CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: decongestant, antihistamine, seasonal allergic rhinitis, perennial allergic rhinitis, acute toxicology, subchronic toxicology, chronic toxicology, reproductive toxicology, and genetic toxicology

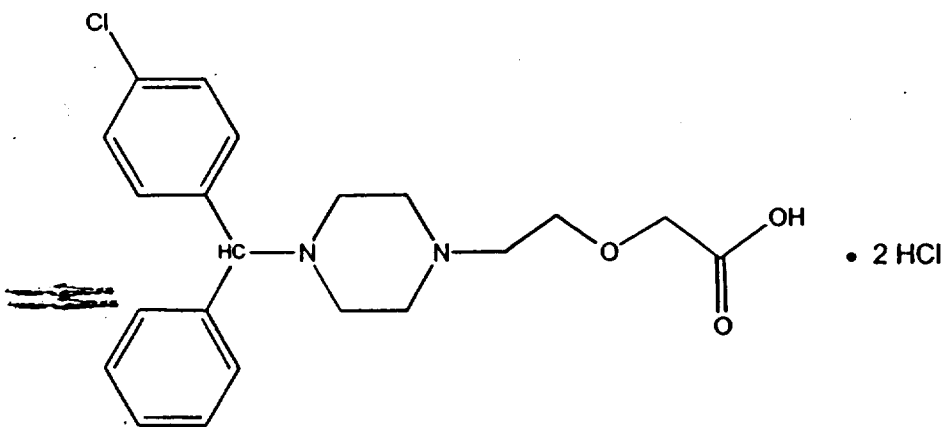
Reviewer Name: Jui R. Shah, Ph.D.
Division Name: Division of Pulmonary and Allergy Drug Products
HFD #: 570
Review Completion Date: September 2000

Review Number: Original
IND/NDA Number: NDA 21-150
Serial Number/Date/Type of Submission: 000, January 19, 2000
Information to Sponsor: Yes, see labeling changes (p. 50)
Sponsor (or agent): Pfizer, Inc.
Manufacturer for Drug Substance:
UCB S.A., Chemin du Foriest, 1420 Braine-L'Alleud, Belgium.

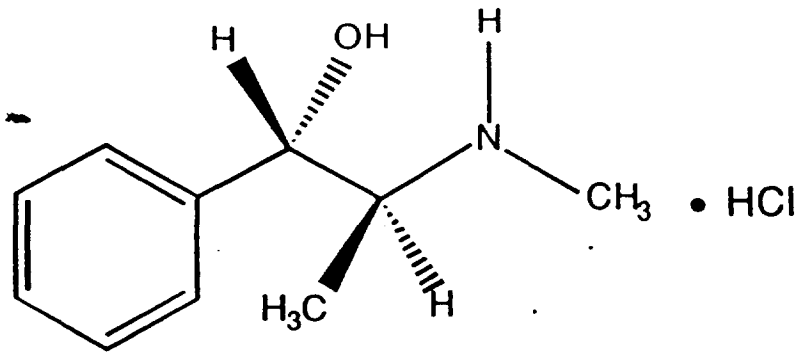
Drug:
Code Name: N/A
Generic Name: Pseudo-Ephedrine:Cetirizine
Trade Name: Zyrtec-D ER
Chemical Name: Cetirizine: (+/-)- [2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride. Pseudo-ephedrine: (1S.2S)-2-methylamino-1-phenyl-1-propanol hydrochloride.

Molecular Formula/ Molecular Weight:
Cetirizine Dihydrochloride: $C_{21}H_{25}ClN_2O_3.2HCl$, 461.82
Pseudo-Ephedrine Hydrochloride: $C_{10}H_{15}NO.HCl$, 201.7

Structure:



Cetirizine Dihydrochloride



Pseudo-Ephedrine Hydrochloride

Relevant INDs/NDAs/DMFs: —— also NDA 19-835, NDA 20-346.

Drug Class: Vasoconstrictor/Antihistamine (H_1 histamine receptor antagonist)

Indication: Seasonal and perennial allergic rhinitis with nasal congestion.

Clinical Formulation: Biconvex tablets, 125 mg ea. (24:1 pseudo-ephedrine: cetirizine)

Route of Administration: Oral

Proposed Clinical Use: ZYRTEC-D 12 HOUR, one 125-mg tablet b.i.d., is indicated for seasonal allergic rhinitis or perennial allergic rhinitis. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, tearing, redness of the eyes and nasal congestion.

Previous Clinical Experience: Both Pseudo-ephedrine and Cetirizine are currently on the market. Pseudo-ephedrine is an OTC product, while cetirizine is by prescription only.

Introduction and Drug History: Cetirizine hydrochloride was first approved in December 1995 for seasonal and perennial allergic rhinitis and chronic urticaria. Pseudo-ephedrine is a monographed drug used for the treatment of nasal congestion. This NDA is for a combination product containing both cetirizine (5 mg for immediate release) and pseudo-ephedrine (120 mg in an HPMC matrix for extended release) as an extended release tablet for the treatment of seasonal and perennial allergic rhinitis with nasal congestion.

Studies Reviewed Within This Submission:

Study No.	Study Title	Vol.	Page #	Review Page #
	ACUTE TOXICOLOGY			7
LE90G111/UCB 331	Acute Oral Toxicity to Mice of a Combination of Pseudo-Ephedrine and Cetirizine	4	25	7
RRLE91C2504/ UCB388	Acute Intravenous Toxicity to the Mouse of a Combination of Pseudo-Ephedrine and Cetirizine	4	45	7
LE88CO23	Acute Toxicity Studies in Rats	4	68	8
LE90G112/UCB 330	Acute Oral Toxicity to Rats of a Combination of Pseudo-Ephedrine and Cetirizine	4	92	8
RRLE91C2503/ UCB 387	Acute Intravenous Toxicity to the Rat of a Combination of Pseudo-Ephedrine and Cetirizine	4	114	9
LE90H281/UCB 332	Pseudo-Ephedrine HCl/Cetirizine 2 HCl Single Dose Study in Beagle Dogs	4	135	9
LE90J048/UCB 341	Pseudo-Ephedrine HCl/Cetirizine 2 HCl Single Administration Study in Cynomolgus Monkeys	4	219	10
	SUBCHRONIC TOXICOLOGY			11
LE90H231/UCB 336	Pseudo-Ephedrine HCl/Cetirizine 2HCl Pilot Toxicity Study in Rats by Repeated Oral Administration for 2 Weeks	4	292	11
LE90L192/UCB 337	Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride Toxicity to Rats by Repeated Oral Administration for 4 Weeks	5	378	11
LE90L192/UCB 364	Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride Preliminary Toxicity and Pharmacokinetic Study in Rats by Dietary Administration for 4 Weeks	5	571	13
	CHRONIC TOXICOLOGY			15
RRLE93A2508/ UCB414	Pseudo-Ephedrine/Cetirizine Toxicity to Rats by Repeated Oral Administration for 26 weeks Followed by a 6 Week Recovery Period	5	757	15
RRLE91B2501/ UCB 347	Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride Toxicity in Cynomolgus Monkeys By Repeated Oral Administration for 13 Weeks with a 4-Week Recovery Period for Selected Animals	8	1770	19
RRLE93E0501/	Pseudo-Ephedrine/Cetirizine Toxicity to	9	2085	23

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Studies not Reviewed Within This Submission:

Study No.	Study Title	Vol.	Page #
	ACUTE TOXICOLOGY		
LE88C023	Pseudo-Ephedrine Sulphate and Cetirizine 2 Hydrochloride: Acute toxicity Report in Rats*	4	68
	SUBCHRONIC TOXICOLOGY		
LE901M141/UC B346	Pseudo-Ephedrine Hydrochloride and Cetirizine Dihydrochloride: Preliminary Dose Range Finding Study in Cynomolgus Monkeys*	7	1385
RRLE91E2703/ UCB365	Pseudo-Ephedrine/Cetirizine. Preliminary Dose Range Finding Study in Cynomolgus Monkeys (Comparison of Different Formulations)*	7	1506
	REPRODUCTIVE TOXICOLOGY		
LE90L091/UCB 349	A Preliminary Study of Pseudo-Ephedrine/Cetirizine (24:1) on the Pregnant Rat and Offspring*	9	2503
RRLE91B2001/ UCB348	A Preliminary Study of Pseudo-Ephedrine/Cetirizine (24:1) on the Non-Pregnant Rabbit	10	2556
LE91D0801/UC B355	A Preliminary Study of Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride (24:1) on the Pregnancy of the Rabbit*	10	2576

* Indicates previously reviewed studies. For review, refer to [redacted]

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ON ORIGINAL

PHARMACOLOGY:

Mechanism of Action: Cetirizine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. Pseudo-ephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa.

Drug Activity Related to Proposed Indication: Cetirizine, a human metabolite of hydroxyzine (an anti-anxiety agent), is an antihistamine; its effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been documented in a variety of animal and human models and shows negligible anticholinergic and antiserotonergic activity in *in vivo* and *ex vivo* studies. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Pseudo-ephedrine hydrochloride is an orally active sympathomimetic amine and a nasal decongestant. Pseudo-ephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudo-ephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than amphetamines. It has the potential for excitatory side effects.

ACUTE TOXICOLOGY:

Acute Oral Toxicity to Mice of a Combination of Pseudo-Ephedrine and Cetirizine (LE90G111/UCB331, vol. 1.4, p. 25)

This is a GLP and QAed study carried out to assess the toxicity following a single oral dose (320, 640, 800, 1000 & 2500 mg/kg) of cetirizine:pseudo-ephedrine combination in a ratio of 1:24 in CD-1 mice (5/sex/group). Animals were observed immediately after dosing and for the remainder of the day, then clinical signs were monitored twice daily in the survivors for 14 days. All treated animals showed piloerection and pallor of the extremities. Other clinical signs at doses of 640 mg/kg and higher included abnormal body carriage & gait, lethargy, decreased respiratory rate, ptosis, tremors, and clonic convulsions. Survivors were killed on day 15 and a macroscopic exam was conducted. The number of deaths at each dose are shown below. Most deaths occurred within 24 hr.

