosing. In a separate study, dams (n=10) treated with 17-HPC at 1hr prior to LPS treatment (to induce inflammation) on GD 15 delivered between GD16-18, none of whose pups were alive. The significance of the study findings is not known but raises some concerns regarding the assumed safety of the use of 17-HPC for the preterm indication when accompanied by inflammation.
 - 4) The administration of 17-HPC should be discontinued after delivery since significant amounts of the parent drug were found in the milk ingested by the infant in one study.

2.6.6.7 Local tolerance: None

2.6.6.8 Special toxicology studies: None

2.6.6.9 Discussions and Conclusions: None

2.6.6.10 Tables and Figures: None

2.6.7 TOXICOLOGY TABULATED SUMMARY

Summary of relevant nonclinical reproductive toxicity studies conducted with 17-HPC (constructed by the reviewer):

Reference	Species/strain	Dose/route	Gestational Days	Finding
Carbone & Brent, 1993	C57Bl/6J mouse	subQ pellet implants 0.5, 5 or 50 mg/kg	GD 7-19	No effects on dams, fetuses
Courtney & Valerio, 1968	Rhesus Monkey	(IM?) 21 or 41 mg/kg/day for a 6 Kg monkey	1-10 days between GD 7-132	Non-dose dependent increase in abortion incidence: n=4/14 aborted for 21 mg/kg and 1/14 for 41 mg/kg
Seegmiller et., 1983	Swiss Webster mouse	Subcutaneous, 42, 416 or 833 mg/kg	GD 6-15	≥416 mg/kg: reduced fetal weights. Increase in rate of resorptions at 833 mg/kg
Hendrickx et al., 1987	Rhesus Monkey	Intramuscularly in combination with estradiol	7-day intervals between	Maternal weight loss and abortions

⁷ Elovitz & Mrinalini. 17-P and preterm birth: Lessons from a mouse model. Abstract presented at the Annual meeting for Maternal-Fetal Medicine. Denver, Co. Spring 2006

		valerate; 0.1x-1x HDE. Actual dose not specified	GD20-146	
Hendrickx et al., 1987	Cynomolgus monkey	Intramuscular, (same design as Hendrickx above)	7-day intervals between GD20-146	No effects on dams or fetuses

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Due to the lack of adequate non-clinical studies and the availability of human data on the use of the product in the clinic, the nonclinical recommendation on the approvability of this product cannot be sustained by solid nonclinical data.

Unresolved toxicology issues (if any): The potential for adverse effects of treating preterm mothers with 17-HPC on fetal survival and normal post-natal development.

Recommendations: A state of the art, GLP-compliant, multigenerational reproductive toxicology study which covers the stages of pregnancy covered in the clinic, is recommended to evaluate the safety of 17-HPC on maternal and fetal health.

Suggested labeling: No well-controlled nonclinical toxicity studies have been conducted with 17-HPC to support the indication of preterm labor.

APPENDIX/ATTACHMENTS: None

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