

**CIBA Vision**

mg/kg. At doses  $\geq 70$  mg/kg survivors exhibited reduced spontaneous motor activity, red-colored urine, diarrhea, and trembling on the day of dosing and dark red coloring, ulceration, necrosis, and partial sloughing of the tail beginning one day after treatment. There were no treatment-related effects on body weight and the necropsy findings were confined to injection site reactions.

**E. SUMMARY OF TOXICOLOGY** - Studies to assess the toxicity of UF-021 following ocular instillation were conducted in nonpigmented rabbits [up to 90 days], pigmented rabbits, dogs [up to 1 year], and cynomolgus monkeys [up to 2 years]. Formulations used included both [ ] formulations 1 and 2 and the [ ] formulations. The [ ] formulations are essentially the same as the clinical formulation but the concentration of the drug substance was varied. The primary difference between the [ ] and [ ] formulations is in the vehicle excipients [See Appendix 1 for the ingredients in the formulations]. The ocular toxicity studies suggest that, in general, the drug-induced changes are similar for the [ ] and [ ] formulations. The concentration of drug substance and administration frequency for the [ ] formulations ranged from 0.05-0.2% BID-QID in the nonpigmented rabbits, 0.12% in pigmented rabbits [QID], dogs [BID-QID], and monkeys [BID]. The concentration of drug substance in the [ ] formulations ranged 0.06-0.18% BID-QID in nonpigmented rabbits, 0.12-0.15% BID-QID in pigmented rabbits, and 0.15% BID in cynomolgus monkeys.

The principal ocular toxicity that was observed in the rabbits was generally mild ocular irritation [Draize Score generally = 2]. Several animals demonstrated moderate ocular irritation. The irritation in the nonpigmented rabbits was characterized by both iridic congestion and conjunctival vessel injection with the iridic congestion more commonly observed than the conjunctival effects. The irritation in the pigmented rabbits included conjunctival congestion. The iridic congestion was not detected in the Dutch Belted Rabbits, which is probably a function of the pigmentation as well as the mild degree of change. There were several rabbits, both nonpigmented and pigmented, which developed corneal erosions [e.g. fluorescein staining] in  $\leq 25\%$  of the corneal surface. In nonpigmented rabbits, the irritation was observed at drug substance concentrations as low as 0.05%. Several of the studies in both pigmented and nonpigmented rabbits suggested that the excipient vehicle was mildly irritating. Irritation appeared to be somewhat dose and frequency of administration dependent. Frequency of administration seemed to be a greater factor within the first several months of drug administration. Increasing the frequency of administration did not appear to increase the number of animals that exhibited ocular irritation but did tend to increase the total number of incidences of irritation especially within the first 6 months of treatment. In 2/3 of the rabbit studies, irritation prior to dosing was comparable to that observed 1-hour after the last dose, although there was not always a correlation in the animals exhibiting irritation at each time point. No treatment related irritation was identified in either the dog or the cynomolgus monkey. However, the control group for the dogs was administered excipient vehicle. These studies indicate that this vehicle may be mildly irritating.

There were no histopathological changes that could be definitively attributed to treatment with the exception of vasodilation of the ciliary body in 1 study. In several of the studies, there were some mild changes in both the treated and excipient control groups. However, some of the studies suggested that the excipient vehicle was mildly irritating and, therefore, a saline control would have been more appropriate. However, any changes observed were mild.

Miosis, which generally resolved within 18 hours, was induced in a dose-dependent fashion in dogs only. The Sponsor states that this appears to be a species-specific response since it was not observed in rabbits, nonhuman primates, and humans. In addition, they cite *in vitro* work that indicates that the contractile response of the pupillary sphincter muscle in cats and dogs is considerably stronger than that observed in humans and rabbit pupillary sphincter muscle.

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Administration of the  $F_{2\alpha}$  analogue, latanoprost, has been associated with iridic pigmentation changes. The study conducted in cynomolgus monkeys to specifically evaluate the effect on iris color change of latanoprost compared to UF-021 indicated that although the incidence of iris color change occurred at a higher frequency with latanoprost [3/5 males and 1/5 females], iris color change was observed with UF-021 [1/5 males]. Neither treated group exhibited eyelash growth or increased pigmentation.

There were no treatment-related systemic effects following ocular instillation.

The Sponsor conducted studies to delineate the systemic toxicity of UF-021 by administering single or multiple doses by the iv, sc, and po routes in mice, rats, and dogs. The  $LD_{50}$  in mice was >2000 mg/kg and 100-200 mg/kg by the po and iv routes, respectively. The  $LD_{50}$  of UF-021 in rats was approximately 90 and 125 mg/kg in males and females, respectively, following a single iv dose and >1000 mg/kg and <2000 mg/kg following sc administration. The  $LD_{50}$  in rats following the administration of a single iv dose of the M1 metabolite [UF-025] was 118 mg/kg in males and >118 mg/kg but <154 mg/kg in females. CNS signs generally preceded death, including depressed respiration and tonic or clonic convulsions, in both species. These findings were also noted in animals that survived [ $\geq 40$  mg/kg in mice and  $\geq 70$  mg/kg in the rat]. There was also gross and histopathological evidence of pulmonary distress in the premature decedents. Similar findings were observed in mice that received a single iv dose of 70 mg/kg of Rescula, a synthetic precursor, a by-product, 2 degradation products, and deteriorated product. Depressed respiration, prostration, piloerection, and reduced spontaneous motor activity but no deaths or convulsions were observed in mice administered 70 mg/kg of the M1 metabolite. Dogs administered a single iv dose of UF-021 exhibited a non-dose dependent increase in ALT, AST, and SAP at both 10 and 40 mg/kg. The increase in ALT was the greatest ranging from 10-20X control values. Hepatic microgranulomas were also observed in the dogs administered 40 mg/kg. Dogs administered either excipient VH or test article exhibited a apparent hypersensitivity reaction including lip and ocular hyperemia and facial pruritis. Injection site reactions, ranging from swelling to necrosis, was observed in all species following either iv or sc administration.

The observed effects in the studies in which UF-021 was administered by the oral route to rats included a transient and intermittent salivation; a 6% decrease in Hb following a 14-day exposure of 150 and 450 mg/kg; and 15-25% decrease in RBC indices at 1.2 and 12 mg/kg, but not at 3.6 mg/kg following a 4-week exposure. The hematological effects were not considered test article-related. [See discussion above.] There was a 20% increase in absolute and relative liver weights in males administered 450 mg/kg/day for 14 days without any clinical pathology or histopathology correlates. The relationship to treatment is not known. In mice, there were no treatment-related toxicities observed at doses up to 12 mg/kg/day with the possible exception of a 40% decrease in ovarian weights and an increased incidence of ovarian cysts at the high dose.

An increase in the incidence of mammary carcinoma was observed in rats administered 20 mg/kg of UF-021 sc for 1-year but not at 0.2 and 2 mg/kg/day. The total incidence of mammary carcinoma was 1/14 (7%), 3/22 (14%), 2/14 (14%), 1/14 (7%), and 8/21 (38%) for the untreated, vehicle control, 0.2 mg/kg, 2 mg/kg, and 20 mg/kg groups respectively.

In the 3-month study, females at 50 mg/kg/day sc exhibited an 85% increase in ovarian weight that was associated with an increase in the number of corpora lutea. This finding was reversible.

In dogs, clinical signs observed in males and females at 5 mg/kg/day for 1 year included mucoid, bloody feces, miosis, and interdigital swelling. The Sponsor states that these findings are generally observed in beagle dogs.

In both rats and dogs following sc drug administration, there was significant local toxicity at the injection site including hemorrhage, edema, necrosis and/or ulceration. In addition, there were

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generally decreases in RBC indices and total protein and/or albumin in both species. In the rat the RBC changes were accompanied by an increase in medullary hematopoiesis and reticulocyte counts. The Sponsor suggests that these changes are secondary to the injection site reaction. There were statistically significant increases in WBC counts in the dog in both the 3-month and 12-month study that was characterized by a neutrophilia. If hematological perturbations are a function of the injection site toxicity, these findings are of little toxicological significance for the current proposed indication, e.g. ocular administration. Even if these findings do reflect a direct treatment-related effect, these changes can be monitored in the clinical setting. In addition, these changes in the dog were observed at 100X and 50X the human exposure based on body weight and surface area, respectively at a dose of 5 µg/kg. The NOAEL for these hematological changes in the rat [5 mg/kg/day] was ≥2000X human exposure based on AUC at a dose of 5 µg/kg [e.g. two 50µl drops OU BID].

**V. Carcinogenicity:****A. Rat Carcinogenicity Study**

i. Title: Unoprostone Isopropyl:104 week carcinogenicity study in rats with administration by gavage [Vols. 1.35-1.40]

Study Identification: [REDACTED]

Site: [REDACTED]

Study Dates [In-life]: February 19, 1997 – March 3, 1999

Formulation and Lot No.: Rescula [REDACTED]

Vehicle Control

Negative Control: [REDACTED]

Final Report: October 22, 1999

GLP and QA Statements Signed: No [X]

Objective: To assess the carcinogenic potential of Rescula when administered by oral gavage to rats for 104 weeks.

*Dr. Terry Peters reviewed this study as a consult [Review completed April 6, 2000]. This review is provided below.*

Scientific literature reviewed: No

**CARCINOGENICITY:**

Study Type: 2 year gavage study in rats

Species/strain: Crl:CD®BR rats

Number of animals per group; age at start of study: 60/sex/dose.

Animals were 4 weeks old on arrival and acclimated for 2 weeks before study initiation. An additional batch of animals was received in April 1998 to be used for repeating the Day 1 toxicokinetic blood sampling.

Animal housing: 5/sex/dose

Drug Lot/Batch number(s): [REDACTED] It is unclear how the differing expiration dates could apply to the single batch.

Drug Purity / Stability / Homogeneity: Samples were frozen until sent to sponsor for analysis.

They were analyzed by the sponsor or [REDACTED]

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## Doses:

- Basis of Dose Selection: Doses were limited by the maximum dosing volume (10 mL/kg/bw) for chronic administration of the supplied material.
- Relation to Clinical Use:
- CAC Concurrence: None
- Route of Administration: Gavage at 10 mL/kg as a constant dose volume, once/day
- Frequency of Drug Administration: 7 days/week.
- Dual Controls Employed: Control group 1 received only vehicle and control group 2 received
- Interim Sacrifices: None
- Satellite PK or Special Study Group(s): None

## Study Results and Frequency of Monitoring:

- Clinical Observations: Twice/day for viability. Once/week as detailed clinical examination. No treatment-related signs were reported.
- Mortality: There were 414 premature decedents divided across dose groups.

Group	Dose in mg/kg/d	Males	Females
1	0	45	42
2	0	32	40
3	1.2	44	44
4	3.6	38	46
5	12.0	43	43

In males, the placebo group was almost ( $p=0.055$ ) statistically higher than the water controls and in females, statistical significance was reached ( $p=0.020$ ). There were no significant effects of treatment on survival.

However, at issue is the survival at 80 weeks that is deemed adequate (Males: 37, 43, 39, 36 and 34 for the respective groups, and females: 36, 47, 43, 36 and 44 for the respective groups).

- Body Weight: Once/week for the entire study. Rates of gain and body weights were comparable across dose groups.
- Food Consumption: Weekly for the first 13 weeks and every 4 weeks thereafter. Comparable across dose groups.
- Ophthalmoscopy: Prior to dosing for all animals and controls and high dose only Weeks 13, 26, 52, 78 and 103. No treatment-related findings were reported.
- Hematology: First 20 survivors/sex/dose in Weeks 26, 52, 78 and 104 (approximately). No treatment-related findings were reported.
- Clinical Chemistry: Last 20 survivors/sex/dose in Weeks 26, 52, 78 and 104 (approximately). No treatment-related effects were reported.
- Urinalyses: Screens at the same time points as the hematology and clinical chemistries. No treatment-related effects were reported.
- Organs weighed: adrenals, brain, epididymides, extraorbital lacrimal gland, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid. No treatment-related differences from controls were noted.

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- **Gross Pathology:** All main study animals, including dead or moribund animals underwent complete necropsy. No gross findings attributable to treatment were reported.
- **Histopathology:** The sponsor reported histologic evidence of neither a carcinogenic nor a toxicological effect in rats.
  - Non-Tumor: Sporadic findings consistent with aging rats were reported in all groups (e.g., cardiomyopathy, chronic progressive nephropathy, hepatic foci, alveolar macrophage accumulation in the lung, tubular atrophy of the testis). Statistical significance was reached for nephropathy in females (11, 12, 5, 7 and 22 for the respective groups), and the premature decedents had 17/43 high dose animals with the lesion, but values were within historical ranges for the laboratory.
- **Tumor:** Incidental tumors were reported in all dose groups, but no trends or statistical or biological significance is attached to any finding. It is interesting to note that in the 1 year subcutaneous administration study in rats, an increased incidence of mammary carcinoma was reported (1/14 for untreateds, 3/22 for vehicle controls, 2/14 for 0.2 mg/kg animals, 1/14 for the 2.0 mg/kg animals and 8/21 for the 20 mg/kg groups, respectively). The incidences of mammary gland carcinoma and carcinosarcoma were comparable across dose groups in the current study.
- **Toxicokinetics:** Samples were supposed to be taken from 6/sex/dose on Day 1 of dosing at 0, 30 and 60 minutes post-dosing and from the remaining 6/sex/dose at 15, 45 and 120 minutes post-dosing. These samples were not analyzed due to assay methodology issues. The problems remained by Week 26 so those samples were not taken. Samples were actually taken Week 52 at 0, 15, 30, 45, 60 and 120 minutes post-dosing. Final samples were taken Week 80 at 0, 15, 30, 45, and 60 minutes and 2, 4, 8 and 24 hours post-dosing. The Tmax was determined to be 0.25 hours for all except one mid dose female where it was 2 hours. Wide variations were noted and comparisons were confounded by different sampling schedules for Week 52. Increases in systemic exposure were noted for the high dose group only, suggesting some accumulation of the M1 metabolite. M1 plasma levels were accumulated at a higher level in males than females but no gender trends were reported for t 1/2 elimination or tmax.