Dose mg/kg	Deaths	
	Male	Female
320	0	0
640	3	3
800	3	2
1000	1	3
2500	5	5

The acute median lethal oral dose (LD_{50}) for the combination drug product was:

Males and Females combined	813 mg/kg
Males	848 mg/kg
Females	779 mg/kg

Acute Intravenous Toxicity to the Mouse of a Combination of Pseudo-Ephedrine and Cetirizine (RRLE91C2504/UCB388, vol. 1.4, p. 45)

This is a GLP and QAed study carried out to assess the toxicity following a single intravenous dose (100, 126 &160 mg/kg) of cetirizine:pseudo-ephedrine combination in a ratio of 1:24 in CD-1 mice (5/sex/group). Animals were observed immediately after dosing and for the remainder of the day then clinical signs were monitored twice daily in the survivors for 14 days. All treated animals showed piloerection, decreased respiratory rate, and pallor of the extremities. Other clinical signs included abnormal body carriage & gait (LD and some MD mice), ptosis (2M & 2F LD mice), gasping (all HD mice), clonic convulsions, and pale eyes (some LD and all MD and HD mice). Survivors were killed on day 15 and a macroscopic exam was conducted. The number of deaths at each dose are shown below. Most deaths occurred within 24 hr.

Dose mg/kg	Deaths	
	Male	Female
100	1	2
126	3	3
160	5	5

The acute median lethal dose (LD_{50}) for the combination drug product administered I.V. was:

Males and Females combined	114 mg/kg
Males	119 mg/kg
Females	109 mg/kg

Acute Toxicity Studies in Rats (LE88CO23, Vol. 1.4, p 68)

This is a non GLP, non QAed study carried out to obtain information regarding the toxicity of pseudo-ephedrine sulfate alone, in combination with cetirizine 2 HCl (10 or 20%) or cetirizine alone when administered as a single oral dose (by gavage) to 5 week old male & female OFA, SD, SPF rats (5/sex/group, body weight 113-114g). Most animals that died did so within 24 hr. The table below summarizes the deaths at the various doses for each treatment.

Pseudo-ephedrine sulfate mg/kg	Deaths		Pseudo-ephedrine+ cetirizine (10%) mg/kg	Deaths		Pseudo-ephedrine+ cetirizine (20%) mg/kg	Deaths		Cetirizine 2 HCl mg/kg	Deaths	
	M	F		M	F		M	F		M	F
312	0	0	284+28	0	0	260+52	0	0	104	0	0
625	0	0	568+57	0	0	521+104	0	0	208	0	0
1250	2	2	1136+113	1	2	1041+208	1	2	416	0	0
2500	4	2	2273+227	5	5	2083+416	5	4	833	1	1
5000	5	5	4546+454	5	5	4167+833	5	5	1666	4	2

Based on this the LD_{50} values (after 14 days) were:

Pseudo-Ephedrine Sulfate	1734 mg/kg
Pseudo+Cetirizine (10%)	1488 mg/kg
Pseudo+Cetirizine (20%)	1486 mg/kg
Cetirizine 2HCl	1475 mg/kg

This suggests that the toxicity of the two compounds on a mg/kg basis, administered either alone or in combination, is similar.

Acute Oral Toxicity to Rats of a Combination of Pseudo-Ephedrine and Cetirizine (LE90G112/UCB 950, Vol. 1.4, p. 92)

This is a GLP, QAed study carried out to assess the toxicity of a single oral dose of pseudo-ephedrine:cetirizine (120:5) in CD rats (5/sex/group). Rats were administered 640, 1000 & 1600 mg/kg of the combination. Animals were observed immediately after dosing and frequently thereafter for Day 1, and twice daily (days 2-14) thereafter. All animals were subjected to a post mortem macroscopic exam. All deaths occurred within 24 hr of dosing. Clinical signs were piloerection (all doses), salivation, body tremors, collapsed state and decreased respiratory rate (1600 mg/kg), ptosis & pallor of the extremities (1000mg/kg and higher), lethargy, ataxia (1000 mg/kg).

The LD_{50} values calculated from this study were:

Males + Females	1397 mg/kg
Males	1267 mg/kg
Females	1549 mg/kg

Acute Intravenous Toxicity to the Rat of a Combination of Pseudo-Ephedrine and Cetirizine (RRLE91C2503/UCB 387, Vol. 1.4, p. 114)

This is a GLP, QAed study carried out to assess the toxicity of a single I.V. dose of pseudo-ephedrine:cetirizine (120:5) in CD rats (5/sex/group). Rats were administered 100, 160 & 200 mg/kg of the combination. Animals were observed immediately after dosing and frequently thereafter for Day 1, and twice daily (days 2-14) thereafter. All animals underwent a post mortem macroscopic exam. All the deaths occurred within 24 hr of dosing. Clinical signs included piloerection and pallor of the extremities (all doses), abnormal body carriage and gait, increased locomotor activity and increased respiratory rate (all 100mg/kg animals and 1M 160 mg/kg), decreased respiratory rate and clonic convulsions (160 mg/kg and up), mydriasis (all 160 mg/kg females & all 200 mg/kg animals), and gasping (all 200mg/kg).

The LD_{50} values calculated from this study were:

Males + Females	158 mg/kg
Males	140 mg/kg
Females	175 mg/kg

Pseudo-Ephedrine HCl/Cetirizine 2 HCl Single Dose Study in Beagle Dogs (LE90H281/UCB 332, Vol. 1.4, p. 135)

This is a GLP, QAed study carried out to assess the toxicity of a single oral dose (5, 25 & 75 mg/kg) of pseudo-ephedrine:cetirizine (120:5) administered in a gelatin capsule to beagle dogs (1/sex/group). Animals were observed immediately after dosing and frequently during Day 1, and twice daily (days 2-7) thereafter. All animals were subjected to a post mortem macroscopic exam. Repeated convulsions, pupil dilation (HD), agitated behavior (all treated dogs), abnormal gait (LD female), exaggerated jerking movements (MD male and HD dogs) and decreased food consumption on day of dosing (MD animals) were the treatment-related effects. The high dose animals were sacrificed following repeated convulsions.

Plasma levels were measured at predosing and 0.5, 1, 2, 3, 4, 6, 9, 12, 24 and 32 hrs post dose. Measurable plasma levels of both pseudo-ephedrine and cetirizine were achieved following a single dose of the combination. The kinetic parameters are tabulated below.

Parameter	Pseudo-Ephedrine						Cetirizine					
	5		25		75		5		25		75	
	415M	416F	417M	418F	419M	420F	415M	416F	417M	418F	419M	420F
Cmax (ng/ml)												
Tmax (hr)												
$t_{1/2}$ (hr)												
AUC_{0-4hr} (ng.hr/ml)												

This study indicates that 75 mg/kg of the combination test article exceeds the MTD, since the two animals given 75 mg/kg pseudo-ephedrine:cetirizine were sacrificed 4hr after dosing following clonic convulsions. The pharmacokinetic analysis suggests that Cmax and AUC increased in a nonlinear fashion with the dose, but the sample size was only 1/sex/group.

Pseudo-Ephedrine HCl/Cetirizine 2 HCl Single Administration Study in Cynomolgus Monkeys (LE90J048/UCB 341, vol. 1.4, p. 219)

This is non-GLP, non QAed, single, oral dose escalation study using 2 cynomolgus monkeys (1M & 1F) administered doses of 5, 25, 75 & 150 mg/kg of the pseudo-ephedrine:cetirizine combination in a 24:1 ratio. Animals were followed for at least 7 days before the next dose was administered. No clinical signs were seen with the three lower doses. At the 150 mg/kg dose, both animals displayed a marked loss of appetite. The female also showed unsteadiness, trembling, piloerection, agitated behavior, and vocalization, while the male was abnormally quiet, crouched in a corner of the cage and alert only when made to move. The clinical signs persisted throughout the day of dosing.

Plasma levels were measured at 0.5, 1, 2, 4, 6, 9, 12, 24 & 32 hr, and pharmacokinetic parameters are summarized in the table below.

Parameter	Pseudo-Ephedrine								Cetirizine							
	5		25		75		150		5		25		75		150	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Cmax (ng/ml)																
T_{max}(h)																
t1/2 (h)																
AUC (ng.hr/ml)																

In monkeys 75 mg/kg was the NOAEL. Measurable levels of both compounds were detectable in plasma after a single dose. Plasma concentrations of both compounds increased with dose, although concentrations were higher in the female than the male. For pseudo-ephedrine, Cmax and AUC may have increased with dose in a somewhat greater than proportional manner and for cetirizine, Cmax and AUC increased proportional to dose, but the sample size was only 1/sex/group.

SUBCHRONIC TOXICOLOGY

Study Title: Pseudo-Ephedrine HCl/Cetirizine 2HCl Pilot Toxicity Study in Rats by Repeated Oral Administration for 2 Weeks

Study No: LE90H231/UCB336

Amendment #, Vol #, and Page #: Vol. 1.4, p. 292

This is a non-GLP, non QAed study conducted to assess toxicity and determine doses for the 4-week study. Five CD rats/sex/group were administered 50, 250 or 750 mg/kg/day (dosed twice daily) of cetirizine:pseudo-ephedrine in a combination of 1:24 for 14 days. At the highest dose, animals showed clinical signs of ptosis, hunched posture, lack of coordination and animals were sacrificed on day 4 due to the severity of these symptoms (1 died on day 4, one was sacrificed on day 3 and the rest on day 4). Occasional salivation was noted in the mid-dose group. Food intake was lower in all treated groups. Macroscopic exam showed that in the high dose animals, 4M and 2F had roughened epithelium of the forestomach and multiple crater like depressions were noted for 2F in the epithelium of the forestomach. Pale spleens were also seen in 2M and 4F. Absolute heart weights were significantly lower in 250 mg/kg males (1.14 g in control vs. 0.95 in mid dose males), but relative heart weights were not different.

Based on this study 750 mg/kg was greater than the MTD and 250 mg/kg was selected as the high dose for investigation in the 4-week study.