*The current Reviewer added the table below. The figures represent M1 plasma concentration at the 12 mg/kg dose.*

	C <sub>max</sub> [ng/ml]*		AUC <sub>0-24</sub> ng•hr/ml*		Multiples of human exposure** C <sub>max</sub> / AUC <sub>0-24</sub>	
	Male	Female	Male	Female	Male	Female
Week 1	52.13	38.25	57.35	41.79		
Week 52	179.8	94.80	162.6	77.62		
Week 80	169.5	69.90	170.47	70.60		

\*\*Values obtained from Study #C99-UIOS-018. The Day 1 and 14 values for C<sub>max</sub> were 0.576 and 0.526 ng/ml, respectively. The Day 1 and 14 values for AUC<sub>0-24</sub> were 0.28 and 0.292 ng•hr/ml, respectively. These values are an estimation of exposure in humans for a 24-hour period based on a doubling of the AUC<sub>0-24</sub> [0.146 ng•hr/ml on Day 14] obtained after the final dosing on Day 14.

**Overall Interpretation and Evaluation**

- Adequacy of the carcinogenicity studies and appropriateness of the test model: The doses do not appear to be high enough to elicit even minimal toxicity.
- Evaluation of Tumor Findings: No significant tumor findings.

**CIBA Vision****Summary Conclusions and Recommendations**

- **Acceptability of Study(s) or Overall Testing Approach:** Doses did not appear to be high enough to elicit even minimal toxicity. In the one year subcutaneous study in Sprague-Dawley rats, the incidence of mammary carcinoma was 1/14 (7%), 3/22 (14%), 2/14 (14%), 1/14 (7%) and 8/21 (38%) for the untreated, vehicle control, 0.2 mg/kg, 2 mg/kg and 20 mg/kg groups, respectively. No other significant findings were reported in that study, conducted by [redacted].  
[redacted] In the 3 month subcutaneous study in rats, only mild toxicities were reported in the high dose group at 50 mg/kg/d and the reviewer concluded that higher doses should have been used. This dose was 173x the proposed human dose on the basis of mg/m<sup>2</sup>.
- **Major Tumor Findings:** None
- **Non-neoplastic Findings:** Sporadic lesions consistent with the age and species of animal tested.
- **Biological Significance:** As the NOAEL is many multiples (92-224x higher C<sub>max</sub> and 172- 416x higher AUC than humans after a single ocular dose) of the proposed human exposure (4.8 µg/kg), this study is adequate to assess the potential human carcinogenic risks. It would be helpful to know whether repeated human exposures result in significantly higher AUCs.
- **List of Organs and Tissues Examined:** gross lesions, adrenals, aorta, brain, extraorbital lacrimal gland, eye, femur and marrow, GI tract (stomach, duodenum, ileum, jejunum, colon, cecum, rectum), Harderian gland, heart, kidneys, liver, lung, mesenteric lymph node, esophagus, optic nerve, ovary and oviduct, pancreas, pituitary, prostate, sciatic nerve, seminal vesicles, skin and mammary gland, spinal cord (3 segments), sternum with marrow, submandibular lymph node, submaxillary salivary gland, testes, muscle, thymus, thyroid with parathyroid, tongue, trachea, urinary bladder, uterus and Zymbal's gland.

**RECOMMENDATIONS:**

Internal comments: This study should be presented to the Exec. CAC for concurrence on the conclusion that the doses were not high enough. It would be useful to have the human repeat dose AUC data to correlate with the doses used in this study.

**B. Carcinogenicity Summary [current Reviewer] –** Based on the increased incidence of mammary carcinomas in the one-year rat study, the Executive Carcinogenicity Advisory Committee [ECAC] made the following recommendations following a meeting on Aug. 19, 1997.

1. The data from the 1-year rat should be included in the label along with exposure level comparisons for the metabolites in human and rat.
2. There are concerns with respect to the mammary tumors even though they occurred at relatively high exposures compared to the anticipated human exposure. A Phase IV commitment to perform a standard bioassay or an alternative was suggested.
3. Results from two year rodent carcinogenicity studies would be needed to exclude the one year data from the label, but depending on the outcome of the phase IV study [if an alternative assay was conducted], the recommendation for a two year rodent carcinogenicity study could be altered.

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The Sponsor elected to conduct a 2-year bioassay in the rat. Concurrence for the selected doses was not obtained from the ECAC. An MTD was not achieved in this study. However, the ECAC, which met on May 23, 2000, concluded that adequate exposure was obtained based on pharmacokinetic criteria. [ICH Guideline for Industry: S1C - Dose Selection for Carcinogenicity Studies of Pharmaceuticals]. This decision was founded on the following considerations. The major metabolite in the rat following iv and sc administration was M1 with essentially no parent compound detected. The assumption is made that this is the major metabolite following oral administration. M1 levels, therefore, served as the basis for determination of  $C_{max}$  and AUC values in the rat. The Sponsor was unable to detect any other metabolite besides M1 in the plasma of humans following ocular instillation of Rescula. Therefore, comparison of AUC values of M1 in rats and humans is appropriate for determination of multiples of exposure. In addition, *in vitro* studies demonstrated comparable protein binding for rats [96-97%] and humans [99%]. Based on a maximum human exposure of 1 drop BID of Rescula OU, the ratio of rodent to human plasma AUC of M1 is greater than 25. Since the exposure was adequate and there were no findings of carcinogenicity in this study, the ECAC concluded that the findings from the 1-year rat study do not need to be included in the label.

The methodology for determining the M1 exposure in humans has been validated; however, the methodology for sample handling has not. Specifically, the Sponsor has not demonstrated that the M1 metabolite is stable in plasma following freezing and thawing. Therefore, a conclusion that pharmacokinetic endpoints are appropriate for determination of doses in the 2-year bioassay study are contingent on the Sponsor demonstrating the stability of the M1 metabolite under the conditions of sample handling. However, based on the available data, it is anticipated that exposure in the carcinogenicity study will exceed the 25-fold pharmacokinetic criterion. It is projected that this data will be available in approximately 6 months.

**VI. Reproductive Toxicology:****A. Fertility and Early Embryonic Development****a. Rat**

i. Title: Effects of subcutaneous UF-021 administration prior to and in the early stages of pregnancy in rats [Vol. 1.42; pp. 1 - 246]

Study Identification: [REDACTED]

Site: [REDACTED]

Study Dates [In-life]: September 27 - December 24, 1989

Formulation and Lot No.: [REDACTED]

Certificate Analysis: No [X]

Final Report: July 17, 1990

GLP and QA Statements Signed: Yes [X] [REDACTED]

Objective: "To study the effects of UF-021 on reproductive capabilities of parent animals and fetal development in rats".

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*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study below. Additional comments by the current reviewer are in bold italics.*

a. **Methods:** Crj:CD(SD) rats, 22/sex/group, were treated with 0, 0.5, 5.0, or 50.0 mg/kg subcutaneous dose of UF-021. In males, treatment was initiated 3 weeks prior to mating and continued until confirmation of coitus. *[ICH guidance recommends a dosing duration of 4 weeks prior to mating.]* In females, treatment was initiated beginning 2 weeks prior to mating and continued through Day 7 of pregnancy. *[Reviewer's Comment: The doses used in this study were based on a preliminary Segment I study in which doses of 6.7 mg/kg and 20 mg/kg resulted in mild effects at the injection site in the F0 animals and no effects in the F1 generation. Based on these findings, it was determined that a higher dose was needed. The 50 mg/kg dose was ultimately selected based on the results seen in the 3-month toxicity study (D-14). The sponsor did not submit a report for the preliminary Segment I study.]*

Males were sacrificed at the end of the mating period, females on Day 20 of pregnancy. Toxicity was assessed as shown below.

## Toxicity Assessment for Study D11

Group	Assessment
F0 rats	<p>Observations: Males and females were observed daily from the start of treatment until the time of sacrifice.</p> <p>Body weight/Food consumption: Body weight and food consumption were measured weekly in males. These parameters were also measured weekly in females until the beginning of mating. After mating, body weight was measured daily for Days 0 to 8 of pregnancy, then on Days 10, 12, 14, 16, 18, and 20; food consumption was measured daily on Day 1 to 9 of pregnancy and on Days 11, 13, 15, 17, 19, and 20.</p> <p>Reproductive capabilities: In females, estrous cycle was assessed beginning 10 days prior to mating. In males and females, the number of days needed for coitus, copulation rate, and conception rate were calculated.</p> <p>Necropsy: Males were sacrificed for necropsy after mating was complete, females on Day 20 of pregnancy. For pairs in which pregnancy did not occur, the testes, epididymis, seminal vesicles, prostate, and pituitary were examined histopathologically in males, and the ovary, uterus, and pituitary in females.</p>
F1 fetuses	<p>Cesarean observations: On Day 20 of pregnancy, the F0 dams were sacrificed and the following data collected: # resorptions (early and late), # of live and dead fetuses, sex ratio for surviving fetuses, and body weight of surviving fetuses. Approximately 1/3 of the fetuses were prepared for organ examination; 2/3 were prepared for skeletal examination.</p>

*No direct evaluation of spermatid maturation was conducted. This is recommended in the ICH guidelines.*

## b. Results:

## (1) F0 rats:

(a) **Observations:** Neither males nor females in the 0.5 and 5.0 mg/kg groups exhibited any effects. In the 50 mg/kg group, 1 male exhibited scabbing at the injection site in Weeks 7 and 8 of treatment; 5 females in this group displayed alopecia at the injection site from Weeks 2 to 4 of treatment.

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(b) **Body weight/Food consumption:** In males that received 50 mg/kg, body weight was slightly (approximately 5% to 7%) albeit significantly decreased relative to the control group. In females, treatment had no effect on body weight.

At several time points, food consumption was significantly reduced in male rats, but no temporal relationship was apparent. In females, food consumption was essentially unaffected.

(c) **Reproductive capabilities:** Treatment had no effect on reproductive capabilities.

(d) **Necropsy:** The rats did not exhibit any treatment-related effects.

(2) **F1 fetuses:** The fetuses did not exhibit any treatment-related effects.

3. **Reviewer's Comment:** The no-observed-effect-level (NOEL) for general toxicity in the F0 animals was 5 mg/kg (1041 and 173 times the maximum clinical dose based on body weight and surface area, respectively). The NOEL for reproduction was 50 mg/kg (10,410 and 1730 times, the maximum clinical dose, 4.8 µg/kg, based on body weight and surface area, respectively). [Reviewer's Comment - *Although there were deficiencies with respect to evaluation of male fertility, it is felt that the study is adequate primarily because of the large margin of safety for human exposure. The maximum clinical dose is 5 µg/kg/day. This is based on a final clinical formulation of 0.15% UF-021, and not 0.12% as initially proposed, and on a 60-kg individual.*]

**B. Embryofetal Development****a. Rat**

i. **Title:** Preliminary tests of oral UF-021 administration during fetal organogenesis in rats [Vol. 1.42; pp. 247-318]

**Study Identification:** [REDACTED]

**Site:** [REDACTED]

**Study Dates:** November 19 - December 24, 1987

**Formulation and Lot No.:** [REDACTED]

**Certificate Analysis:** No [X]

**Final Report:** March 31, 1988

**GLP and QA Statements Signed:** No [X]

**Objective:** "To establish doses for tests of oral Uf-021 administration during fetal organogenesis in rats as a part of studies on UF-021 safety".

*This study will be summarized here since it is a preliminary study and the definitive study was conducted using the subcutaneous route.*

**Study Design** - Female Crj:CD [SD] rats [N=15] were dosed po [gavage] with 0.5% MC, 50, 150 and 450 mg/kg SID Days 7-17 of gestation. Endpoints included BID clinical observation, body weight and food consumption Days 0-20 of pregnancy, Cesarean endpoints on Day 20 of

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pregnancy [pregnancy, CL, implantations, dead/resorbed fetuses, surviving fetuses, early and late resorptions], and F<sub>1</sub> necropsy on Day 20 of pregnancy [external anomalies, weight, sex]

**Results** – [Note: Summary data only was provided.] Vaginal bleeding was observed in 6/15 and 15/15 dams administered 150 and 450 mg/kg from Days 8-10 until Day 20. Miscarriages or premature deliveries were observed in 1/15, 13/15, and 13/14 dams at 50, 150, and 450 mg/kg, respectively. Uterine contraction was observed in all premature deliveries/miscarriages. The mean number of CL, implantations, or implantation rates/litter was comparable across all treatment groups. There were no surviving fetuses in 3/15 and 12/14 dams at 150 and 450 mg/kg, respectively. There were only 8 and 2 surviving fetuses at 150 and 450 mg/kg, respectively. Implantation scars only were observed with 38/58 and 145/162 implantations at 150 and 450 mg/kg. Based on embryofetal survival, the NOAEL was 50 mg/kg following the oral route of exposure. The NOAEL for maternal toxicity based on body weight and food consumption was 150 mg/kg.

ii. Title: Reproductive and developmental toxicity study of UF-021 dosed subcutaneously in rats during the period of fetal organogenesis [Vol. 1.44]

Study Identification: [REDACTED]

Site: [REDACTED]

Study Dates [In-Life]: August 24 – December 20, 1989

Formulation and Lot No.: [REDACTED]

Certificate Analysis: No [X]

Final Report: February 29, 1996

GLP and QA Statements Signed: Yes [X] [REDACTED]

Objective: "To assess the effects of UF-021 on fetal development, and on growth, behavior and functions of the birth offspring" in rats.