Study Title: Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride Toxicity to Rats by Repeated Oral Administration for 4 Weeks.
Study No: LE90L192/UCB337
Amendment #, Vol #, and Page #: Vol. 1.5, p. 378
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: March 13, 1990
GLP Compliance: Yes
QA- Report Yes
Methods: Rats were dosed twice daily by the oral route
Dosing:
Species/Strain: CD
#/Sex/Group or Time Point: 10/sex/group
Age: 33 days
Satellite Groups used for Toxicokinetics or Recovery: None.
Dosage Groups in Administered Units: 0, 10, 50 & 250 mg/kg
Route, Form, Volume, and Infusion Rate: Oral, solution in distilled water, 5ml/kg

Drug, Lot#, Radiolabel, and % Purity:
Pseudo-Ephedrine HCl: 900105, [redacted]
Cetirizine Dihydrochloride: 2005, [redacted]

Formulation/Vehicle: Solution in distilled water

Observations and Times:

Clinical Signs:	Daily
Body Weights:	Twice pretreatment, then weekly
Food Consumption:	Weekly
Ophthalmoscopy:	Pretreatment for all animals and then week 4 for control and high dose groups.
Hematology:	Week 4
Clinical Chemistry:	Week 4
Urinalysis:	Week 4
Organ Weights:	Terminal
Gross Pathology:	Terminal
Organs Weighed:	See addendum list
Histopathology:	Terminal, all groups
Toxicokinetics:	N/A

Results:

Clinical Signs: Signs included post-dosing salivation (high dose group, week 1), hypersensitive behavior (mid and high dose females, week 4), and alopecia (8/10 males and 6/10 females, high dose group).

Body Weights: Body weight gain was lower in treated animals at doses above 10 mg/kg.

Weight Gain (g)	0 mg/kg	10 mg/kg	50 mg/kg	250 mg/kg
M	131	150	123	88**
F	59	60	52	35**

** Indicates significantly ($p<0.01$) different from control.

Food Consumption: Lower in high dose group (control males: 166 g/rat, HD males: 127* g/rat, control F: 119 g/rat, HD females: 99* g/rat)

Ophthalmoscopy: No changes

Hematology: No changes

Clinical Chemistry: The changes in various parameters are documented below.

Dose (mg/kg)	Albumin (g/dL)		BUN (mg/dL)		Creatinine (mg/dL)		GPT (mU/ml)		GOT (mU/ml)		Ca (mEq/L)		Cl (mEq/L)		Na (mEq/L)	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0	2.9	2.9	14	16	.49	.52	32	24	64	60	5.2	5.2	103	102	143	142
10	2.8	3.0	12	19	.46	.50	28	28	57	67	5.2	5.3	102	99	142	139
50	2.8	3.0	14	18	.45	.48	33	28	61	63	5.3	5.4	100	100	140	140
250	2.7	2.9	18	21	.44	.46	50	33	79	78	5.4	5.5	101	99	140	140

Shaded cells indicate significantly ($p<0.05$) different from control.

However, none of these values are of toxicological significance since they are within the normal range (electrolytes) or the changes are not large enough to be toxicologically relevant.

Urinalysis: No significant changes were seen.

Organ Weights: There was a decrease in spleen weights in treated females (C: 0.51 g, LD: 0.48 g, MD: 0.43 g, HD: 0.40 g). This was not considered to be significant since the alterations were small (20% or less) and no accompanying histopathologic changes were seen; in addition, this decrease may be due to lower body weights of the animals (relative weights were not provided). However, the decreased spleen weights may be related to the pale spleens seen in the 750-mg/kg animals in the 2-week study.

Gross Pathology: No significant changes were observed.

Histopathology: No significant changes were observed.

Key Study Findings: The rats tolerated all the administered doses of pseudo-ephedrine/cetirizine combination for 4 weeks. Most of the findings were in the high dose group. These included post-dosing salivation, hypersensitive behavior, lower body weight gain, decreased food consumption, and alopecia. Observations at the MD were limited to some hypersensitive behavior and minimal decrease in body weight gain; therefore, 50 mg/kg was selected as the NOAEL.

Study Title: Pseudo-Ephedrine Hydrochloride/Cetirizine Dihydrochloride Preliminary Toxicity and Pharmacokinetic Study in Rats by [redacted] or 4 Weeks.
Study No: LE91B0701/UCB364
Amendment #, Vol #, and Page #: Vol. 1.5, p. 571
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: 22 Aug. 1990
GLP Compliance: Yes
QA- Report: Yes

Dosing:
Species/Strain: CD rats

#/Sex/Group or Time Point: Main: 4/sex/group
TK: 16/sex/group
Age: 28 days old
Satellite groups used for: TK
Dosage Groups in Administered Units: 0, 10, 50 & 250 mg/kg
Route, Form, Volume, and Infusion Rate: dietary, powder admixed with diet

Drug, Lot #, and % Purity: Pseudo-Ephedrine HCl: 900105,
Cetirizine 2HCl: 2005,
Formulation/Vehicle: Admixed into diet

Observations and Times:
Clinical Signs: Daily
Body Weights: Twice pretreatment and then weekly
Food Consumption: Weekly
Pharmacokinetics: Determined during week 4
4/timepoint/group
Sampled at: 0, 2, 4, 6, 8, 10, 12, 15, 18, 20, 22, 24 hr

Results:
Clinical Signs: None
Body Weights: Body weight gain was lower in mid and high dose animals.

Wt. Gain (g)	0 mg/kg	10 mg/kg	50 mg/kg	250 mg/kg
Males	164	167	144	91*
Females	69	79	63	37*

*indicates significantly ($p<0.05$) different from control.

Food Consumption: Food consumption was lower in the mid and high dose animals. No statistical analysis was performed.

Food Intake – week1-4 (g/rat)	0 mg/kg	10 mg/kg	50 mg/kg	250 mg/kg
Males	747	739	688	554
Females	520	543	476	486

Achieved Intakes of Test Article: The achieved intakes are tabulated below and matched the intended doses.

Dose (mg/kg)	Achieved Intake	
	M	F
10	10.2	10.1
50	50	49.6
250	234	240

Organ Weights: Slight changes were noted in the weights of adrenals (63 mg in controls vs. 39.4* mg in high dose), spleen (0.6 g in controls vs. 0.46* g in high dose) and heart (0.89 g vs. 0.8* g, 0.78* g and 0.72* g at 10, 50 and 250 mg/kg doses) of females. In

males, thyroid weights were altered from a control value of 47.5 mg to 33.9 mg, 16.9* mg and 26.1* mg at the ~~10~~, 50 and 250 mg/kg doses. Except for the change in thyroid weights, the decrease in absolute organ weights parallels the lower body weights and may not be toxicologically relevant.

Gross Pathology: No changes were seen.

Histopathology: No changes were seen.

Pharmacokinetics: Achieved dietary intakes of Pseudo-Ephedrine:Cetirizine are documented above. The AUC for pseudo-ephedrine increased in a greater than proportional manner. This may be due to saturation of elimination. At comparable doses, AUC tended to be ~ 30% higher in females. Plasma concentrations of cetirizine were measurable only in the high dose animals, and the ratio of cetirizine to pseudo-ephedrine was similar in males and females. The table below shows the AUCs achieved after administration of the test article.

Dose (mg/kg)	AUC $_{0\text{-}24}$ (ng.hr/ml), n=4/sex/timepoint			
	Males		Females	
	Pseudo-Ephedrine	Cetirizine	Pseudo-Ephedrine	Cetirizine
10	-	-	685	-
50	4135	-	7632	-
250	44277	559	59144	663

Key Study Findings: Expected levels of drug intake were achieved by admixture into the diet. Body weight gain was significantly lower at the highest dose. Thyroid weights were lower in males at the two higher doses. Based on the decreased body weight gain, the NOAEL in this study was determined to be 50 mg/kg. The levels of pseudo-ephedrine increased in a greater than proportional manner with dose and at the same dose, exposure was greater in females than males. Cetirizine was measurable in plasma only following the highest dose, and exposure appeared to be similar at this dose between males and females.

CHRONIC TOXICOLOGY

Study Title: Pseudo-ephedrine/Cetirizine Toxicity to Rats by Repeated Oral ~~Administ~~istration for 26 weeks Followed by a 6 Week Recovery Period.

Study No: RRLE93A2508/UCB414
Amendment #, Vol #, and Page #: Vol. 1.5, p 757

Conducting Laboratory and Location: [redacted]
Date of Study Initiation: 16 December, 1991
GLP Compliance: Yes
QA- Report: Yes

Dosing:

Species/Strain:	CD rats
#/Sex/Group or Time Point:	20/sex/group – Toxicology 5/sex/group – Recovery (control and high dose only) 16/sex/group - Toxicokinetics
Age:	28 days
Satellite Groups used for Toxicokinetics or Recovery:	Toxicokinetics
Dosage Groups in Administered Units:	0, 30, 60, 120 or 240 mg/kg/day, administered twice daily 5 hr apart by oral gavage.
Route, Form, Volume, and Infusion Rate:	Oral, solution, 5 ml/kg

Drug, Lot #, Radiolabel, and % Purity: Pseudo-Ephedrine Hydrochloride: 1MG 36, 99.6%
Cetirizine Dihydrochloride: 2058,

Formulation/Vehicle: Solution in water

Observations and Times:

Clinical Signs:	Daily
Body Weights:	Start and death days, and weekly in the interim.
Food Consumption:	Weekly
Ophthalmoscopy:	Pretreatment, weeks 13, 26 and R6
Hematology:	Weeks 13, 26 & R6
Clinical Chemistry:	Weeks 13, 26 & R6
Urinalysis:	Weeks 13, & 26
Organ Weights:	Terminal
Gross Pathology:	Terminal
Organs Weighed:	See addendum list
Histopathology:	Terminal, in control and HD only
Toxicokinetics:	4/sex/group @ weeks 1, 4, 12, and 18 at 5 hr after 1st subdose, and 4/sex/timepoint @ 0.5, 1, 1.5, 3, 5, 5.5, 6.5, 8, 10, 12 & 24 hr on day 6 of week 26.

Results:

Mortality: One control animal died week 13 following routine blood sampling.

Clinical Signs: Dose-related post dosing salivation and hyperreactivity were noted in the three higher dose groups, and isolated incidences were also seen in the lowest dose group. Paddling of forelimbs was noted for treated animals at the 120 and 250 mg/kg doses and for the 60-mg/kg dose females. These signs were seen throughout the study, but not during recovery.

Marked hair loss was seen in 240 mg/kg animals (especially females). Wetness and/or urogenital fur staining was seen in all treated females. At the end of recovery, there was a reduction in the degree of hair loss, and no fur staining was seen.