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study [REDACTED] This review is provided below in conjunction with the developmental study in rats. Additional comments by the current reviewer are in bold italics.*

b. Rabbit

i. Title: Effects of subcutaneous UF-021 administration during fetal organogenesis in rabbits [Vol. 1.45]

Study Identification: [REDACTED]

Site: [REDACTED]

Study Dates [In-Life]: October 8 – December 11, 1991

Formulation and Lot No.: [REDACTED]

Certificate Analysis: No [X]

Final Report: December 11, 1991

GLP and QA Statements Signed: Yes [X] [REDACTED]

Objective: "To assess the effects of UF-021 on fetal development in rabbits".

*The following review is for both the rat and rabbit teratology studies.*

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**Methods:** Presumed pregnant rats (n = 36) and rabbits (n = 18) were treated with single subcutaneous injections with UF-021 on Days 7 to 17 and Days 6 to 18 of pregnancy, respectively, as indicated in the table below. [Reviewer's Comment: The doses used in these studies were based on preliminary studies for which reports were not submitted. In rats, the preliminary studies revealed miscarriages and premature births at doses greater than or equal to 8 mg/kg; rats in the 3 mg/kg group did not exhibit any miscarriages, premature births, or abnormalities at cesarean section. Based on these findings, 5 mg/kg was selected as the high dose for rats. In the preliminary studies conducted in rabbits, pregnancy could not be maintained at 0.8 mg/kg; 0.16 mg/kg resulted in a bloody discharge and miscarriages. Based on these findings 0.3 mg/kg was selected as the high dose for rabbits.]

## Treatment Protocol for Studies D-12 and D-13

Species	n	Dose	
		mg/kg	mL/kg
Rat/CRJ:CD(SD)	36/treatment group	0	0.1
		0.8	
		2.0	
		5.0	
Rabbit	18/treatment group*	0	1.0
		0.03	
		0.10	
		0.30	

\*There were 16, 14, 17, and 11 litters available for evaluation. The ICH guidelines recommend between 16-20 litters for evaluation.

Toxicity was assessed as shown below.

## Toxicity Assessment for Studies D12 and D13

Group	Assessment
Rats/F0 dams	<p>Observations: Dams were observed at least daily on Days 0 - 20 of pregnancy and from Day 20 of pregnancy - Day 22 after delivery.</p> <p>Body weight: The dams were weighed on Day 0 of pregnancy, daily from Day 7 of pregnancy until Day 20 of pregnancy or until delivery, and on Days 4, 7, 14, and 21 after delivery.</p> <p>Food consumption: Food consumption was measured on Day 0 of pregnancy, daily from Day 7 of pregnancy until Day 20 of pregnancy or until delivery and on Days 1, 5, 8, 15, and 22 after delivery.</p>
Rats/F1 fetuses	<p>Cesarean observations: On Day 20 of pregnancy 2/3 of the F0 dams were sacrificed and the following data collected: # resorptions (early and late), # of live and dead fetuses, sex ratio for surviving fetuses, and body weight of surviving fetuses. Approximately 1/3 of the fetuses were prepared for organ examination; 2/3 were prepared for skeletal examination.*</p>

\*ICH guidelines recommend that 50% of the fetuses be evaluated for organ examination and 50% for skeletal examination. This study, however, was conducted prior to issuance of SSA Document; Detection of Toxicity to Reproduction for Medicinal Products.

Group	Assessment
Rats/F1 delivered offspring	<p>Birth observations: On the day of birth, the following were observed/measured: # of stillborn fetuses, # of perinatal deaths, # of live offspring, sex ratios of live offspring, and external surfaces.</p> <p>Culling: On Day 4 after birth, the number of offspring was adjusted to 8, 4/sex.</p> <p>Lactation period observations: Body weights were obtained on Days 4, 7, 14, and 21. Growth and differentiation were assessed by monitoring the following: pinna development, dorsal fur growth, mandibular incisor budding, 4-legged walking, eyelid cleavage, testicular descent.</p> <p>Post-weaning observations: Weanlings were observed daily and body weight measured weekly. 1/sex was sacrificed for skeletal examination on the day of weaning. Females were examined for vaginal opening on Day 36 after birth. 1/sex underwent reactivity, water maze, and open field examinations, then were sacrificed 10 weeks after birth. 2/sex were allowed to reach sexual maturity for assessment of their reproductive capabilities.</p>
Rats/F2 fetuses	Same as F1 fetuses.
Rabbits/F0 dams	<p>Observations: Dams were observed daily.</p> <p>Body weight: Body weight was measured on Day 0 of pregnancy; daily from Day 6 to Day 20 of pregnancy, on Days 22, 24, 26, and 28 of pregnancy.</p> <p>Food consumption: Food consumption was measured on Day 1 of pregnancy, daily from Day 7 to 21 of pregnancy, and on Days 23, 25, 27, and 28 of pregnancy.</p>
Rabbits/F1 fetuses	Cesarean observations: On Day 28 of pregnancy, the F0 dams were sacrificed and the following data collected: # resorptions (early and late), # of live and dead fetuses, sex ratio for surviving fetuses, and body weight of surviving fetuses. Approximately 1/2 of the fetuses were prepared for organ examination; 1/2 were prepared for skeletal examination.*

*\*ICH guidelines recommend that fetuses be evaluated by fresh dissection and that 100% of the fetuses be evaluated for both visceral and skeletal examination. This study, however, was conducted prior to issuance of SSA Document; Detection of Toxicity to Reproduction for Medicinal Products.*

**b. Results:**

**(1) F0 dams:**

**(a) Observations:** Rats in all treatment groups exhibited scabbing at the injection site. In addition, rats in the 2 and 5 mg/kg groups displayed alopecia. In the 5 mg/kg group 5 rats miscarried on Day 19 of pregnancy and 1 on Day 20. On Day 21 of pregnancy, 1 rat died during delivery.

In rabbits that received 0.03 mg/kg, 1 miscarriage occurred on Day 24 of pregnancy; in the 0.3 mg/kg group a miscarriage occurred on Days 16, 21, and 24 of pregnancy. *In addition, in 1 other animal at the 0.3 mg/kg dose, the Sponsor states that "something ... believed to have been a miscarriage was seen".*

**(b) Body weight:** Treatment had no effect on body weight in either species.

**(c) Food consumption:** Treatment had no effect on food consumption in either species.

(2) F1 fetuses: Examination of rat fetuses did not reveal any effects.

Cesarean findings in rabbits are shown in the table below. The number of early resorptions was increased in rabbits that received 0.3 mg/kg. [Reviewer's Comment: According to the study report, no abnormalities in number of fetal resorptions were seen. The basis for this conclusion is not clear.]

**Cesarean Observations in Rabbits that Received UF-021**

Parameter	Vehicle	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg
# Dams	16	14	17	11
# Corpora lutea*	160 (10 ± 3.03)	146 (10.4 ± 1.95)	190 (11.2 ± 2.58)	123 (11.2 ± 2.64)
# Implantations*	152 (9.5 ± 3.01)	127 (9.1 ± 3.02)	185 (10.9 ± 2.91)	118 (10.7 ± 2.83)
# Preimplantation losses**	8 (5.0)	19 (13)	5 (2.6)	5 (4.1)
# Resorptions***	15 (9)	10 (7.9)	22 (11.9)	38 (32.2)
Early	6 (3.9)	7 (5.5)	10 (5.4)	28 (23.7)
Late	9 (5.9)	3 (2.4)	11 (5.9)	10 (8.5)
# Live fetuses*	137 (8.6 ± 3.2)	117 (8.4 ± 2.65)	163 (9.8 ± 2.65)	80 (7.3 ± 3.26)

\* Parenthetical value = mean ± S.D. per dam

\*\* Parenthetical value = # losses/corpora lutea X 100

\*\*\* Parenthetical value = # resorptions/implantations X 100

**(3) F1 delivered offspring:**

(a) Birth observations (Day 0): As shown in the table below, rats in the 5 mg/kg group exhibited a decrease in the live birth index (# of live pups at birth/# of implantations X 100). In addition, only 69.2% of the dams in the 5 mg/kg group delivered live newborns, compared to 100% for the other 3 groups. No other treatment-related effects were observed; however, the birth weight of males and females in the 0.8 and 2.0 mg/kg groups was slightly, albeit significantly, increased (10 to 12%) relative to the control group.

**Live Birth Index in Rats that Received UF-021**

Dose (mg/kg)	0	0.8	2.0	5.0
# implantations	178	173	187	187
# live births	170	166	174	96
Live birth index	95.5	95.9	93.0	51.3

(b) Nursing period observations (Day 0 - Day 21): The percentage of rat pups that survived to Day 4 in the 2.0 and 5.0 mg/kg groups (94.2 and 91.7%, respectively) was slightly less than the percentage that survived in the control and 0.8 mg/kg groups (100% and 98.8%, respectively). Male and female rat pups in the 0.8 and 2.0 mg/kg groups exhibited periodic significant increases (approximately 10%) in body weight relative to control, but this effect had no clear relationship to time or dose. Treatment during organogenesis had no apparent effect on growth and differentiation in rats.

(c) Post-weaning observations: The rats did not exhibit any treatment-related effects. *There was a slight decrease in vaginal opening on Day 36 in the high dose vs. control females [57.1% and 80%, respectively].*

(4) F2 fetuses: No treatment-related effects were observed.

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c. **Reviewer's Comment:** In rats, the no-observed-effect-level (NOEL) for maternal toxicity was 0.8 mg/kg (166 and 27 times the maximum clinical dose based on body weight and surface area, respectively); the NOEL for developmental toxicity was 2.0 mg/kg (416 and 69 times the maximum clinical dose, based on body weight and surface area, respectively).

In rabbits, the no-observed-effect-level for maternal and reproductive toxicity was ~~1 mg/kg (208 times the maximum clinical dose based on body weight and surface area, respectively).~~ **0.3 mg/kg and 0.1 mg/kg, respectively. Based on the NOAEL for embryofetal toxicity, the 0.1 mg/kg dose represents 20 and 7 times the maximum clinical dose based on body weight and surface area, respectively.**

## C. Prenatal and Postnatal Development

## a. Rat

i. **Title: Effects of subcutaneous UF-021 administration during perinatal and lactation periods in rats [Vol. 1.46-1.47]**

Study Identification: [redacted]

Site: [redacted]

Study Dates [In-life]: August 19 – December 30, 1990

Formulation and Lot No. [redacted]

Certificate Analysis: No [X]

Final Report: December 11, 1991

GLP and QA-Statements Signed: Yes [X] [redacted]

Objective: "To study the effects of UF-021 on live offspring growth, behavior and function in rats".

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this [redacted] This review is provided below. Additional comments by the current reviewer are in bold italics.*

**Methods:** Pregnant female rats [Crj:CD(SD)] received a subcutaneous injection (0, 0.2, 0.5, or 1.25 mg/kg in 0.1 mL/kg) from Day 17 of pregnancy to Day 21 after delivery. **[Reviewer's Comment:** According to the study report, these doses were based on preliminary studies in which miscarriages, premature deliveries, and a failure of offspring to survive until Day 4 after delivery were seen when the dams received 4 mg/kg and higher. In the 0.8 mg/kg group, a tendency for decreased 4-day survival was observed; 0.16 mg/kg had no effects on reproduction. The sponsor did not submit a report for this preliminary study.]

Toxicity was assessed as shown below.

**Toxicity Assessment for Study D14**

Group	Assessment
F0 Dams	<p>Observations: Rats were observed daily from Day 0 of pregnancy to Day 22 after delivery.</p> <p>Body weight: Body weight was measured on Days 0, 7, and 14 of pregnancy, daily from Day 17 of pregnancy until delivery, and on Days 4, 7, 14, and 21 after delivery.</p> <p>Food consumption: Food consumption was measured on Days 1, 8, and 15 of pregnancy, from Day 18 of pregnancy until delivery, and on Days 1, 5, 8, and 15 after delivery.</p> <p>Necropsy: Dams were sacrificed on the day of weaning. The uteri were excised and the number of implantation scars counted.</p>
F1 Offspring	<p>Birth observations: On the day of birth, numbers of stillborn fetuses, numbers of perinatal deaths, numbers of live offspring, sex ratios of live offspring, and external surfaces of live offspring were observed/measured.</p> <p>Lactation period observations: Condition was assessed daily. Body weight was measured on Days 4, 7, 14, and 21. On Day 4 after birth, the litters were culled to 4/sex.</p> <p>Reflex ontogeny: In 1/sex righting reflex and total body pain reflex were assessed on Day 5 after birth, negative geotaxia on Day 8 after birth, pinna reflex on Day 13 after birth, and corneal reflex on Day 17 after birth.</p> <p>Growth and differentiation: Pinna unfolding (Day 4 after birth), dorsal hair growth (Day 8 after birth), mandibular incisor eruption (Day 11 after birth), quadruped walking and eyelid cleavage (Day 14 after birth), testicular descent (Day 21 after birth), and vaginal opening on (Day 36 after birth) were assessed on the days indicated in parentheses. If the items were not present on the day of observation, observations were continued until the items were present.</p> <p>Necropsy at weaning: On the day of weaning, 1/sex was sacrificed for necropsy, skeletal examination, and organ weight measurement.</p> <p>Post-weaning observations: General condition was assessed daily for 10 weeks in the 3/sex remaining after weaning. Body weights were measured weekly. Open field and water maze examinations were performed in Week 6 and Week 8 after birth, respectively.</p> <p>Post-weaning necropsy: In Week 10 after birth, 2/sex were sacrificed for necropsy and measurement of organ weights.</p> <p>Reproductive capacity: In Week 10 after birth, 1/sex were mated. The number of days required for coitus, copulation rate, and conception rate were assessed. Body weights of females for which coitus was confirmed were measured on Days 0, 4, 8, 12, 16, and 20 of pregnancy. Males were sacrificed when coitus was confirmed, females on Day 20 of pregnancy.</p>
F2 fetuses	<p>Cesarean observations: On Day 20 of pregnancy the dams were sacrificed, and the following data collected: # implantations, # resorptions (early and late), # of live and dead fetuses, sex ratio for surviving fetuses, and body weight of surviving fetuses. Approximately 1/2 of the fetuses were prepared for organ examination; the other half was prepared for skeletal examination.</p>

**Results:**

**(1) F0 dams:**

(a) **Observations:** The rats in the 0.2 and 0.5 mg/kg groups did not exhibit any effects. In contrast, the rats in the 1.25 mg/kg group exhibited premature delivery (7 animals on Day 20 of gestation), "poor lactation state" in 6 rats, and scabbing at the injection site in 1 rat from Day 17 to 22 of pregnancy. [Reviewer's Comment: No further information is available regarding the "poor lactation state". The Sponsor will be asked to further describe what they mean by this statement]

(b) **Body weight:** The rats did not exhibit any toxicologically significant effects.

(c) **Food consumption:** The rats did not exhibit any toxicologically significant effects.

(d) **Necropsy:** At the end of the weaning period, the dams that received UF-021 exhibited an increased incidence of hemorrhage at the injection site. In the control group 10/24 dams exhibited this effect; in the 0.2, 0.5, and 1.25 mg/kg groups, 17/25, 20/25, and 24/24 animals, respectively exhibited the effect. Treatment had no effect on the number of implantation sites.

**(2) F1 offspring:**

(a) **Birth observations:** As shown in the table below, rats in the 1.25 mg/kg group exhibited a decrease in the live birth index (# of live pups at birth/# of implantations X 100). In addition, the body weight of the surviving pups in the 1.25 mg/kg group was decreased approximately 20% relative to the control group. *In addition, at 0.5 mg/kg there was an increase in the incidence of stillborn pups compared to control values.*

**Live Birth Index in Rats that Received UF-021**

Dose (mg/kg)	0	0.2	0.5	1.25
# implantation sites	360	388	358	376
# live births	329	368	321	240
Live birth index	91.4	94.8	89.7	63.8*
Number of stillborn	1 [0.3%]	0	15 [4.2%]	59 [15.7%]

\*Significantly different from control @ p < 0.01

(b) **Lactation period observations:** As shown in the table below, the number of live newborns on Day 4 was significantly decreased in the 1.25 mg/kg group. *Although not significant, the % survival of newborns also tended to decrease in the 0.5 mg/kg group.* Data are expressed as the percentage of live newborns at birth. Treatment had no effect on survival from Day 4 of lactation to Day 21 of lactation.

**Day 1 to Day 4 Survival in Rats that Received UF-021**

Dose (mg/kg)	0	0.2	0.5	1.25
Number of pups dying Days 1-4	8 [2.4%]	5 [1.4%]	59 [18.4%]	84 [35%]
Survival (% of live newborns)	97.6	98.6	81.6	65.3*

\*Significantly different from control @ p < 0.01

On Days 4 and 7 of lactation, body weight in males in females in the 1.25 mg/kg groups was decreased approximately 12% relative to the control group.

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*[Note: Fewer F<sub>1</sub> pups were evaluated for behavior changes, etc. in the high dose group compared to control pups [about 50% of the control numbers].*

(c) **Reflex ontogeny:** The offspring did not exhibit any treatment-related effects.

(d) **Growth and differentiation:** Male and female offspring in the 1.25 mg/kg group exhibited delayed incisor eruption, ~~quadruped walking~~, and/or eye opening.

(e) **Necropsy at weaning:** Data for this parameter could not be identified in the study report. *[These data were provided in the NDA submission.]*

(f) **Post-weaning observations:** Although male and female offspring in the 1.25 mg/kg group exhibited significant decreases in body weight relative to the controls at Weeks 4 to 6 and Weeks 4 and 5, respectively, the decrease was less than 10%. In general, treatment had no significant effect on performance in the open-field and water maze tests.

(g) **Post-weaning necropsy:** Necropsy did not reveal any effects. However, changes in absolute and relative organ weight were noted. Males in the 1.25 mg/kg group exhibited increases in absolute (16.3%) and relative (21%) *thymus weights* relative to the control group. Females in all treatment groups exhibited decreases in absolute and relative thyroid weight of approximately 15%. Females in the 0.5 and 1.25 mg/kg group exhibited decreases of 12% to 18% in absolute and relative pituitary weight. *[Reviewer's Comment: In the absence of histopathology data, the toxicological significance of these effects cannot be completely assessed.]*

(h) **Reproductive capacity:** Treatment of the F0 females from Day 17 of pregnancy through the lactation period had no effect on the reproductive capacity of the F1 generation.

(3) **F2 fetuses:** The fetuses did not exhibit any treatment-related effects.

**Reviewer's Comment:** The no-observed-effect-level (NOEL) for maternal toxicity was 0.5 mg/kg (104 and 17 times the maximum clinical dose based on body weight and surface area, respectively). The NOEL for reproduction was 0.2 mg/kg (41 and 7 times the maximum clinical dose based on body weight and surface area, respectively).

**D. Summary of Reproductive Toxicity Studies** – There were no effects on fertility in either male or female rats up to doses of 50 mg/kg. Although there were deficiencies in the study design [e.g. dosing of males for 3 instead of 4 weeks and no direct evaluation of spermatid maturation], these were not considered to negatively impact the study since the multiples of the human exposure were so large [approximately 10,000, 1,700 and >15,000X human exposure based on body weight, surface area, and AUC].

With the exception of scabbing at the injection sites in the rat, maternal toxicity was not observed in either the rat or the rabbit at maximum doses of 5 and 0.3 mg/kg administered during organogenesis. An increased incidence of miscarriages was observed in the rat at 5 mg/kg and in the rabbit at 0.3 mg/kg. Only 69% of the dams in the 5 mg/kg group delivered newborn pups compared to 100% in the other groups. There was an increased incidence of early resorptions in does administered 0.3 mg/kg [23.7%] compared to control does [3.0%]. There was no evidence of teratogenicity. Based on ICH recommendations, there were not an adequate number of litters for evaluation for the dams administered 0.03 and 0.3 mg/kg. However, based on negligible exposure

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in the clinical setting, this study is considered adequate. The NOAEL for developmental toxicity in the rat was 2.0 mg/kg (400 and 67 times the maximum clinical dose, based on body weight and surface area, respectively). The NOAEL for embryofetal toxicity in the rabbit was 0.1 mg/kg dose, which represents approximately 20 and 7 times the maximum clinical dose based on body weight and surface area, respectively.

A "poor lactation state" [The Sponsor did not characterize this condition.] and premature deliveries were observed in dams administered 1.25 mg/kg during late gestation through weaning [Gestation Day 17 through Postpartum Day 21]. In the litters from dams administered 1.25 mg/kg, there was a decrease in the live birth index [64% vs. 94% in the high and control litters, respectively] and a 20% decrease in birth weight compared to controls. There was an increase in the number of stillborn at doses of 0.5 and 1.25 mg/kg compared to the control values. Postnatal survival was decreased at  $\geq 0.5$  mg/kg. The increase in the number of pups dying Days 1-4 in the mid-dose litter and the high dose litter was 59 (18.4%) and 84 (35%) pups, respectively, compared to 8 (2.4%) in the control litters. Body weight of the pups in the 1.25 mg/kg group was still decreased by 12% on Lactation Days 4-7. Growth and differentiation, specifically incisor eruption and eye opening, were delayed in males and females in the high dose group. The toxicological significance of the changes in organ weight observed in F<sub>1</sub> is unclear. No effects were apparent on reflex ontogeny, reproductive capacity of the F<sub>1</sub> generation, or F<sub>2</sub> fetuses. The NOAEL for pre and postnatal toxicity was 0.2 mg/kg (40 and 7 times the maximum clinical dose based on body weight and surface area, respectively).

**VII. Genotoxicity:****A. *In vitro* Studies****a. Mutation Assays with UF-021 and UF-025**

i. Title: Reverse mutation test of UF-21 on bacteria [Vol. 1.48; pp. 16-85]

Study Identification: [REDACTED]

Site: [REDACTED]

Assay Dates: May 7-24, 1990

Formulation and Lot No.: [REDACTED]

Certificate Analysis: No [X] Concentration analysis conducted

Final Report: September 10, 1990

GLP and QA Statements Signed: Yes [X] [REDACTED]

Objective: To determine the mutagenic potential of UF-021 in a bacterial reverse mutation assay.

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study [REDACTED] This review is provided below in conjunction with the in vivo and in vitro chromosomal aberration assays with UF-021.*

ii. Title: UF-025 reverse mutagenicity test using bacteria [Vol. 1.48; pp. 86-157]

Study Identification: [REDACTED]

Site: [REDACTED]

Assay Dates: January 8-25, 1991

Formulation and Lot No.: [REDACTED]

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Certificate Analysis: No [X] Concentration analysis conducted; Sponsor indicates that drug was not detectable at 39.1 and 78.1 µg concentrations; the actual concentration at the higher levels was approximately 90% of the theoretical concentration

Final Report: December 18, 1991

GLP and QA Statements Signed: Yes [X] [redacted] guidelines

Objective: To determine the mutagenic potential of UF-025 in a bacterial reverse-mutation assay.

The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study [redacted] This review is provided below in conjunction with the in vitro chromosomal aberration assays with UF-025.

iii. Title: Unoprostone isopropylate; Mouse lymphoma mutation assay [Vol. 1.48; pp. 158-225]

Study Identification: [redacted]

Site: [redacted]

Assay Dates: April 9-May 29, 1997

Formulation and Lot No.: [redacted]

Certificate Analysis: No [X] Concentration analysis was not conducted

Final Report: September 23, 1997

GLP and QA Statements Signed: Yes [X] [redacted]

Objective: "To determine the potential of ...[UF-021]...to induce forward mutation at the tk<sup>+</sup>tk<sup>-</sup> locus of mouse lymphoma-L5178Y cells."

Study Design - Mouse lymphoma L5178Y cells [tk<sup>+</sup>tk<sup>-</sup>] were incubated with UF-021 dissolved in DMSO in the presence or absence of S9 activation. The following concentrations were selected:

	S9	Concentrations [µg/ml]
Assay 1	-	[redacted]
Assay 2	+	
Assay 3	-	
Assay 4	+	

Concentrations were selected based on preliminary toxicity studies conducted at concentrations ranging from 3.9-1000 µg/ml. The positive controls included ethyl methanesulphonate [EMS], methyl methanesulphonate [MMS], and 3-methylcholanthrene. Duplicate cell cultures were performed on all treatments except for the vehicle control [quadruplicate]. Two parallel cloning assays were conducted to determine [1] viability and [2] mutation selection. Cloning efficiency, relative total growth, and total mutant count were determined. [Colony size distribution was conducted only in the vehicle and positive control groups.] A response was considered negative if mutation counts were not significantly higher than those in the vehicle control and there was a reduction of relative total growth to 20%. A response was considered positive if the mean mutant fraction was ≥1.7X the mean control value.

Results - Assay 1 [redacted]

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- Assay 2 -

- Assay 3 -

- Assay 4 -

**Reviewer's Comments – Study Design and Data Presentation –**

1. Adequate toxicity of at least 80%, based on ICH guidelines [S2A: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals] was obtained only in Assays 2 and 3. The level of toxicity in Assay 3 was marginal. A determination of a negative response, therefore, can only be based on these 2 assays.
2. The Sponsor provided historical controls. However, it is not clear as to whether the values for VH control represent the data for DMSO only or for other solvents.

**Sponsor's Conclusion and Reviewer's Comment –**

1. UF-021 was not mutagenic in mouse lymphoma L5178Y cells, with or without S9 activation, "at concentrations extending into the toxic range". **Reviewer's Comment –** In general, the Reviewer concurs with the caveats already stated.