Body Weights: There was decreased body weight gain in all treated animals, with partial recovery of body weight during the recovery period.

Gain (g)	0 mg/kg		30 mg/kg		60 mg/kg		120 mg/kg		240 mg/kg	
	M	F	M	F	M	F	M	F	M	F
Weeks 0-26	412	155	364	141	356	126	312	107	290	102
Weeks R0-R6	36	18							79	33

Shaded cells indicate significantly ($p<0.05$) different from control.

Food Consumption: Food intake was significantly decreased at all time points at the three higher doses (90-85% of control) except in the 240 mg/kg females, but especially during week 1 (94-74% of control). This appeared to be reversible, since during recovery, food consumption was increased in the high dose group compared to controls. The decrease in body weight gain may be at least partially accounted for by the decreased food intake.

Ophthalmoscopy: No changes seen.

Hematology: Slight, but statistically significant changes in hemoglobin (high dose males), RBC counts (high dose females), neutrophils (high dose females) as well as platelets (high dose males) were seen at 13 weeks. At 26 weeks, besides the parameters tabulated below, statistically significant increases were also seen in packed cell volumes, neutrophils, and eosinophils, and TT in HD females, while platelets were increased in HD males.

Dose (mg/kg)	Hb (g/dL)		RBC ($X10^6/mm^3$)		MCHC (%)	
	M	F	M	F	M	F
0	15	14.9	7.2	6.6	28.9	29.9
30	14.8	14.8	7.0	6.5	29.2	30.0
60	14.7	14.9	7.1	6.5	28.8	30.0
120	15.5	14.7	7.3	6.6	29.3*	29.4
240	15.8*	15.5*	7.4	7.0*	29.6*	29.9

*Indicates significantly different ($p<0.05$) from control.

All these changes were within the normal range for these parameters and were not considered toxicologically significant.

Clinical Chemistry: Minor changes were noted which are documented below.

At 13 weeks, glucose was decreased in rats at the two higher doses (~12%) and also in females at 60 mg/kg dose (~12%), while at 26 weeks, glucose was decreased in all treated males, but not females, and at recovery was not different from controls. At 13 weeks, GPT & GOT were significantly higher for high dose females (GPT: ~65%, GOT: ~19%), but no differences were seen at 26 weeks or at either time point in treated males; therefore, the changes seen in females at 13 weeks may not be of toxicological significance. Cholesterol was significantly decreased at 26 weeks in high dose females (99 vs. 70 mg/dL).

Na was slightly decreased in some treated groups at weeks 13, 26, & R6. K (high dose males and females), P (high dose males), and Ca (males from the three higher dose groups) were increased and Cl was decreased (females from two higher dose groups) at 13 weeks. There was an increase in K in some groups (high dose females, males treated with the three higher

doses) at 26 weeks. However, the values for all electrolytes were within the normal range, showed no dose dependence and are not considered to be toxicologically significant.

Minor increases in alkaline phosphatase were seen in both sexes at 13 weeks at the two higher doses and at the two higher doses in males and all treated females at 26 weeks. Males showed a decrease in albumin at the 3 higher doses while females showed lower levels only at the highest dose. The values for albumin and alkaline phosphatase were within the normal range and are therefore not considered to be toxicologically significant.

Urinalysis: No notable changes.

Organ Weights: There were treatment-related increases in liver, kidney, & brain weight, but these changes showed no dose relationship in females. The table below shows 'adjusted' (for body weight, adjusted values not provided for F brain weight) values at 26 weeks. Recovery group values were not different between treated and control groups.

Dose (mg/kg)	Body Wt. (g)		Brain (g)		Liver (g)		Kidneys (g)	
	M	F	M	F unadjusted	M	F	M	F
0	580	288	2.11	1.92	20.5	10.4	3.37	1.97
30	530	273	2.16	1.98*	22.8	10.0	3.65*	2.04
60	522	261	2.17	1.97*	20.9	10.4	3.69*	2.09
120	477	241	2.21*	1.98*	21.7	10.9	3.72*	2.27*
240	453	239	2.21*	1.99*	24.7*	11.8*	3.92*	2.27*

* Indicates significantly different from control.

Ovary weights increased from 57.6 in control to 73.3 in high dose females, but this was mostly due to one animal while the rest were within the normal range. Unadjusted thyroid weights were lower (R6 males and 120 & 240 mg/kg females), but this was probably an effect of decreased body weight rather than treatment.

Gross Pathology: Rats showed treatment related changes in incidence of fur staining, hair loss and uterine distention. These are tabulated below.

Dose (mg/kg)	Stained Fur		Hair Loss		Uterine Fluid Distention
	M	F	M	F	F
0	1	1	1	3	1
30	3	5	4	0	1
60	1	4	0	3	1
120	3	16	2	2	4
240	1	14	14	20	7

Histopathology: Treatment related changes (documented below) were seen in the liver, spleen, and uterus. The hepatocyte enlargement, splenic hemosiderosis and uterine

dilation appear to be treatment related, suggesting that these organs are the target organs for toxicity.

Dose (mg/kg)	0		30		60		120		240	
Organ	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Liver										
Hepatocyte Enlargement	0	0	0	0	0	0	1	0	7	1
Spleen										
Hemosiderosis	11	10	6	8	8	8	11	12	17	16
Uterus										
Luminal Dilation	-	5	-	4	-	2	-	7	-	9

Key Study Findings:

The clinical signs of salivation, forelimb paddling, & hyperreactivity are undesirable pharmacological effects of pseudo-ephedrine along with inappetance, which may account for the reduced body weight gain. No NOAEL was determined for this study based on the decreased body weight gain. Toxicity was seen in this study as hepatocyte enlargement & hemosiderosis in the spleen, primarily in the 240-mg/kg animals. The hepatocyte enlargement may account for the increased relative liver weight and minor increases in alkaline phosphatase and decreases in albumin. The splenic hemosiderosis may be due to the slightly increased Hb (high dose animals), RBC counts and packed cell volume (high dose females), but the background incidence of hemosiderosis was also fairly high.

All treatment-related effects reversed in the high dose recovery group except for the slightly increased alkaline phosphatase and red cell parameters and decreased albumin. The decrease in body weight gain rebounded partially during recovery. Unlike the liver, the increased kidney and brain weights may not be toxicologically important since no histopathology was associated with them.

Study Title: Pseudo-Ephedrine Hydrochloride / Cetirizine Dihydrochloride Toxicity in Cynomolgus Monkeys By Repeated Oral Administration for 13 Weeks with a 4-Week Recovery Period for Selected Animals
Study No: RRLE91B2501/UCB 347
Amendment #, Vol #, and Page #: 000, Vol. 1.8, p. 1770
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: 11, July, 1990
GLP Compliance: Yes
QA- Report: Yes

Dosing:
Species/Strain: Cynomolgus Monkeys
#/Sex/Group or Time Point: 4 (3 main study, 1 recovery)/sex/group for control and high dose groups
3/sex/group for low and mid dose groups

Age: 2-4 years
Weight: 2-4 kg
Satellite Groups used for Toxicokinetics or Recovery: Recovery (1/sex/group) for control and high dose.
Dosage Groups in Administered Units: 0, 10, 20 & 40 mg/kg in two equal doses administered 5 hr apart.
Route, Form, Volume, and Infusion Rate: Oral gavage, Solution, 5ml/kg.

Drug, Lot#, Radiolabel, and % Purity: Pseudo-Ephedrine Hydrochloride: 900105
Cetirizine Dihydrochloride: 2005,
Formulation/Vehicle: Solution in Distilled Water

Observations and Times:
Clinical Signs: Daily
Body Weights: Weekly from week –4 to 2 and the biweekly from weeks 2-13 and during recovery.
Food Consumption: Daily
Ophthalmoscopy: Once pretreatment, week 13 and week R4
EKG: Day 1, Week 13, Week R4 (before 1st subdose, 2 hr after 1st subdose and 2 hr after 2nd subdose).
Hematology: Pretreatment, Weeks 6, 13 and R4
Clinical Chemistry: Pretreatment, Weeks 6, 13 and R4
Urinalysis: Pretreatment, Weeks 6, 13 and R4
Organ Weights: Terminal
Gross Pathology: Terminal
Organs Weighed: See addendum list (page 29)
Histopathology: Terminal, all groups
Toxicokinetics: On day 6 of week 13, samples were taken predosing, 1, 2, 3, 5, 6, 7, 10, 12, and 24 hr after the 1st subdose.

Results:

Clinical Signs: Various clinical signs were seen in all animals as tabulated below, however the incidence of most clinical signs, including abnormal behavior (not shown below) was higher in treated animals.

Clinical Sign	Control	10 mg/kg	20 mg/kg	40 mg/kg
Repetitive Behavior	2/8	6/6	6/6	8/8
Unsteadiness/Limb Tremors	0/8	2/6	4/6	7/8
Lethargy	1/8	3/6	4/6	4/8
Pilo-Erection	8/8	6/6	6/6	8/8
Salivation	0/8	1/6	5/6	3/8
Huddled Posture	5/8	6/6	6/6	8/8

Body Weights & Food Consumption: At the end of the treatment period (13 weeks), treated animals had an overall weight loss and reduced food intake. This reduced food intake was transient in most animals, i.e. more marked in the first 3-5 weeks and the animals showed a partial recovery during the remainder of the treatment, but the inappetance persisted for most

females (esp. mid and high dose) during the entire treatment period. One mid-dose female had marked weight loss and so was not dosed during week 7; treatment was resumed for week 8 following partial recovery. The data for the incidence of weight loss and the weight change are tabulated below.

Dose (mg/kg)	Males		Females	
	Incidence	Weight change (g)	Incidence	Weight change (g)
0	0/4	293	0/4	98
10	2/3	3	2/3	-47
20	1/3	33	3/3	-431
40	3/4	-8	3/4	-77

Ophthalmoscopy: No treatment related changes were seen.

Electrocardiography: The sponsor states that no treatment related changes were seen in EKG parameters (data not provided). Heart rates (only control and high dose data provided) were significantly higher at 13 weeks; however, the individual heart rates do not appear to be different from the pretreatment heart rates, so this finding is of questionable toxicological significance.