**b. Chromosomal Aberration Assays with UF-021 and UF-025**

i. Title: Chromosomal aberration tests of UF-021 using cultured mammalian cells  
[Vol. 1.48; pp 226-317]

Study Identification: [REDACTED]

Site: [REDACTED]

Assay Dates: May 28-July 16, 1990

Formulation and Lot No. [REDACTED]

Certificate Analysis: No [X] Concentration analysis conducted with actual concentration approximately 91-107% of the theoretical concentration

Final Report: December 18, 1991

GLP and QA Statements Signed: Yes [X] [REDACTED]

Objective: To determine the potential of UF-021 to induce chromosomal aberrations in cultured mammalian cell assay.

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study [REDACTED] This review is provided below in conjunction with the in vivo and in vitro chromosomal aberration assays with UF-021.*

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ii. Title: Chromosomal aberration tests with mammalian cells in culture of UF-025

[Vol. 1.49; pp. 1-81]

Study Identification: [redacted]

Site: [redacted]

Assay Dates: February 1 – March 1, 1991

Formulation and Lot No.: [redacted]

Certificate Analysis: No [X] Concentration analysis conducted with actual concentrations ranging from approximately [redacted] of the theoretical concentration; levels  $\leq 18.8$   $\mu\text{g}/\text{plate}$  were not detectable

Final Report: March 12, 1992

GLP and QA Statements Signed: Yes [X] [redacted]

[redacted]

Objective: To determine the potential of UF-025 to induce chromosomal aberrations in cultured mammalian cell assay.

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study [redacted] This review is provided below in conjunction with the in vitro mutagenic assay with UF-025. Additional comments by the current Pharmacology/Toxicology Reviewer are in italics.*

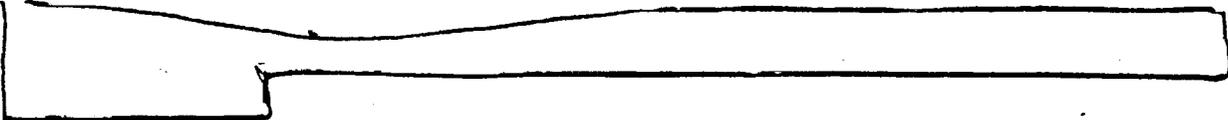
The methods used in these studies are summarized in the table below.

Study	Methods
Reverse mutation	
Chromosome aberration <i>in vitro</i>	

[redacted]

**Results:** Under the conditions of these assays, UF-025 was not genotoxic.

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**B. In vivo Studies**

ii. Title: **Micronucleus test of UF-021 in mice [Vol. 1.49; pp. 82-137]**

Study Identification: [redacted]

Site: [redacted]

Study Dates: April 23 – July 6, 1990

Formulation and Lot No.: [redacted]

Certificate Analysis: No [X]

Final Report: September 10, 1990

GLP and QA Statements Signed: Yes [X] [redacted]

Objective: To determine the potential of UF-021 to induce chromosomal aberrations in the mouse micronucleus assay.

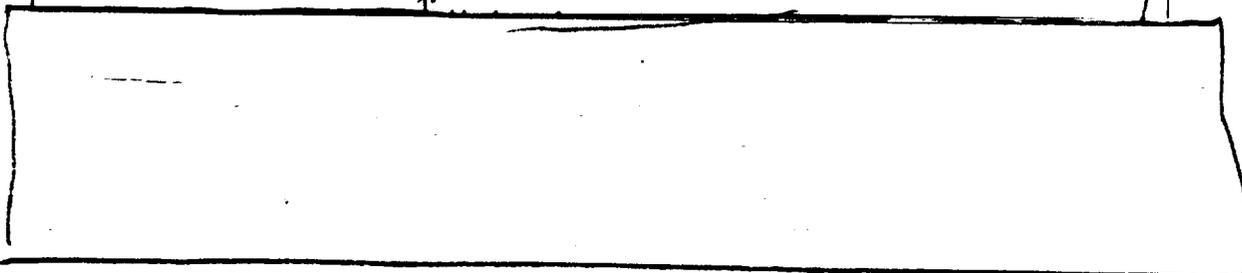
*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study for [redacted] This review is provided below in conjunction with the in vitro mutagenic and chromosomal aberration assays with UF-021. Additional comments by the current Pharmacology/Toxicology Reviewer are in italics.*

The methods used in these studies are summarized in the table below.

Study	Methods
Reverse mutation	

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ON ORIGINAL**

Study	Methods
Chromosome aberration <i>in vitro</i>	
Mouse micronucleus	



**Results:** *In the in vivo mouse micronucleus assay, mortality was observed in 3/5 animals administered 200 mg/kg ip after 2-3 administrations. There was no evidence of bone marrow cytotoxicity following either single or multiple doses. The Sponsor has not demonstrated bioavailability of UF-021 by the ip route of administration. A cause of death was not identified; therefore, death due to local toxicity can not be ruled out. Under the conditions of these assays, UF-021 did not exhibit any evidence of genotoxicity.*

C. **Summary of Genotoxicity** – Under the conditions tested, UF-021 and UF-025 were negative for mutagenicity in the Ames Assay. Under the conditions tested, UF-021 and UF-025 were negative for clastogenicity in the *in vitro* Chinese hamster lung-derived fibroblast cell assay. UF-021 was also negative for genotoxicity in the mouse lymphoma assay and the *in vivo* mouse micronucleus assay, under the conditions tested. As noted above, the bioavailability of UF-021 has not been demonstrated following the ip route.

**VIII. Special Toxicology:**

A. Antigenicity Studies

a. Guinea pig, mouse, rabbit

ii. Title: Tests of UF-021 antigenicity [Vol. 1.41; pp. 1-94]

Study Identification: [redacted]

Site: [redacted]

Study Dates: June 27 – December 26, 1989

Formulation and Lot No.: [redacted]

Certificate Analysis: No [X]

Final Report: December 26, 1989

GLP and QA Statements Signed: Yes [X] [redacted]

[redacted]

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**Objective:** To determine the potential of UF-021 to induce an antigenic response in rabbits, mice, and guinea pigs.

*The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study  
his review is provided below.*

**Study Design -** The antigenic potential of UF-021 was assessed using guinea pigs (male Hartley), mice [redacted], rats (female Sprague-Dawley), and rabbits (male Japanese white). Prior to conducting the antigenicity assays, the animals were sensitized as shown in the table below. Abbreviations used in the table are as follows: CFA = complete Freund's adjuvant and EA = egg albumin.

**Sensitization Procedures**

Species	Treatments	n	Route	Dosing Frequency
Guinea pig	FU-021 (1 mg/kg)	6	Subcutaneous	Once per day every other day for 3 treatments.
	UF-021 (10 mg/kg)	6		
	UF-021 (10 mg/kg) EA	6		
	Untreated	3		
	EA(2 mg/kg) + CFA	6		
	Untreated	3		
Mouse	Untreated	5	Intraperitoneal	Once per week for 4 weeks.
	UF-021 (1 µg/kg) + Alum	5		
	UF-021 (10 µg/kg) + Alum	5		
	UF-021 (100 µg/kg) + Alum	5		
	EA (100 µg/kg) + Alum	5		
Rabbit	Untreated	3	Subcutaneous	Once per day for 5 days.
	UF-021 (10 mg/kg)	3		
	UF-021 (10 mg/kg) + CFA	3		
	EA (2 mg/kg) + CFA	3		

**Antigenicity Assays**

Species	Procedure
Guinea pig	[redacted]
Mouse/Rat	[redacted]
Rabbit	[redacted]

**Results:** Under the conditions of these assays, UF-021 was not antigenic. *Since this product is instilled into the eye, assessment of the potential for dermal sensitization, either in the guinea pig or the mouse, would have been more appropriate.*

**IX. Overall Summary** – The pharmacology studies need to be interpreted with the caveat that, in general, [1] they were conducted in ocular normotensive animals and [2] the majority of these studies were conducted with formulations other than that intended for clinical use. Frequently, the drug substance concentration in the test article was different than in the clinical formulation. Based on comparative studies, both pharmacology and pharmacokinetic studies, it is not anticipated that the formulation differences, with respect to excipients, would significantly impact interpretation of the results.

IOP was reduced in all species tested [generally ocular normotensive animals] in a dose- and time-dependent fashion following ocular instillation of UF-021. The rank order of sensitivity to the IOP reducing effects of UF-021 was cats > rabbits > monkeys. Maximum  $\Delta$ IOP generally occurred within 3 hours and generally persisted for 4-6 hours. The decrease in IOP was significantly greater at night than during the day in rabbits. However following daytime UF-021 treatment, Rescula®, unlike latanoprost, did not appear to cause a transient increase in IOP prior to the IOP reduction. The magnitude of the IOP decrease with UF-021 was comparable to that achieved with timolol in rabbits and latanoprost in dogs. In addition, tolerance did not appear to develop with UF-021 following 50 days of dosing nor was there cross tolerance with timolol.

Reductions in IOP with UF-021 appear to be mediated by an increase in aqueous humor outflow rather than a reduction in aqueous humor production. Although PGs, at low doses, have been shown to increase outflow through the uveoscleral pathway<sup>9</sup>, the Sponsor states that the data suggest that outflow is facilitated through the trabecular meshwork. The primary support for this hypothesis was lack of modulation of UF-021 IOP effects following the coadministration of a [redacted] pilocarpine. Additional studies are necessary to support this conclusion. UF-021 effects were not altered by concomitant administration of timolol, latanoprost, or epinephrine and UF-021 did not reduce the effects of either brimonidine or dorzolamide.

The mechanism of action of UF-021 has not been clearly defined. Binding studies [bovine corpora lutea or membrane bound E1, E2, IP, TP receptors] suggested that neither UF-021 nor M1 bind to PG receptors. In the general pharmacology studies, UF-021 [*in vivo*] and M1 [*in vitro*] exhibited little activity especially when compared to PGF<sub>2 $\alpha$</sub> . M1 did increase the contractile tension of the nonpregnant estrous rat uterus by approximately 20-30% as well as the frequency of contractions by approximately 3 fold. M1, however, under the conditions tested, did not affect uterine motility of late term gestation rats [*in situ* uterus]. [Note: Both reproductive toxicology studies and repeat dose toxicology studies in rats demonstrated that UF-021 has reproductive effects.] M1 increased the adrenaline-induced contraction of isolated guinea pig thoracic artery. IV administration of UF-021 [1 mg/kg] in dogs resulted in a transient [ $\leq$ 30 minutes] increase of approximately 80% in the respiratory rate. UF-021 and/or M1 reduced ET-1 induced *in vitro* contraction of pig retinal arteries, bovine trabecular meshwork and ciliary muscle, and ET-1 induced *in vivo* reduction of choroid blood flow in monkeys. This was not anticipated based on the generally contractile action of PGF<sub>2 $\alpha$</sub>  on ophthalmic blood vessels. Incubation of UF-021, M1, or latanoprost with rabbit iris ciliary body tissue resulted in an increase in cAMP. The mechanism for this increase is not known since activation of the primary PGF<sub>2 $\alpha$</sub>  receptors, E1 and FP, is coupled to phospholipase C and not adenylate cyclase.

<sup>9</sup>Gelatt, K.N. and Brooks, D.E. The Canine Glaucomas In *Veterinary Ophthalmology 3<sup>rd</sup> Edition* [K.N. Gelatt, ed.] Lippincott Williams & Wilkins, Philadelphia, 1998, p. 737.

## CIBA Vision

The Sponsor proposes the following metabolic pathway for UF-021.

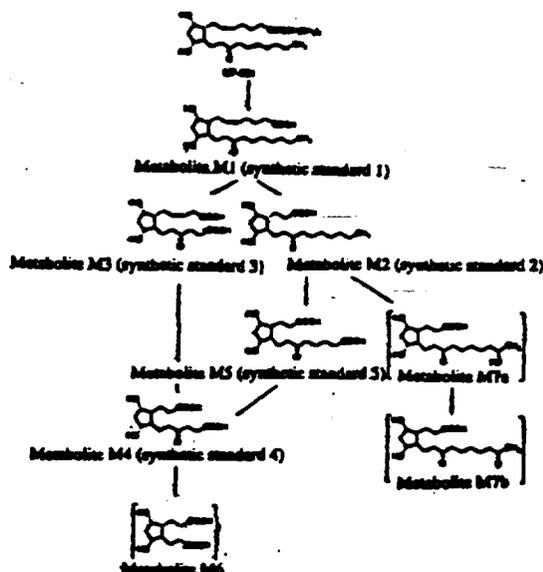


Figure 17. Proposed metabolic pathway for UF-021 (proposed structures shown in brackets)

In *in vitro* systems UF-021, parent compound accumulates in the cornea in a linear fashion where it appears to be converted to the free acid, M1, by the corneal esterases. Parent compound was not detected in the aqueous humor. However, in the rabbit, M1 accumulates in the aqueous humor until it appears to reach an equilibrium between production and diffusion. Ocular metabolism appears to occur in the epithelium but not in the endothelium or stroma. The major metabolites present in the aqueous humor are M1, M2, and M8, but M3-M7 were not determined. Corneal permeation of drug appears to be low [ $<1\%$  of the dose].