Heart Rate (bpm)	Predosing		2 hr After 2nd Sub-Dose	
	Week 1	Week 13	Week 1	Week 13
Control	246	214	240	229
High Dose	243	246*	233	257*

* indicates significantly different ($p<0.05$) from control.

Hematology: No changes were seen.

Clinical Chemistry: During weeks 6 and 13, statistically significant changes were seen in various parameters including γGT, Na, K, P & GOT, but these were within the normal range for these parameters and so are of questionable toxicological significance.

Urinalysis: No notable changes were seen.

Bone Marrow Exam: Exams were carried out on all animals and were found to be normal in cellularity, distribution, and morphology.

Organ Weights: The majority of organs were unremarkable with the exception of the spleen & thymus. Mean spleen weights were lower for all treated groups and significantly lower at the high dose. However, individual spleen weights were within normal limits as determined by comparison to the control animals (no historic control data provided).

Dose (mg/kg)	Low Thymus Weight	Thymic Involution	Thymus Weight (g)	Spleen Weight (g)
0	0	0	4.6	9.9
10	3F	2F	3.5	7.4
20	3F, 1M	1F, 1M	3.2	7.1
40	2F, 1M	1F, 2M	2.7	6.1*

*Indicates significantly ($p<0.05$) different from control.

For thymus weights, both males with low weights were outside the normal weight range for animals of that size compared to controls. In addition, one high dose male with normal weight showed thymic involution. These data suggest that the spleen and thymus may be the target organs for toxicity.

Gross Pathology: Minor abnormalities were seen in all animals including controls; no treatment-related changes were seen.

Histopathology: Thymic involution was the only treatment related change seen, as documented above.

Toxicokinetics: The $AUC_{0\text{-}24hr}$ and Cmax (after 1st subdose on the penultimate dosing day) are tabulated below.

Dose (mg/kg)	Pseudo-Ephedrine						Cetirizine					
	Males		Females		Combined		Males		Females		Combined	
	$AUC_{0\text{-}24}$	C_{max}	$AUC_{0\text{-}24}$	C_{max}	$AUC_{0\text{-}24}$	C_{max}	$AUC_{0\text{-}24}$	C_{max}	$AUC_{0\text{-}24}$	C_{max}	$AUC_{0\text{-}24}$	C_{max}
10												
20												
40												

For both pseudo-ephedrine and cetirizine, AUC and C_{max} increased with dose with little evidence of non-linearity. The half-life for pseudo-ephedrine was between 2-5 hrs, and for cetirizine was between 2-4 hr.

Key Study Findings:

This study was conducted to determine the toxicity of the 24:1 combination of pseudo-ephedrine:cetirizine administered by oral gavage at doses of 10, 20 and 40 mg/kg to cynomolgus monkeys for 13 weeks. Animals tolerated the drug combination well. Toxicity was seen mainly in the form of dose-dependent manifestations of clinical signs (repetitive behavior, unsteadiness/limb tremors, lethargy and salivation), body weight loss and inappetance; these changes were reversible upon discontinuation of treatment. Animals showed reduced spleen (38% at the high dose) and thymus weights (41% at high dose) and thymic involution. Based on the decreased body weight gain and thymic changes, the NOAEL for this study was not determined and appears to be below 10 mg/kg. The kinetics were almost linear and showed dose-dependence.

Study Title: Pseudo-Ephedrine/Cetirizine Toxicity to Cynomolgus Monkeys by Repeated Oral Administration for 29-Weeks with a 6-Week Recovery Period for Selected Animals.

Study No: RRLE93E0501/UCB415

Amendment #, Vol #, and Page #: 000, Vol. 1.9, p. 2085

Conducting Laboratory and Location: [redacted]

Date of Study Initiation: 12 February 1992

GLP Compliance: Yes

QA- Report: Yes (√) No ()

Dosing:

Species/Strain: Cynomolgus Monkeys

#/Sex/Group or Time Point: 5 (4 main, 1 recovery)/sex/group for control and high dose, 4/sex/group for low and mid dose animals

Age: 2-4 years

Weight: 2-4.3 kg

Satellite Groups used for Toxicokinetics or Recovery: Recovery (1/sex/group for control and high dose groups)

Dosage Groups in Administered Units: 0, 10, 20 & 40 mg/kg (dose increased slowly over 4 weeks) and administered as two subdoses 5 hr apart.

Route, Form, Volume, and Infusion Rate: Oral gavage, solution, 5 ml/kg

Drug, Lot #, Radiolabel, & %Purity: Pseudo-Ephedrine: 1 MG 36, [redacted]
Cetirizine: 2058,

Formulation/Vehicle: Solution in distilled water

Observations and Times:

Clinical Signs: Daily

Body Weights: Weekly

Food Consumption: Daily

Ophthalmoscopy: Pretreatment, Weeks 16 & 29

EKG: Pretreatment, Weeks 16 & 29 @ 2 hr prior dosing and 2 hr after 2nd subdose

Hematology: Pretreatment, Weeks 16, 29 & R6

Clinical Chemistry: Pretreatment, Weeks 16, 29 & R6

Urinalysis: Pretreatment, Weeks 16, 29 & R6

Organ Weights: Terminal

Gross Pathology: Terminal

Organs Weighed: Terminal, see addendum list

Histopathology: Terminal, all groups

Toxicokinetics: During the increasing dose phase, sampled on the last day of each week immediately prior to dosing and then 1 hr. after 2nd subdose. On the first day of week 4 and once during weeks 7, 17 and 23, sampled immediately prior to 2nd dosing and 1 hr after administration of 2nd subdose. On the last day of week 29, samples drawn prior to dosing and then at 1, 2, 3, 5, 6, 7, 10, 12 & 24 hr. in relation to 1st subdose.

Results:

Clinical Signs: The % incidence of clinical signs was greater in treated animals and was generally dose related.

Dose (mg/kg)	0	10	20	40
Number of animals on study	10	8	8	10
Constant movement/Overreaction	0.0	4.1	9.4	22.5
Agitation/Aggression	0.2	2.7	14.0	22.2
Nervousness	0.1	31.4	50.3	67.2
Quietness	7.8	37.0	62.1	57.8
Huddled/Unusual posture	0.3	10.0	32.1	36.7
Pilo-erection	1.4	36.1	63.1	77.2
Reluctance to move	0.0	0.9	7.7	7.0
Constricted pupils	0.0	27.8	20.8	51.1

Most clinical signs were not seen in the two high dose animals during recovery except for nervousness (452F) and quietness (451M) in 1 animal each and piloerection in both. One mid dose animal (441M) showed reduced body temperature during weeks 9 & 10 accompanied by huddled posture, inactivity, and low food consumption; this animal was offered extra dietary supplements and placed under a heat lamp. By day 1 of week 13 the animal had improved and was returned to its cage and remained there for the study duration.

Body Weights: The weight gain of males in the mid and high dose groups was slightly lower while the remainder of the animals were unaffected. However, during recovery, the high dose animals actually gained weight faster than the controls (males: 336 g in controls vs. 972* g in high dose; females: 76 g in controls vs. 464* g in high dose).

Dose (mg/kg)	Body Wt. Gain (g)		Food Consumption (g/week)			
	Male	Female	Male		Female	
	Week 0 to 29		Wk -4 to -1	Wk 1 to 29	Wk -4 to -1	Wk 1 to 29
0	615	398	854	849	815	799
10	441	258	859	826	817	757
20	205	215	904	721	804	766
40	48*	289	870	742*	771	767

* Indicates significantly ($p<0.05$) different from control.

Food Consumption: There was reduced appetite noted among the mid and high dose males and food consumption remained below controls for the duration of the study. One mid dose animal (441M) showed considerable weight loss associated with inappetance and was offered extra supplements. One high dose animal (451M) also showed weight loss although body weight was stable from week 24 onwards. During recovery, the high dose animals gained weight faster than the controls.

Ophthalmoscopy: Eye exams were essentially normal except for incomplete pupil dilation (Clinical Signs table) in treated animals.

Electrocardiography: Predose EKGs done on all animals revealed no abnormalities. EKGs were done only on control and high dose animals at weeks 16 and 29. The sponsor states that the combined (M+F) HR values were higher for the 40-mg/kg group at 16 weeks and 29 weeks. However, although these changes may have had statistical significance, they do not appear to be toxicologically important as the changes were slight (< 5%).

Hematology: No toxicologically significant changes were seen. PT in 40 mg/kg males and males + females was significantly ($p<0.05$) lower, but since the decrease was within the normal range it is not toxicologically significant. Mean corpuscular volume was also decreased (70* vs. 74 fl) at 16 weeks for 40 mg/kg males, but while statistically significant, was of doubtful toxicological significance since this is also within the normal range.

Clinical Chemistry: Most of the changes were minor and seen only in the high dose animals. High dose males showed statistically significant changes in albumin (16 weeks: ↓ from 4.5 to 4.0* g/dL) and GPT (16 weeks: ↑ from 15 to 19* mU/ml). High dose females showed a statistically significant increase in creatinine from 0.7 to 0.8 mg/dL (week 16). When the clinical chemistry data from these animals were combined (M+F), the animals showed a significant decrease in plasma albumin at all doses at 16 weeks (control: 4.5, low dose: 4.1*, mid dose: 4.3* & high dose: 4.1* g/dL) and at the highest dose at 29 weeks (4.5 vs. 4.1* g/dL). At 29 weeks, plasma GPT was decreased from 25 to 22*mU/ml in the high dose group. These altered parameters were either within the normal range, very small or unaccompanied by any histopathological changes and therefore of questionable significance.

Urinalysis: There were no noteworthy changes.

Organ Weights: Adjusted pancreas weights were decreased in all treated groups (M+F values for control: 5.9 g, low dose: 4.8* g, mid dose: 5.2* g and high dose: 5.2* g), but were unaccompanied by any histopathological changes. Adjusted heart weights were also lower in treated females (control: 10.6 g, low dose: 9.3* g, mid dose: 9.2* g and high dose: 9.4* g), but not males. All other organs were unremarkable.

Gross Pathology: No notable abnormalities were seen.

Histopathology: Minor abnormalities were seen in various tissues but the incidence did not differ between controls and treated animals.

Toxicokinetics: Measurable plasma levels of both compounds were present in the plasma at 29 weeks. The following values were obtained during week 29 and show that Cmax and AUC increased with increasing dose, in a greater than proportional manner. For both compounds exposure (Cmax 1 hr after 2nd subdose) at 29 weeks was approximately 2X greater than at week 4, which may be due to a time-dependent decrease in elimination according to the sponsor. Following Cmax, the plasma concentrations declined apparently monoexponentially with a $t_{1/2}$ of 2-4 hr (pseudo-ephedrine) and 2-3 hr (cetirizine). The data do not indicate a statistically significant difference in exposure between males and females.

Dose (mg/kg)	Pseudo-Ephedrine				Cetirizine			
	Males		Females		Males		Females	
	Cmax (ng/ml)	Tmax (h)	Cmax (ng/ml)	Tmax (h)	Cmax (ng/ml)	Tmax (h)	Cmax (ng/ml)	Tmax (h)
10								
1st subdose								
2nd subdose								
AUC (ng.hr/ml)								
20								
1st subdose								
2nd subdose								
AUC (ng.hr/ml)								
40								
1st subdose								
2nd subdose								
AUC (ng.hr/ml)								

Key Study Findings:

In this 29-week cynomolgus monkey study no target organ for toxicity was identified. The animals tolerated all administered doses of the combination product. The main adverse effects were monitorable clinical signs of toxicity such as altered behavior (agitation, lethargy etc), and inappetance (considered a pharmacological effect of pseudo-ephedrine) leading to a decrease in bodyweight. These reversed partially during recovery. Based on the decrease in body weight gain, the NOAEL appears to be 10 mg/kg. The kinetics showed dose-dependent increases in exposure to both compounds, which were slightly greater than predicted by linear relationship. The data also suggest a greater exposure over time, which may be due to a time-dependent decrease in elimination or altered absorption.

Overall Toxicology Summary:

In acute, single dose toxicity studies, the LD_{50}s for pseudo-ephedrine:cetirirzine (24:1) combination are as follows.

Species/Route	Dose (mg/kg)
Mouse-Oral	
M+F	813
Mouse-IV	
M+F	114
Rat-Oral	
M+F	1397
Rats-IV	
M+F	158

An acute, oral study in dogs given 5, 25 and 75 mg/kg of the pseudo-ephedrine:cetirizine combination indicates that 75 mg/kg is greater than the MTD since the two animals receiving that dose were sacrificed 4-hr post-administration, following chronic convulsions. Cmax and AUC increased in a greater than dose proportional manner. In cynomolgus monkeys administered 5, 25, 75 and 150 mg/kg PO, 75 mg/kg was the NOAEL based on marked appetite suppression and clinical signs. PK data suggests that the Cmax and AUC increased with dose in a greater than proportional manner.

Rats tolerated all the administered doses (10, 50 & 250 mg/kg) of pseudo-ephedrine/cetirizine combination for 4 weeks. Most of the findings were in the high dose group. These included post-dosing salivation, hypersensitive behavior, lower body weight gain, decreased food consumption, and alopecia. Although there was a slight decrease (~6%) in body weight gain at the MD, the effect was minimal and not statistically significant; therefore, 50 mg/kg was selected as the NOAEL.

In the 4-week rat study where the pseudo-ephedrine:cetirizine drug combination was administered via admixture with diet, expected levels of drug intake (10, 50 and 250 mg/kg) were achieved by admixture into the diet. Body weight gain was significantly lower at the highest dose. Thyroid weights were lower in males at the two higher doses. Based on the decreased body weight gain, the NOAEL in this study was determined to be 50 mg/kg. The levels of pseudo-ephedrine increased in a greater than proportional manner with dose and at the same dose, exposure was greater in females than males. Cetirizine was measurable in plasma only following the highest dose, and exposure appeared to be similar at this dose between males and females.

In the 26-week study with a 6-week recovery, rats were dosed at 30, 60, 120 and 240 mg/kg. For treated rats, clinical signs of salivation, forelimb paddling, & hyperreactivity are undesirable pharmacological effects of pseudo-ephedrine along with inappetance, which may account for the reduced body weight gain. No NOAEL was determined for this study based on the decreased body weight gain. Toxicity was seen in this study as hepatocyte enlargement & hemosiderosis in the spleen, primarily in the 240-mg/kg animals. The hepatocyte enlargement may account for the increased relative liver weight and minor increases in alkaline phosphatase and decreases in albumin. The splenic hemosiderosis may be due to the slightly

increased Hb (high dose animals), RBC counts and packed cell volume (high dose females), but the background incidence of hemosiderosis was also fairly high.

All treatment-related effects reversed in the high dose recovery group except for the slightly increased alkaline phosphatase and red cell parameters and decreased albumin. The decrease in body weight gain rebounded partially during recovery. Unlike the liver, the increased kidney and brain weights may not be toxicologically important since no histopathology was associated with them.

A study was conducted to determine the toxicity of the 24:1 combination of pseudo-ephedrine:cetirizine at doses of 10, 20 and 40 mg/kg, administered by oral gavage to cynomolgus monkeys for 13 weeks. Animals tolerated the drug combination well. Toxicity was seen mainly in the form of dose-dependent manifestations of clinical signs (repetitive behavior, unsteadiness/limb tremors, lethargy and salivation), body weight loss and inappetance; these changes were reversible upon discontinuation of treatment. Animals showed reduced spleen (38% at the high dose) and thymus weights (41% at high dose) and thymic involution. Based on the decreased body weight gain and thymic changes, the NOAEL for this study was not determined and appears to be below 10 mg/kg. The kinetics were almost linear and showed dose-dependence.

In a 29-week cynomolgus monkey study no target organ for toxicity was identified. The animals tolerated all administered doses of the combination product. The main adverse effects were monitorable clinical signs of toxicity such as altered behavior (agitation, lethargy etc), and inappetance (considered a pharmacological effect of pseudo-ephedrine) leading to a decrease in bodyweight. These reversed partially during recovery. Based on the decrease in body weight gain, the NOAEL was 10 mg/kg. The kinetics showed dose-dependent increases in exposure to both compounds, which were slightly greater than predicted by linear relationship. The data also suggest a greater exposure over time, which may be due to a time-dependent decrease in elimination or altered absorption.

Addendum List:

Addendum 1

Histopathology Inventory for NDA # 21-150

Study	4-week gavage	26-week	13-week	29-week
Species	Rat	Rat	Cynomolgus Monkeys	Cynomolgus Monkeys
Adrenals	X	X	X	X
Aorta			X	X
Bone Marrow smear				
Bone (femur)				
Brain	X	X	X	X
Cecum	X	X	X	X
Cervix				
Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis	X	X	X	X
Esophagus	X	X	X	X
Eye	X	X	X	X
Fallopian tube				
Gall bladder			X	X
Gross lesions	X	X	X	X
Harderian gland				
Heart	X	X	X	X
Hyphophysis				
Ileum	X	X	X	X
Injection site				
Jejunum	X	X	X	X
Kidneys	X	X	X	X
Lachrymal gland				
Larynx	X	X	X	X
Liver	X	X	X	X
Lungs	X	X	X	X
Lymph nodes, cervical	X	X	X	X
Lymph nodes mandibular				
Lymph nodes, mesenteric	X	X	X	X
Mammary Gland	X	X	X	X
Nasal cavity				
Optic nerves				
Ovaries	X	X	X	X
Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve				

Pharynx				
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum	X	X	X	X
Salivary gland	X	X	X	X
Sciatic nerve			X	X
Seminal vesicles			X	X
Skeletal muscle			X	X
Skin			X	X
Spinal cord	X	X	X	X
Spleen	X	X	X	X
Sternum	X	X	X	X
Stomach	X	X	X	X
Testes	X	X	X	X
Thymus	X	X		X
Thyroid	X	X	X	X
Tongue			X	X
Trachea	X	X	X	X
Urinary bladder	X	X	X	X
Uterus	X	X	X	X
Vagina			X	X
Zymbal gland				

Shaded cells indicate organ weight obtained

REPRODUCTIVE TOXICOLOGY

Study title:	A Study of the Effect of Pseudo-ephedrine Hydrochloride/Cetirizine Dihydrochloride (24:1) on Fertility and General Reproductive Performance of the Rat
Study No: and Number:	RRLE91J1803/UCB359
Amendment #, Volume # and Page #:	000, Vol. 1.11, p. 2993
Site and Testing Facility:	[redacted]
GLP Compliance:	Yes
QA- Reports:	Yes (√) No ( )
Lot and Batch numbers:	Pseudo-Ephedrine: 900105, Cetirizine: 2005, [redacted]
Methods:	
Species/Strain:	CD rats.
Doses Employed:	0, 10, 40 and 160 mg/kg of pseudo-ephedrine/cetirizine in a ratio of 24:1 as 2 equal doses administered 5 hr apart.
Route of Administration:	Oral gavage administered in 2 doses 5 hr apart.

APPEARS THIS WAY
ON ORIGINAL

[redacted]

Study Design:

Strain	CD (SD) BR VAF/plus		
	Males		Females
# and sex	135 males		132 females
Age	5 weeks		7-8 weeks
Weight	111-135 g		135-171 g
Doses	0, 10, 40, & 160 mg/kg given as 2 equal doses, administered 5 hr apart		
Treatment	Health check, acclimation, assignment to 4 groups, 5/sex/cage		
	Males		Females
Age @ study start	7 weeks		9-10 weeks
Dosing prior to mating	9 weeks		2 weeks
During mating	Yes		Yes
During gestation/ lactation	Yes		Yes
#/group	30		30
Females only			
Gestational day 20	14 females /group were sacrificed		16 females/group were allowed to litter
	Dams necropsied		
	½ litter preserved in Bouin's solution Visceral exam	½ litter stained in 74OP industrial methylated spirit Macroscopic exam, evisceration & skeletal exam	Pups weighed on days 0, 4, 8, 16, and 21
			Litter tested for developmental reflexes – startle, pupillary, surface and air righting.
			1 male & 1 female/litter were retained and tested for general aspects and reproductive capacity. F1 animals were also tested post weaning for development using the Rotarod, Actimat and passive avoidance tests.

Number of Animals/Sex/Dosing Group: 30/sex/group. Males dosed for 9 weeks prior to mating and then throughout until sacrifice on day 21 postpartum. Females were dosed 2 weeks prior to mating, during mating, and through the gestation and weaning periods.