Biodistribution and kinetic analysis conducted with 0.12% [4 studies] and 0.15% [1 study] UF-021 was generally comparable following ocular administration in pigmented and nonpigmented rabbits. In general, the rank order of tissue concentration [ $C_{max}$ ] based on radioactivity was cornea > nictitating membrane, anterior sclera, conjunctiva >> aqueous humor, iris, ciliary body >> choroid, optic nerve, retina, vitreous, lens. Contralateral passage of UF-021 to the untreated eye was low. The following ocular kinetic parameters were calculated in pigmented and nonpigmented rabbits eyes: [1] corneal epithelial permeability which was approximately  $3-5 \times 10^{-3}$  cm/hour; [2] apparent elimination rate from the aqueous humor, based on a 2-compartment model of the cornea and anterior chamber, which was reported to range from approximately  $0.2-0.9 \text{ hr}^{-1}$ ; and [3] apparent absorption rate which ranged from  $1.3-1.8 \text{ hr}^{-1}$ . The ocular pharmacokinetics following administration of a single dose of MS-028 [the clinical formulation] to pigmented rabbits are provided in the table below.  $AUC_{0-24h}$  for the lens, vitreous humor, retina, choroid, and optic nerve was  $<570 \text{ ng-Eq}\cdot\text{hr/g}$ .

	Nictitating Membrane	Conjunctiva	Cornea	Aqueous Humor	Iris	Ciliary Process	Sclera
<b>C<sub>max</sub> [ng-Eq]</b> (% of radioactive dose)							
MS-028	2584.33 [0.23%]	4596.84	15264.87 [2.43%]	1039.44 [0.5%]	734.56 [0.1%]	389.05 [0.01%]	1748.08
<b>AUC<sub>0-24h</sub> [ng-Eq·hr/g]</b> (% of radioactive dose)							
MS-028	1595.28 [0.13%]	4215.97	44330.14 [7.17%]	4953.48 [2.49%]	3845.25 [0.49%]	1658.65 [0.04%]	2812.15

Following ocular instillation in rabbits, systemic absorption was rapid with a  $t_{max}$  in Dutch Belted rabbits of approximately 15 minutes. The AUC<sub>0-24h</sub> and C<sub>max</sub> following a single ocular instillation of MS-028 formulation into the eyes of Dutch Belted rabbits was 45.04 ng-Eq·hr/ml and 36.72 ng-Eq/ml, respectively. In an ocular PK study in NZW rabbits, C<sub>max</sub> plasma concentrations represented approximately 10% of the radioactivity administered. As for the aqueous humor, no parent compound was found in the plasma of rabbits following ocular instillation. The major metabolite was M1 with lesser amounts of M2, M4, and M6. In humans, only M1 could be quantitated.

Excretion was predominantly by the urinary route following ocular instillation in rabbits with approximately 99% of the radioactivity eliminated in the urine by 168 hours following dosing. The primary metabolite identified in the urine was M4 with lesser amounts of M6 and M7a. Although M4 was detected in the urine of humans following ocular administration, the levels could not be quantitated.

In general, the pharmacokinetics of UF-021 following parenteral administration to rabbits, rats, and dogs was qualitatively but not quantitatively similar to the pharmacokinetics of UF-021 following ocular instillation in rabbits. With the exception of negligible plasma levels in the dog, parent compound was not present in the plasma. The primary metabolite in all species evaluated, including humans, was M1. Urinary excretion was the principal route of elimination of the radioactive dose with M4 the predominant metabolite. However, fecal excretion was increased in rats and dogs following iv administration with approximately 30% and 13% of the radioactive dose eliminated by this route, respectively. Drug accumulated in the plasma and tissues of rats following repeat iv dosing.

*In vitro* protein binding of the free acid [e.g. de-esterified <sup>3</sup>H-UF-021; M1] was 96-99% in rats, rabbits, dogs, and humans. *In vivo* protein binding at 5 minutes was 60% and 85% in rats and dogs, respectively and 15% and 29% at 6 hours.

There did not appear to be any significant interactions with hepatic microsomal enzymes evaluated nor was enzyme induction demonstrated in rats at the doses tested [e.g. up to 0.5 mg/kg X 7 days].

Studies to assess the toxicity of UF-021 following ocular instillation were conducted in nonpigmented rabbits [up to 90 days], pigmented rabbits and dogs [up to 1 year], and cynomolgus monkeys [up to 2 years]. Formulations used included both [ ] formulations 1 and 2 and the [ ] formulations. The primary difference between the [ ] and [ ] formulations is in the vehicle excipients [See Appendix I for the ingredients in the formulations]. However, the ocular toxicity studies suggest that, in general, the drug-induced changes are similar for the [ ] and [ ] formulations.

The most sensitive species with respect to ocular toxicity/irritation was the rabbit, with generally negative findings in the dog and monkey at UF-021 concentrations up to 0.12%. In a dose-ranging study in monkeys, mild to moderate irritation was observed at drug substance

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concentrations of 0.15% and 0.18%. In general, ocular toxicity was characterized by mild iridic congestion, mild conjunctival vessel injection, and corneal erosions of  $\leq 25\%$  of the corneal surface. Several animals demonstrated moderate ocular irritation. Anterior uveitis was also described in a dose-ranging study in NZW rabbits. In 2/3 of the rabbit studies, irritation prior to dosing was comparable to that observed 1-hour after the last dose, although there was not always a correlation in the animals exhibiting irritation at each time point. Iridic congestion was observed more frequently than the conjunctival changes and was observed only in the nonpigmented rabbits. Pigmentation in the Dutch Belted rabbits and potentially in the dog and monkey may have obscured iridic congestion if it was mild as it was in the nonpigmented rabbits. In nonpigmented rabbits, the irritation was observed at drug substance concentrations as low as 0.05%. The severity of the irritation tended to be dose- and frequency of administration- dependent. In addition, increasing the frequency of administration did not appear to increase the number of animals that exhibited ocular irritation but did tend to increase the total number of incidences of irritation especially within the first 6 months of treatment.

There were no histopathological changes that could be definitively attributed to treatment with the exception of vasodilation of the ciliary body in 1 study. In several of the studies, there were some mild changes in both the treated and excipient control groups. However, some of the studies suggested that the excipient vehicle was mildly irritating and, therefore, a saline control would have been more appropriate. However, any changes observed were mild.

Miosis, which generally resolved within 18 hours, was induced in a dose-dependent fashion in dogs. It was also observed in cats in the efficacy studies and in a single non-GLP dose-ranging study in rabbits. The Sponsor states that this appears to be a species-specific response since it was generally not observed in rabbits, nonhuman primates, and humans. In addition, they cite *in vitro* work that indicated that the contractile response of the pupillary sphincter muscle in cats and dogs was considerably stronger than that observed in humans and rabbit pupillary sphincter muscle.

Administration of the  $F_{2a}$  analogue, latanoprost, has been associated with iridic pigmentation changes. The study conducted in cynomolgus monkeys to specifically evaluate the effect on iris color change of latanoprost compared to UF-021 suggested that although the incidence of iris color change occurred at a higher frequency with latanoprost [3/5 males and 1/5 females], iris color change was observed with UF-021 [1/5 males]. Neither treated group exhibited eyelash growth or increased pigmentation.

Administration of UF-021 at 0.12% did not aggravate inflammation in rat models of conjunctivitis nor did it inhibit corneal avulsion wound repair in rabbits.

There were no treatment-related systemic effects following ocular instillation.

The majority of the ocular toxicology studies were conducted with formulations in which the drug substance concentration was equal to or less than that to be used in the clinical formulation. In addition, the maximum frequency of administration was QID as compared to the BID dosing frequency recommended for clinical administration. With respect to ocular toxicity, the nonclinical studies do not provide a large margin of safety.

The Sponsor conducted studies to delineate the systemic toxicity of UF-021 by administering single or multiple doses by the iv, sc, and po routes in mice, rats, and dogs. The most significant finding was an increased incidence of mammary carcinoma in female rats administered 20 mg/kg/day for 1 year. The incidence of tumors was not increased at the mid-dose of 2 mg/kg which represents approximately 400X, 70X, and 1900X human exposure at a dose of 5  $\mu$ g/kg based on body weight, surface area, and AUC, respectively. [Note: AUC values were obtained following a single SC dose in rats and the repeat dose iv study suggests that there is accumulation following repeat dosing. In addition, the Sponsor has not validated sample stability for the human

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PK data. Therefore, exposure comparisons based on AUC throughout this study are contingent on demonstration of sample stability by the Sponsor].

Drug-related effects on the female reproductive tract was observed in rats administered 50 mg/kg/day sc for 3 months and included an 85% increase in ovarian weight and increase in the number of corpora lutea. These effects were reversible. Mice administered 12 mg/kg/day po for 4 weeks exhibited a 40% decrease in ovarian weight and increase in the incidence of ovarian cysts. The relationship to treatment is not known.

No clearly defined drug-induced toxicity was observed at oral doses of 12 mg/kg/day in rats, with the exception of transient and intermittent salivation, and mice. The toxicities observed in the iv and sc studies occurred at large multiples of human exposure. Therefore, these toxicities are considered not to be relevant to the clinical application. In addition, the toxicities observed in the sc studies in rats and dogs [e.g. decreases in RBC indices and total protein and/or albumin with associated increases in reticulocytes and medullary hematopoiesis, increases in WBC] were considered to be 2° to the injection site reactions [hemorrhage, edema, necrosis, and/or ulceration]. Furthermore, even if the hematological changes are due to treatment effects other than injection site reactions, this is a parameter that can be readily monitored in the clinical setting.

Under the conditions tested, UF-021 and UF-025 were negative for mutagenicity in the Ames Assay. Under the conditions tested, UF-021 and UF-025 were negative for clastogenicity in the in vitro Chinese hamster lung-derived fibroblast cell assay. UF-021 was also negative for genotoxicity in the mouse lymphoma assay and the in vivo mouse micronucleus assay, under the conditions tested. As noted above, the bioavailability of UF-021 has not been demonstrated following the ip route.

The Sponsor conducted a 2-year bioassay in rats in which drug was administered by gavage at a maximum dose of 12 mg/kg/day. MTD was not achieved since not even minimal toxicity was observed in this study. However, the ECAC, which met on May 23, 2000, concluded that adequate exposure was obtained based on pharmacokinetic criteria. [ICH Guideline for Industry: SIC - Dose Selection for Carcinogenicity Studies of Pharmaceuticals]. Since the exposure was judged to be adequate and there were no findings of carcinogenicity in this study, the ECAC concluded that the findings in the 1-year rat study do not need to be included in the label. [Note: As indicated above, the methodology for determining the M1 exposure in humans has been validated; however, the methodology for sample handling has not. Therefore, a conclusion that pharmacokinetic endpoints are appropriate for determination of doses in the 2-year bioassay study are contingent on the Sponsor demonstrating the stability of the M1 metabolite under the conditions of sample handling. However, based on the available data, it is anticipated that exposure in the carcinogenicity study will exceed the 25-fold pharmacokinetic criterion.]

There were no effects on fertility in either male or female rats up to doses of 50 mg/kg. Although there were deficiencies in the study design [e.g. dosing of males for 3 instead of 4 weeks and no direct evaluation of spermatid maturation], these were not considered to negatively impact the study since the multiples of the human exposure were so large [approximately 10,000, 1,700, and >15,000X human exposure based on body weight, surface area, and AUC, respectively].

With the exception of scabbing at the injection sites in the rat, maternal toxicity was not observed in either the rat or the rabbit at maximum doses of 5 and 0.3 mg/kg administered during organogenesis. Placental transfer of radiolabeled UF-021 was observed in pregnant rats with the greatest fetal tissue levels in the liver. An increased incidence of miscarriages was observed in the rat at 5 mg/kg and in the rabbit at 0.3 mg/kg. And a rat administered 5 mg/kg died during delivery on Day 21. Only 69% of the dams in the 5 mg/kg delivered newborn pups compared to 100% in the other groups. There was an increased incidence of early resorptions in does administered 0.3 mg/kg [23.7%] compared to control does [3.9%]. There was no evidence of teratogenicity. Based on ICH recommendations, there was not an adequate number of litters for evaluation for the

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rabbits administered 0.03 and 0.3 mg/kg. However, based on negligible exposure in the clinical setting, this study is considered adequate. The NOAEL for developmental toxicity in the rat was 2.0 mg/kg (400 and 67 times the maximum clinical dose, based on body weight and surface area, respectively). The NOAEL for embryofetal toxicity in the rabbit was 0.1 mg/kg dose, which represents approximately 20 and 7 times the maximum clinical dose based on body weight and surface area, respectively.

A "poor lactation state" [The Sponsor did not characterize this condition.] and premature deliveries were observed in dams administered 1.25 mg/kg during late gestation [Days 17-21]. In the litters from dams administered 1.25 mg/kg there was a decrease in the live birth index [64% vs. 94% in the high and control litters, respectively] and a 20% decrease in birth weight compared to controls. There was an increase in the number of stillborn at doses of 0.5 and 1.25 mg/kg compared to the control values. Postnatal survival was decreased at  $\geq 0.5$  mg/kg. The increase in the number of pups dying Days 1-4 in the mid-dose litter and the high dose litter was 59(18.4%) and 84(35%) pups, respectively, compared to 8(2.4%) in the control litters. Body weight of the pups in the 1.25 mg/kg group was still decreased by 12% on Lactation Days 4-7. Growth and differentiation, specifically incisor eruption and eye opening, were delayed in males and females in the high dose group. The toxicological significance of the changes in organ weight observed in F<sub>1</sub> is unclear. No effects were apparent on reflex ontogeny, reproductive capacity of the F<sub>1</sub> generation, or F<sub>2</sub> fetuses. Following an iv injection of radiolabeled UF-021 to lactating rats, radioactivity was detected in the milk. The NOAEL for pre and postnatal development was 0.2 mg/kg (40 and 7 times the maximum clinical dose based on body weight and surface area, respectively).