Parameters and endpoints evaluated:

F0 Generation:
Clinical signs, food consumption, body weight changes, pregnancy index, mating performance, gestation period, pre- & post-implantation loss.
Litter data (dams sacrificed day 20): # of corpora lutea, # and distribution of live young, number and distribution of embryo-fetal deaths, individual fetal weights and litter weight. Fetal abnormalities including malformations, anomalies and variants.

F1 generation:
Litter data (dams allowed to bear young): Clinical signs, food consumption, body weight changes, external abnormalities, autopsy, surface righting reflex, startle reflex, air righting reflex, pupil reflex, general aspects, reproductive capacity

Statistical evaluations:

Litter data: Kruskal-Wallis test followed by Shirley's test, if significant. Where 75% of the values were one number, Fisher's exact t-test was used.
Behavioral data & Rotarod data: ANOVA.
Avoidance test: Kruskal-Wallis or Fisher's t-test as appropriate.
Other parameters: ANOVA and Williams test.

Results:
For the purpose of clarity and ease of explanation, this study will be divided into three parts. Part 1 deals with fertility and fecundity of the F0 generation, Part 2 with embryo-fetal toxicity and Part 3 with peri- and postnatal development of the F1 animals.

PART I
For the F0 generation:
Mortality:

None.

Clinical signs:

Salivation: was seen in almost all group 3 animals and the incidence and severity were greater in group 4 animals.

Aggression: Group 2 females were similar to controls, Group 3 females showed aggression prior to mating when housed 5/cage during the first week of dosing. All group 4 females had 9 incidents over 5 days during the first week of dosing, while during the second week of dosing, all females had 6 incidents over 3 days except for 9 animals (#s 216, 223, 229-235) which had 7 incidents over 4 days.

Body weight:

Males: For groups 3 & 4 body weights were significantly lower (10-20% at the end of treatment) for the entire duration of the treatment. For group 2, body weight was significantly lower from weeks 4-16; however, the decrease in bodyweight was between 5-10%.

Females: Body weights were significantly lower for groups 3 & 4 (10% or less) for the 1st two weeks of treatment and although the body weights for treated females tended to be lower for the duration of treatment, they did not attain statistical significance.

Food consumption:

Males: Showed evidence of significantly decreased food intake during the first 9 weeks for groups 3 & 4. Group 2 only showed decreased intake during week 4. Females: The decrease in food intake was small and did not attain significance.

Mating Performance:

A total of 4 males failed to induce pregnancy, 1 control male (#18), 2 group 2 males (#s 35 & 36) and 1 group 4 male (#103). The group 4 male had small, blue and flaccid testes at autopsy. No abnormalities were seen in any other males.

Parameters assessed were median precoital time, cell types in vaginal smear at mating, pregnancy rate (97, 93, 100 and 97% in groups 1-4 respectively) and pregnancy duration. All measured parameters were similar in all groups.

Necropsy:

Necropsy revealed no remarkable findings in any animals except for the 160 mg/kg male with blue, small and flaccid testes which failed to induce pregnancy.

Part I Summary

The observations included clinical signs of salivation, as well as decreased food intake and body weight gain, and aggression in females prior to mating. These observations suggest that the doses used ~~in this~~ study were adequately high. Treatment with either 10, 40 or 160 mg/kg pseudo-ephedrine:cetirizine mixture in a 24:1 ratio had no effect on fertility and pregnancy index in CD rats.

PART II

Part I documents the clinical signs, body weight changes, food consumption, mating performance of males, and pregnancy index. Part II deals with embryofetal toxicity.

Pre-& Post-Implantation Loss:

Pre-implantation loss is presented as the mean of the percentage per litter and was not altered by treatment. The post implantation loss was significantly greater in all treated groups; however, the loss was not dose related and individual animal data shows the incidence of post-implantation loss increased, but not the extent of the loss except in the mid dose group where one animal showed a 30% loss. Thus the increase in post implantation loss may not be toxicologically relevant. Number of implantations, number of corpora lutea, and the sex ratio did not differ between groups.

Dose (mg/kg)	# of females	Corpora lutea	Implants	Pre-implantation loss (%)	Post-implantation loss (%)	Sex Ratio (% males)
0	14	18.6	17.0	7.8	2.4	47.1
10	13	17.6	16.3	7.1	7.6*	45.8
40	14	16.9	16.1	5.1	7.7*	45.5
160	14	17.0	16.4	3.8	4.2*	50.4

* indicates significantly different ($p<0.05$) from control.

Fetal Weights:

Did not differ between groups.

Fetal Morphology:

The occurrence of fetal malformations and anomalies are documented in the table below. Malformations, mainly rib distortions, were increased significantly in the 160 mg/kg group. The incidences of rib distortions across groups were 0, 0, 0 and 3.

No change in the number of visceral abnormalities attributable to treatment was seen. The number of skeletal anomalies was doubled at the 40 and 160 mg/kg doses; however, the numbers were at the high end of the range of the historical control data.

The number of fetuses with variant sternebrae increased from 48.4% in controls to 67.6*% in the 160 mg/kg group and the number of normal sternebrae decreased from 51.6% in controls to 32.4*%. Thus, treatment with 160 mg/kg lead to an increase in malformations (rib distortions) and skeletal variants (unossified sternebrae) in the fetus.

Dose (mg/kg)	Fetal Malformations		Fetal Anomalies			
			Visceral		Skeletal	
	# affected (litter)/ # examined	Mean %	# affected (litter)/ # examined	Mean %	# affected (litter) / # examined	Mean %
0	0/232	0	8(7)/116	6.7	19(10)/116	15.6
10	0/196	0	4(3)/97	4.3	18(7)/99	19.3
40	2 (2)/209	0.8	7(6)/104	6.9	32(11)/103	30.0
160	5 (4)/219	2.4*	5(5)/107	5.1	33(12)/107	31.7

Part II Summary
Treatment at 10 and 40 mg/kg doses did not appear to induce any changes in fetal morphology. The 160-mg/kg dose was associated with changes in the skeleton, seen as an increased number of malformations (rib distortions) and skeletal variants (unossified sternebrae).

PART IIIa
Part IIIa covers peri- and post-natal development prior to weaning.

Litter Data (F1):

Of the 30 dams/group, 16/group were allowed to litter and rear the litter (F1) to weaning. For the 160 mg/kg animals, pup viability was significantly decreased (including the complete loss of 4/15 litters). Similar, but less marked pup losses were seen in the 40-mg/kg group, and litter size was lower than controls, but did not achieve statistical significance. No effects were seen in the low dose group. Litter and pup weight at birth were not significantly affected (see below). However, as of day 4 there was a significant decrease in pup weight in the high dose group. The decreased litter size as well as the lower individual pup weights may explain the decrease in litter weight for the high dose group. The ratio of male to female pups did not differ between groups.

Dose (mg/kg)		0	10	40	160
Implant sites		16.8	16.6	15.8	14.8[a] (14.1[b])
Sex Ratios	At Birth	50.5	52.9	50.5	44.9
	Day 21	50.0	54.5	48.2	41.7
At Birth	Litter size	15.3	14.4	14.0	13.7[a] (13.0[b])
	Pup Loss (%)	0.4	2.0	4.3	1.6[a] (0.6[b])
	Litter Wt. (g)	90.7	86.1	81.8	(73.2[b])
	Mean Pup Wt. (g)	6.0	6.0	5.9	(5.8[b])
Day 4	Litter size	14.9	14.1	13.2	7.7*[a] (10.0*[b])
	Cum. Pup Loss (%)	2.5	3.3	12.5	39.5*[a] (21.1*[b])
	Litter Wt. (g)	139.1	135.7	120.1	(75.4*[b])
	Mean Pup Wt. (g)	9.3	9.7	9.0	(7.6*[b])
Day 8	Litter size	14.9	14.1	13.0	7.3*[a] (9.9*[b])
	Cum. Pup Loss (%)	2.5	3.3	13.7	42.0*[a] (21.7*[b])
	Litter Wt. (g)	235.1	227.8	202.3	(124.1*[b])
	Mean Pup Wt. (g)	15.8	16.2	15.5	(12.7*[b])
Day 21	Litter size	14.9	13.9	13.0	7.3*[a] (9.9*[b])
	Cum. Pup Loss (%)	2.9	5.0	13.7	42.5*[a] (21.7*[b])
	Litter Wt. (g)	650.8	629.1	549.2	(383.4*[b])
	Mean Pup Wt. (g)	43.9	45.8	43.6	(39.9*[b])

* indicates significantly different ($p<0.05$) from control.
[a] represents all females with litters initially.
[b] represents only females rearing young to weaning.

Pre weaning developmental reflexes: Prior to weaning, the pups were tested for developmental milestones including surface and air righting reflexes, startle response and pupil reflex. The mean age for attaining all reflexes, excluding the startle response, was similar in the control and treated pups. The 160 mg/kg animals had a delay in attaining the startle response (34.2 days in control vs. 35.4* days in the high dose group).

Necropsy: Unremarkable.

Part IIIa Summary:
Treatment of F0 animals with either 10, 40 or 160 mg/kg pseudo-ephedrine:cetirizine mixture in a 24:1 ratio had no effect on pregnancy duration or litter and mean pup weight at birth in CD

rats. However, the 160-mg/kg dose was associated with decreased litter size and pup viability (including the complete loss of 4/15 litters), as well as lower mean pup weights from day 4 onward. Reflex development was unaffected, except for a minor delay in attaining the startle reflex.

PART IIIb: Post weaning, one male and one female from each of 12 litters per group were retained for study and the remainder of the animals sacrificed and necropsied. The selected F1 animals were mated one:one to study reproductive function and sib-sib mating were avoided.

Results:

Clinical signs (F1): None.

Mortality (F1): One control female died during week 8, but the cause of death was not established.

Body weight (F1): The decreased pup weight observed preweaning persisted throughout development in males and sporadically through week 7 in females. Mid dose males were also affected, but the finding is difficult to interpret because there was no preweaning effect on body weight at the mid dose.

Sexual Maturation (F1): One female offspring (#335) of 160 mg/kg treated parents had a marked delay in vaginal opening (48 days vs. ~32 days for the remainder of treated and untreated animals). Since this female weighed less than the rest of the animals this may be due to a delay in maturation.