These findings are consistent with known effects of PGF<sub>2 $\alpha$</sub>  on reproduction.

**X. Recommendations:**

2. **Internal Comments:** The following ocular toxicities, observed in the rabbit, dog, and monkey in repeat dose ocular toxicity studies, are considered clinically relevant: [1] mild iridic congestion; [2] mild to moderate conjunctival congestion; [3] corneal erosion ( $\leq 25\%$  of the corneal surface); [4] iris pigmentation changes; and [5] mild anterior uveitis. The majority of these studies were conducted with formulations in which the drug substance concentration was equal to or less than that to be used in the clinical formulation. The maximum frequency of administration was QID as compared to the BID dosing frequency recommended for clinical administration. With respect to ocular toxicity, the nonclinical studies do not provide a large margin of safety.

The most significant finding was an increased incidence of mammary carcinoma and a reduced time to onset in rats administered 20 mg/kg/day sc for 1 year. This dose is  $>15,000X$  human exposure based on AUC at a dose of 5  $\mu\text{g}/\text{kg}/\text{day}$ . An increased incidence of tumors was not observed at 2 mg/kg/day. This dose is approximately 1900X human exposure based on AUC<sub>0-24h</sub> at a dose of 5  $\mu\text{g}/\text{kg}/\text{day}$ . [This is based on a single sc dose in rats.]

The genotoxicity assays were adequate and were considered negative under the conditions tested.

The 2-year rat bioassay was considered adequate and negative for carcinogenicity. The ECAC recommended that, based on this study, the findings of increased mammary carcinomas in the 1-year study not be included in the label. [Note: This is, in part, contingent on the Sponsor validating sample stability for the human pharmacokinetics study.]

There were no effects on fertility and no evidence of teratogenicity, although an adequate number of rabbit litters were not available for evaluation. Reproductive toxicity, consistent with PGF<sub>2 $\alpha$</sub>  effects, was observed in both the embryofetal and pre and postnatal studies and included

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miscarriages, premature delivery, decreased live birth index, increased resorptions, decreased pup viability, and delayed growth and differentiation. The NOAEL for developmental toxicity in the rat was 400 and 67X the maximum clinical dose, based on body weight and surface area, respectively. The NOAEL for embryofetal toxicity in the rabbit was approximately 20 and 7 times the maximum clinical dose based on body weight and surface area, respectively. The NOAEL for pre and postnatal development was 40 and 7 times the maximum clinical dose based on body weight and surface area, respectively. AUC data is not available for pregnant rabbits and rats nor for the doses selected for the reproductive study. However, based on the apparently negligible systemic exposure in humans and on the AUC data available in nonpregnant animals, it is likely that the actual multiples of human exposure [e.g. based on AUC] which were achieved in these studies are significantly greater than those based on either body weight or surface area.

Approval is recommended contingent on resolution of labeling concerns.

b. **External Recommendations:** None at this time.

**XII. Labeling Review:** The text in red that has been struck out is the labeling proposed by the Sponsor. The highlighted text is the labeling proposed by the Reviewer. The remaining text is labeling proposed by the Sponsor with which the Reviewer concurs.

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**CLINICAL PHARMACOLOGY*****Mechanism of Action***

When instilled in the eye, RESCULA® is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor

[REDACTED]

**Pharmacokinetics / Pharmacodynamics:**

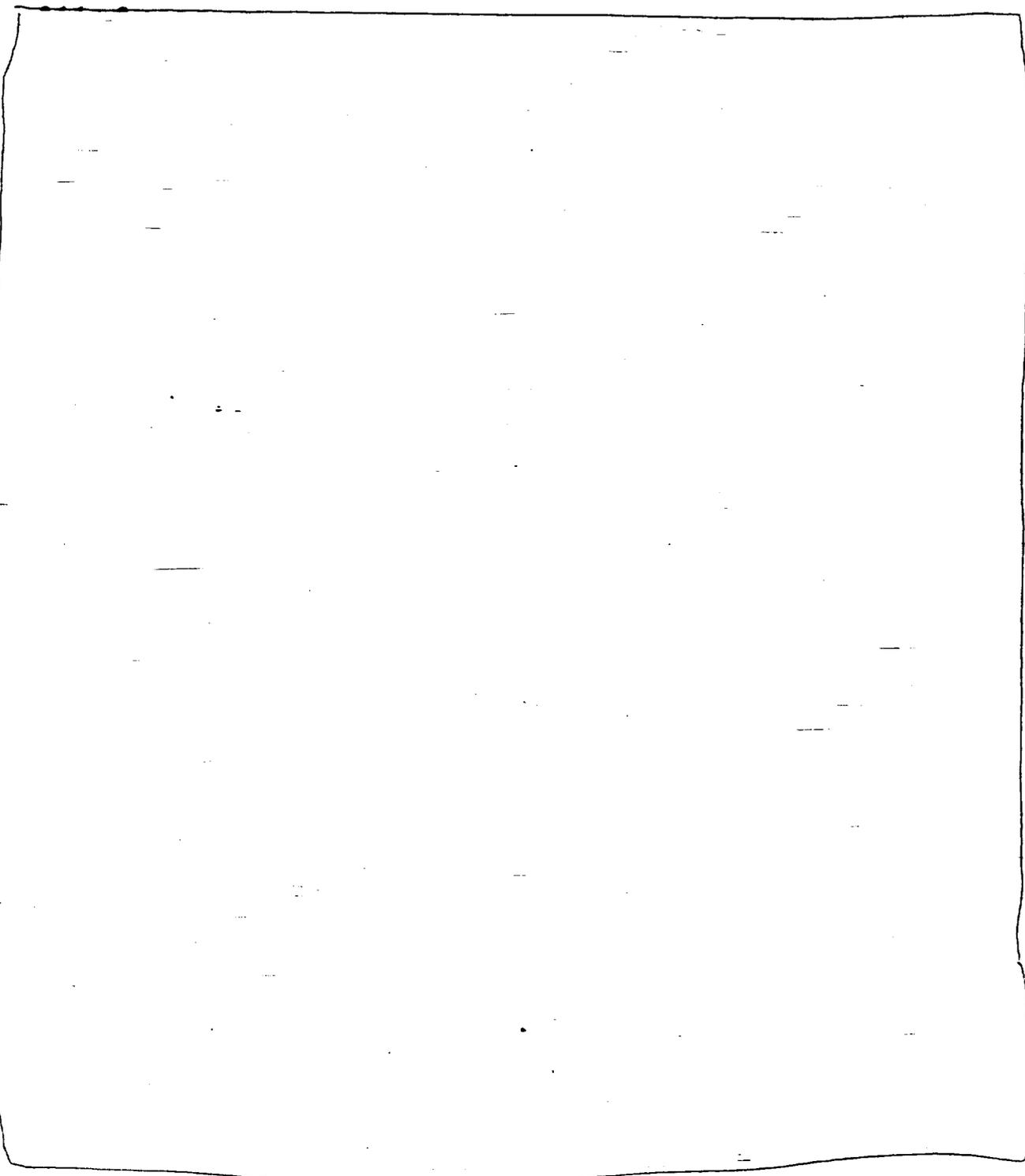
**Absorption:** After application to the eye, unoprostone isopropyl is absorbed through the cornea and conjunctival epithelium where it is hydrolyzed by esterases to unoprostone free acid.

[REDACTED]

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metabolized to several inactive metabolites with lower molecular weight and increased polarity via  $\omega$ - or  $\beta$ -oxidation. No secondary conjugation is found and no significant effect on hepatic microsomal enzyme activity has been observed.

*Elimination:* Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. Plasma levels  following ocular instillation. The metabolites are excreted predominantly in urine.



**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Rescula® was not carcinogenic in rats administered oral doses up to 12 mg/kg/day for up to 2 years (approximately 580 and 240 fold the recommended human dose of 0.005 mg/kg/day<sup>1</sup> based on AUC<sub>0-24</sub><sup>2</sup> in male and female rats, respectively) [redacted]

<sup>1</sup> The human dose was determined as follows: 1.5 mg/ml UF-021 X 50 µl [1 drop] X 2 eyes X BID administration = 0.3 mg/day. Based on a 60-kg individual and assuming 100% absorption, this represents a dose of 0.005 mg/kg/day.

<sup>2</sup> The AUC<sub>0-24</sub> in male and female rats administered Rescula® by oral gavage at 12 mg/kg/day [Week 80] was 170.5 and 70.6 ng•hr/ml for male and female rats, respectively. These data are from Report No. 17499: Unoprostone isopropyl: 104 week carcinogenicity study in rats with administration by gavage. The AUC<sub>0-24hr</sub> in humans administered the clinical dose BID was estimated to be 0.292 ng•hr/ml on Day 14. The AUC<sub>0-4</sub> was of 0.146 ng•hr/ml on Day 14 following the last dose. This represents only 1 of the 2 peaks that would be observed following BID dosing. Therefore, this value was doubled to obtain a theoretical AUC<sub>0-24hr</sub>. The sample stability under the conditions of the clinical trial has not been validated. Therefore, the labeling is contingent on this validation.

Under the conditions tested, unoprostone isopropyl and unoprostone free acid were neither mutagenic in an Ames assay nor clastogenic in a chromosome aberration assay in Chinese hamster lung-derived fibroblast cells. Under the conditions tested, unoprostone isopropyl was not genotoxic in a mouse lymphoma mutation assay nor clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow.

Unoprostone isopropyl did not impair male or female fertility in rats at subcutaneous doses up to 50 mg/kg (approximately 10,000 fold the recommended human dose of 0.005 mg/kg/day).

**Pregnancy: Teratogenic Effects:**  
Pregnancy Category C -

[redacted]

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*Nursing Mothers:* Unoprostone isopropyl has been identified in breast milk in rats following intravenous administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when RESCULA® is administered to a nursing mother.

2.1.1, p. 12

#### OVERDOSAGE

There are no published information available regarding overdose with RESCULA 0.15% [redacted]. The risk of adverse effects due to accidental oral ingestion is very low since the amount of active ingredient in each bottle is [redacted] limited (7.5 mg in a 5 mL vial). Accidental ingestion of a vial by a child with 30 kg body weight will amount to 0.25 mg/kg body weight [redacted].

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/S/

XII. Reviewer's Signature:

Susan D. Wilson, D.V.M., Ph.D.

26 June 2000

Date

/S/

Team Leader Concurrence:

Robert E. Osterberg, RPh, PhD

6/29/2000

Date

CC: list:

- cc:
- Original -NDA 21-214
- HFD-550:Division Files
- HFD-550:DivDir/KMidthun
- HFD-550:DepDir/WChambers
- HFD-550/Pharm/SDWilson
- HFD-550/MO/WBoyd
- HFD-550/CHEM/AFenslau
- HFD-550/CSO/RRodriguez

Appendix:

Draft Date: June 13, 2000

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

HFD 550  
RODRIGUEZ

**REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:  
PATHOLOGY CONSULT TO HFD-550**

**KEY WORDS:** Unoprostone isopropyl, carcinogenicity study in rats, oral

**Reviewer Name:** Terry S. Peters, D.V.M.

**Division Name:** Anti-Infective Drug Products

**HFD #:** 520

**Review Completion Date:** 3/15/00

**IND/NDA number:** NDA-21214

**Information to sponsor:** No

**Sponsor (or agent):** Ciba Vision Corporation, Duluth, GA

**Drug:**

**Generic Name:** Unoprostone isopropyl

**Trade Name:** Rescula

**Drug Class:** Ophthalmic drug for ocular instillation as therapy for increased intraocular pressure

**Studies reviewed within this submission:**

**Unoprostone Isopropyl: 104 Week Carcinogenicity Study in Rats with Administration by Gavage; Report #17499.**

**Scientific literature reviewed:** No

**CARCINOGENICITY:**

**Study Title:** Unoprostone Isopropyl: 104 Week Carcinogenicity Study in Rats with Administration by Gavage

**Study Number:** Report [redacted]

**Volume Numbers:** 35-40

**Test Facility:** [redacted]

**Study Date(s):** 2/19/97- 3/12/99

**GLP Compliance/Quality Assurance:** Yes

**QA Report- Yes (x)**

**Study Type:** 2 year gavage study in rats

**Species/strain:** CrI:CD@BR rats

**Number of animals per group; age at start of study:** 60/sex/dose. Animals were 4 weeks old on arrival and acclimated for 2 weeks before study initiation. An additional batch of animals was received in April 1998 to be used for repeating the Day 1 toxicokinetic blood sampling.

**Animal housing:** 5/sex/dose

**Drug Lot/Batch number(s):** Batch # 63502 (exp. 8/98 and exp. 3/31/99). It is unclear how the differing expiration dates could apply to the single batch.

**Drug Purity / Stability / Homogeneity:** [redacted] They were analyzed by the sponsor or [redacted]

**Doses:**

- **Basis of Dose Selection:** Doses were limited by solubility of the product at 120 mg/mL and the maximum dosing volume (10 mL/kg/bw) for chronic administration.
- **Relation to Clinical Use:**
- **CAC Concurrence:** None
- **Route of Administration:** Gavage at 10 mL/kg as a constant dose volume, once/day
- **Frequency of Drug Administration:** 7 days/week.
- **Dual Controls Employed:** Control group 1 received only vehicle and control group 2 received distilled water.
- **Interim Sacrifices:** None
- **Satellite PK or Special Study Group(s):** None

### Study Results and Frequency of Monitoring:

- Clinical Observations: Twice/day for viability. Once/week as detailed clinical examination. No treatment-related signs were reported.
- Mortality: There were 414 premature decedents divided across dose groups.

Group	Dose in mg/kg/d	Males	Females
1	0	45	42
2	0	32	40
3	1.2	44	44
4	3.6	38	46
5	12.0	43	43

In males, the placebo group was almost ( $p=0.055$ ) statistically higher than the water controls and in females, statistical significance was reached ( $p=0.020$ ). There were no significant effects of treatment on survival.

However, at issue is the survival at 80 weeks that is deemed adequate (Males: 37, 43, 39, 36 and 34 for the respective groups, and females: 36, 47, 43, 36 and 44 for the respective groups).

- Body Weight: Once/week for the entire study. Rates of gain and body weights were comparable across dose groups.
- Food Consumption: Weekly for the first 13 weeks and every 4 weeks thereafter. Comparable across dose groups.
- Ophthalmoscopy: Prior to dosing for all animals and controls and high dose only Weeks 13, 26, 52, 78 and 103. No treatment-related findings were reported.
- Hematology: First 20 survivors/sex/dose in Weeks 26, 52, 78 and 104 (approximately). No treatment-related findings were reported.
- Clinical Chemistry: Last 20 survivors/sex/dose in Weeks 26, 52, 78 and 104 (approximately). No treatment-related effects were reported.
- Urinalyses: Screens at the same time points as the hematology and clinical chemistries. No treatment-related effects were reported.
- Organs weighed: adrenals, brain, epididymides, extraorbital lacrimal gland, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid. No treatment-related differences from controls were noted.
- Gross Pathology: All main study animals, including dead or moribund animals underwent complete necropsy. No gross findings attributable to treatment were reported.
- Histopathology: The sponsor reported histologic evidence of neither a carcinogenic nor a toxicological effect in rats.

Non-Tumor: Sporadic findings consistent with aging rats were reported in all groups (e.g., cardiomyopathy, chronic progressive nephropathy, hepatic foci, alveolar macrophage accumulation in the lung, tubular atrophy of the testis). Statistical significance was reached for nephropathy in females (11, 12, 5, 7 and 22 for the respective groups), and the premature decedents had 17/43 high dose animals with the lesion, but values were within historical ranges for the laboratory.

- Tumor: Incidental tumors were reported in all dose groups, but no trends or statistical or biological significance is attached to any finding. It is interesting to note that in the 1 year subcutaneous administration study in rats, an increased incidence of mammary carcinoma was reported (1/14 for untreateds, 3/22 for vehicle controls, 2/14 for 0.2 mg/kg animals, 1/14 for the 2.0 mg/kg animals and 8/21 for the 20 mg/kg groups, respectively). The incidences of mammary gland carcinoma and carcinosarcoma were comparable across dose groups in the current study.
- Toxicokinetics: Samples were supposed to be taken from 6/sex/dose on Day 1 of dosing at 0, 30 and 60 minutes post-dosing and from the remaining 6/sex/dose at 15, 45 and 120 minutes post-dosing. These samples were not analyzed due to assay methodology issues. The problems remained by Week 26 so those samples were not taken. Samples were actually taken Week 52 at 0, 15, 30, 45, 60 and 120 minutes post-dosing. Final samples were taken Week 80 at 0, 15, 30, 45, and 60 minutes and 2, 4, 8 and 24 hours post-dosing. The  $T_{max}$  was determined to be 0.25 hours for all except one mid dose female where it was 2 hours. Wide variations were noted and comparisons were confounded by different sampling schedules for Week 52. Increases in systemic exposure were noted for the high dose group only, suggesting some accumulation of the M1 metabolite. M1 plasma levels were

accumulated at a higher level in males than females but no gender trends were reported for  $t_{1/2}$  elimination or  $t_{max}$ .

#### Overall Interpretation and Evaluation

- Adequacy of the carcinogenicity studies and appropriateness of the test model: The doses do not appear to be high enough to elicit even minimal toxicity.
- Evaluation of Tumor Findings: No significant tumor findings.

#### Summary Conclusions and Recommendations

- Acceptability of Study(s) or Overall Testing Approach: Doses did not appear to be high enough to elicit even minimal toxicity. In the one year subcutaneous study in Sprague-Dawley rats, the incidence of mammary carcinoma was 1/14 (7%), 3/22 (14%), 2/14 (14%), 1/14 (7%) and 8/21 (38%) for the untreated, vehicle control, 0.2 mg/kg, 2 mg/kg and 20 mg/kg groups, respectively. No other significant findings were reported in that study, conducted by [redacted].  
[redacted] In the 3 month subcutaneous study in rats, only mild toxicities were reported in the high dose group at 50 mg/kg/d and the reviewer concluded that higher doses should have been used. This dose was 173x the proposed human dose on the basis of  $mg/m^2$ .
- Major Tumor Findings: None
- Non-neoplastic Findings: Sporadic lesions consistent with the age and species of animal tested.
- Biological Significance: As the NOAEL is many multiples (92- 224x higher  $C_{max}$  and 172- 416x higher AUC than humans after a single ocular dose) of the proposed human exposure (4.8  $\mu g/kg$ ), this study is adequate to assess the potential human carcinogenic risks. It would be helpful to know whether repeated human exposures result in significantly higher AUCs.

- List of Organs and Tissues Examined: gross lesions, adrenals, aorta, brain, extraorbital lacrimal gland, eye, femur and marrow, GI tract (stomach, duodenum, ileum, jejunum, colon, cecum, rectum), Harderian gland, heart, kidneys, liver, lung, mesenteric lymph node, esophagus, optic nerve, ovary and oviduct, pancreas, pituitary, prostate, sciatic nerve, seminal vesicles, skin and mammary gland, spinal cord (3 segments), sternum with marrow, submandibular lymph node, submaxillary salivary gland, testes, muscle, thymus, thyroid with parathyroid, tongue, trachea, urinary bladder, uterus and Zymbal's gland.

#### RECOMMENDATIONS:

Internal comments: This study should be presented to the Exec. CAC for concurrence on the conclusion that the doses were not high enough. It would be useful to have the human repeat dose AUC data to correlate with the doses used in this study.

Reviewer signature

/S/

cc: list

HFD-520/PT/Peters  
HFD-550/PharmTox/Weir/Wilson  
HFD-550/MO/Boyd  
HFD-550/CSO/Rodriguez  
HFD-550/DepDivDir/Chambers  
Draft date (# of drafts): 3/15/00 (#1)

Concurrence Only:  
HFD-520/DepDivDir/Gavrilovich  
HFD-520/PTTeamLdr/Osterberg

/S/ 4/16/00  
4/14/00

**Executive CAC**  
**May 23, 2000**

**Committee:** Joseph DeGeorge, Ph.D, HFD-024, Chair  
Al DeFelice, Ph.D., HFD-110, Alternate Member  
Jasti Choudary, Ph.D., HFD-180, Alternate Member  
Susan D. Wilson, DVM, Ph.D., HFD-550, Presenting Reviewer

**Author of Draft:** Susan D. Wilson

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed information can be found in the individual review.

**NDA- 21-214**  
**Unoprostone Isopropylate Ophthalmic Solution**  
**CIBA Vision**

### **Rat Carcinogenicity Study**

Unoprostone isopropylate ophthalmic solution [UIOS] is a prostaglandin  $F_{2\alpha}$  analog for the treatment of glaucoma and ocular hypertension. The drug is applied topically. In a one-year subcutaneous study in the Sprague Dawley rat, the females at the highest dose tested, 20 mg/kg/day, showed an increased incidence of mammary carcinoma. In addition, there was an earlier time to onset.

Systemic exposure to the parent compound by either the ocular route in humans or the oral and subcutaneous routes in the rat was not measurable. Therefore, comparison of exposure between species was based on the AUC of the major metabolite, M1. Based on a single sc dose of 20 mg/kg drug substance, AUC of the M1 metabolite in the rat was >15,000 fold higher than the human AUC at the recommended clinical dose.

The following recommendations were made by the ECAC following an Aug. 18, 1997 meeting. [1] Data from this 1-year rat study should be included in the label along with the exposure level comparisons for the metabolites in human and rat. [2] "Given the early observation of the tumors, there [were] concerns about the rat mammary findings even though they were observed at the high exposures versus exposures achieved in the clinical setting... Results from two year carcinogenicity studies would be needed to exclude the one year data from the label". The Sponsor was also given the option of conducting an alternative assay.

The Sponsor opted to conduct a 2-year bioassay in the rat and did not seek concurrence on dose selection. They conducted a 2-year bioassay in the CD-1 rat in which the drug substance was administered at a maximum dose of 12 mg/kg by the oral route. Incidental tumors were reported in all dose groups, but no trends or statistical or biological significance is attached to any finding. Based on an oral dose of 12 mg/kg drug substance, AUC of the M1 metabolite in the male and female rat was approximately than 580 and 280 fold higher, respectively, than the human AUC at the recommended clinical dose.

The committee discussed [1] the fact that an MTD was not achieved in the study; [2] that exposure to the M1 metabolite in the 1-year rat study [sc administration] was significantly greater than the exposure achieved at the maximum dose used in the 2-year rat bioassay [po administration]; and [3] whether the data from the 2-year bioassay were robust enough to preclude inclusion in the label of the findings of increased incidence of mammary tumors in the 1-year rat study.

**Executive CAC Recommendations and Conclusions:**

1. If the exposure, based on AUC, to the parent compound/metabolites in the rat is  $\geq 25X$  than human exposure at the recommended human clinical dose, if protein binding in rats and humans is comparable, and since the drug substance is negative in the standard genotoxicity battery of assays, then the maximum dose selected by the Sponsor for the 2-year rat bioassay should be adequate. This is based on ICH recommendations.
2. If the exposure, based on AUC, to the parent compound/metabolites in the rat is  $\geq 25X$  than human exposure at the recommended human clinical dose and if protein binding in rats and humans is comparable, then the results of the 2-year bioassay preclude the need to include the findings in the 1-year rat study of increased incidence of mammary tumors in the label.
3. The reviewer agreed to provide additional data to the committee that supports use of pharmacokinetic endpoints as a basis for dose selection. This information is provided as an attachment.
4. The reviewer agreed to provide the histopathology summary tables to the committee. These have been provided under separate cover.

Note: The methodology for determining the M1 exposure in humans has been validated; however, the methodology for sample handling has not. Specifically, the Sponsor has not demonstrated that the M1 metabolite is stable in the plasma following freezing and thawing. However, it is the opinion of the ECAC that there is sufficient data to determine that  $>25$ -fold exposure based on AUC was achieved at the highest dose used. Therefore, the ocular administration of Rescula® at the proposed clinical dose does not constitute a risk for the development of mammary tumors in humans.

*ISI 06/19/00*  
Joseph DeGeorge, Ph.D.  
Chair, Executive CAC

cc:\  
Original - NDA 21-214  
HFD-550 Division File: NDA 21-214  
HFD-550: WBoyd  
HFD-550: SWilson  
HFD-024: ASeifried

## ADDENDUM

NDA 21-214

**Unoprostone Isopropylate Ophthalmic Solution**  
**CIBA Vision**

1. **Comparative metabolism:** Systemic exposure to the parent compound by the ocular route in humans and the sc route in rats was not measurable. The major metabolite detected in rats [regardless of route of exposure] and humans was M1. M1 exposures, therefore, served as the basis for correlating rat and human exposure. No other metabolite, besides M1, was detected in the plasma of humans. The other metabolites observed in the plasma of rats following SC administration of the drug substance were M4, M2, and M6. M4, the major metabolite in the urine in rats, was detected in human urine samples. However, it was not quantifiable since the levels were below the LOQ. The full metabolite profile was not determined in the rat, but the exposure to M1 was determined.

The methodology for determining the M1 exposure in humans has been validated; however, the methodology for sample handling has not. Specifically, the Sponsor has not demonstrated that the M1 metabolite is stable in the plasma following freezing and thawing. Therefore, a conclusion that pharmacokinetic endpoints are appropriate for determination of doses in the 2-year bioassay study are contingent on the Sponsor demonstrating the stability of the M1 metabolite under the conditions of sample handling. [Note: It is anticipated that this data may not be available for 6 months.]

The table below provides the multiples of the human exposure to the major metabolite, M1, based on the data provided by the Sponsor for [1] the 1-year study at 20 mg/kg/day administered subcutaneously and [2] the 2-year study at 12 mg/kg/day administered by gavage.

	AUC <sub>0-24hr</sub> , ng•hr/ml]*		Multiples of human exposure** C <sub>max</sub> / AUC <sub>0-24hr</sub>	
	Male	Female	Male	Female
Day 1	4825	-	16,254	-
Week 80	170.47	70.60	583	282

\* AUC<sub>0-24hr</sub>, ng-Eq •hr/ml for the subcutaneously administered drug

\*\*Values obtained from Study #C99-UIOS-018. The Day 1 and 14 values for C<sub>max</sub> were 0.576 and 0.526 ng/ml, respectively. The Day 1 and 14 values for AUC<sub>0-24hr</sub> were 0.140 and 0.146 ng•hr/ml, respectively. The Day 1 and 14 values for AUC<sub>0-24hr</sub> were 0.28 and 0.292 ng•hr/ml, respectively.

2. **Protein binding - *In vitro* protein binding** of M1 at concentrations ranging from 1 ng/ml to 1 µg/ml was approximately  in rat plasma and approximately 99% in human plasma.