The mean age for occurrence of skin fold cleavage was delayed from 42.5 to 44.4 days (not statistically significant) in male offspring of 160 mg/kg treated parents. This again may reflect a delayed growth/development effect. No differences were seen at the lower doses.

Post-weaning Behavioral Tests (F1): No differences were observed between offspring of treated and untreated parents for the Rotarod, Actimat® and passive avoidance tests.

Mating Performance (F1): Animals were paired one:one in cages and sib-sib mating was avoided. The mating behavior of these animals was unimpaired. The median precoital time was between 2.5-4 days. The pregnancy duration was similar among groups (21.7-22.1 days).

One male/group failed to induce pregnancy. At autopsy, the control male that failed to induce

pregnancy had small, blue testes. There were no notable findings in any other males.

Terminal Necropsy (F1): Unremarkable except for the one male with small, blue testes.

Litter Data(F2):

Implantation: There was a reduction in the number of implants derived from 160 mg/kg F1 parents. This was not seen at the lower doses.

Litter Size: Litter size was lower in animals derived from 160 mg/kg F1 parents, but not other treated groups.

Litter and Pup Weights: There were no notable differences. The significant decrease in litter weights in group 4 offspring can be explained by the smaller litter size, which is related to the decreased implant sites. Sex ratios were similar across groups.

Dose (mg/kg)		0	10	40	160
Implant sites		17.2	16.4	17.7	[redacted]
Sex Ratio - day 21 (% males)		50.8	46.5	50.3	50.5
At Birth	Litter size	16	15.5	17.4	13.7
	Pup Loss (%)	1.4	0	0.5	3.1
	Litter wt. (g)	99.7	97.7	106.9	88.2
	Mean pup wt (g)	6.3	6.4	6.2	6.5
Day 4	Litter size	15.7	15.4	17.3	13.6
	Cum. Pup Loss (%)	3.3	0.5	1.1	3.8
	Litter wt. (g)	176.0	160.3	173.0	149.0
	Mean pup wt (g)	11.3	10.6	10.0	11.0
Day 12	Litter size	15.6	15.4	17.1	13.6
	Cum. Pup Loss (%)	3.9	0.5	2.0	3.8
	Litter wt. (g)	417.1	392.8	402.1	356.7*
	Mean pup wt (g)	27.0	25.9	23.6	26.8
Day 21	Litter size	15.6	15.4	17.1	13.6
	Cum. Pup Loss (%)	3.9	0.5	2.0	3.8
	Litter wt. (g)	770.7	723.8	764.9	670.1
	Mean pup wt (g)	49.8	47.8	44.9	50.3

Necropsy: Unremarkable.

Part IIIb Summary

The F1 pups culled for reproductive function analysis were also tested using the Rotarod®, Actimat® and passive avoidance tests and no differences were seen between groups. The body weight deficit observed preweaning persisted in these animals, particularly in the males. Males also showed a delay (not statistically significant) in skin fold cleavage from 42.5 to 44.4

days. When tested for reproductive function, F1 offspring of parents treated with 160 mg/kg showed a slightly lower number of implants. This was reflected in smaller litter size (not significant) and weight.

Summary and Evaluation:

The F0 animals treated with pseudo-ephedrine:cetirizine mixture, exhibited clinical signs of salivation, as well as decreased food intake for both sexes, decreased body weight gain in males and aggression in females prior to mating. These observations suggest that the doses used in this study were adequately high. Treatment with either 10, 40 or 160 mg/kg pseudo-ephedrine:cetirizine mixture in a 24:1 ratio had no effect on fertility and pregnancy index in CD rats. The two lower doses did not appear to induce any changes in fetal morphology. The 160 mg/kg dose was associated with changes in the skeleton, seen as an increased number of malformations (rib distortions) and skeletal variants (unossified sternebrae).

In the F0 dams allowed to litter, treatment had no effect on litter and mean pup weight at birth in CD rats. However, the 160-mg/kg dose was associated with decreased litter size and pup viability (including the complete loss of 4/15 litters), as well as lower mean pup weights from day 4 onward. Reflex development was unaffected, except for a minor delay in attaining the startle reflex.

The F1 pups culled for reproductive function analysis were also tested using the Rotarod®, Actimat® and passive avoidance tests and no differences were seen between groups. The body weight deficit observed preweaning persisted in these animals, particularly in males. Males also showed a delay (not statistically significant) in skin fold cleavage from 42.5 to 44.4 days. When tested for reproductive function, F1 offspring of parents treated with 160 mg/kg showed a slightly lower number of implants. This was reflected in smaller litter size (not significant) and weight.

The doses used in the reproductive toxicology study in rats were 10, 40, and 160 mg/kg of a 24:1 combination of pseudo-ephedrine:cetirizine which are 0.3, 1.3, and 5.2X the maximum recommended daily human dose on a mg/m^2 basis. Embryofetal toxicity was seen in rats at the highest dose used, as was decreased pup viability and weight.

Labeling Recommendations:

See p. 50 for proposed labeling.

GENETIC TOXICOLOGY:

Study Title:	**Pseudo-Ephedrine:Cetirizine Mixture in the Ratio of 120:5: Bacterial Mutation Assay**
Study No:	LE90H081/UCB343
Study Type:	
Amendment #, Volume # and Page #:	000, vol. 1.11, p. 3243
Conducting Laboratory:	
Date of Study Initiation/Completion:	16 March 1990 and 8 April 1990
GLP Compliance:	Yes
QA- Reports:	Yes
Drug Lot Number:	Pseudo-Ephedrine: 900105, 99.1% Cetirizine: 2005, 99.77%
Study Endpoint:	2X or greater increase in revertants due to treatment with test article

Methodology:

Strains/Species/Cell line:	*S. Typhimurium* TA1535, TA1537, TA1538, TA98, & TA100
Dose Selection Criteria:	
Basis of dose selection:	Maximum required dose of 5000 µg/plate
Test Agent Stability:	Not determined.
Metabolic Activation System:	S9 (from 1254-induced rats)
Controls	
Vehicle:	Water
Negative Controls:	Water
Positive Controls:	9-Aminoacridine, N-ethyl-N'-nitro-N-nitrosoguanidine, 2-nitrofluorene, 2-aminoanthracene
Exposure Conditions:	
Incubation and sampling times:	Plate incorporation technique, 3 days @ 37°C
Doses used in definitive study:	50, 150, 500, 1500, & 5000 µg/plate
Analysis:	
No. slides/plates/replicates/animals analyzed:	3 plates/dose/strain/paradigm
Counting method:	
Cytotoxic endpoints:	Diminution in background lawn/ substantial reduction in revertant colony counts
Criteria for Positive Results:	2X or greater increase in revertants due to treatment with test article

Results:

Study Validity:	Two independent tests were performed and evaluated for each strain with and without metabolic activation. Positive controls were appropriate and induced revertants. The highest dose used was 5000 µg/plate, which is the limit dose for this test.
Study Outcome	The 120:5 combination of pseudo-ephedrine:cetirizine did not increase revertants in any strains and

therefore may be considered nonmutagenic in this assay.

Comments This assay does not use all the required strains, since neither of the A-T reversion stains (eg. TA 102 or WP2uvrA) were used. However, this is acceptable since mutagenicity testing of the combination product is not required for marketing.

Study Title: **An Assessment of the Mutagenic Potential of Pseudo-Ephedrine:Cetirizine Mixture (120:5) Using the Mouse Lymphoma TK Locus Assay.**
Study No: RRLE91E1302
Amendment #, Volume # and Page #: 000, Vol. 1.11, p. 3270
Conducting Laboratory: [redacted]
Date of Study Initiation/Completion: 5 Dec. 1990 – 26 Feb. 1991.
GLP Compliance: Yes
QA- Reports: Yes
Drug Lot Number: Pseudo-Ephedrine: 2559013MR90, [redacted]
Cetirizine: 2005, [redacted]
Study Endpoint: Reproducible, statistically significant and dose-dependent increases in mutant frequency.

Methodology:
Strains/Species/Cell line: Mouse Lymphoma L5178Y cells
Dose Selection Criteria:
Basis of dose selection: Drug levels that allow between 100 – 10% survival.
Test Agent Stability: Not determined
Metabolic Activation System: S9 (from 1254-induced rats)
Controls
Vehicle: Water
Negative Controls: Water
Positive Controls: Ethylmethane sulphonate, 20-methylcholanthrene
Exposure Conditions:
Incubation and sampling times: 3-hr. incubation with test substance, 48-hr incubation, cloning in agar and determination of mutant colony numbers
Doses used in definitive study: Test 1 – 0, 1, 625, 800, 1000 µg/ml -S9
Test 2 – 0, 200, 600, 800 & 1000 µg/ml –S9
Test 1 – 0, 1, 300, 625, & 800 µg/ml +S9
Test 2 – 0, 100, 600, 800, & 1000 µg/ml +S9

Analysis:
No. slides/plates/replicates/animals analyzed: Duplicate
Counting method: Automatic
Cytotoxic endpoints: Cell survival

Results:

Study Validity: Four independent tests were performed, 2 with and 2 without metabolic activation, to test for mutagenic potential in the mouse lymphoma thymidine kinase locus assay. Positive controls were appropriate and induced mutants. Choice of concentration was based on survival between 100 & 10%. Under –S9 conditions, treatment with pseudo-ephedrine:cetirizine combination resulted in ~90-25% growth, while under +S9 conditions growth was 100-15%.

Study Outcome: There was no increase in mutant frequency in the –S9 treated cells; however, +S9 treated cells in test 1 showed a significant increase in mutants. The increase showed no dose dependence and was less than 2X (control: 80, 81, 96 & 117, highest concentration: 111 & 119). Furthermore, in test 2, +S9 treated cells showed no increase in mutants. Thus, the combination of pseudo-ephedrine:cetirizine was concluded not to be mutagenic in the mouse lymphoma thymidine kinase locus assay.

Study Title: **Pseudo-Ephedrine:Cetirizine Mixture (120:5) Metaphase Chromosome Analysis on Human Lymphocytes Cultured *in vitro*.**

Study No: LE90J062/UCB 344

Amendment #, Volume # and Page #: 000, Vol. 1.11, p. 3300

Conducting Laboratory:

Date of Study Initiation/Completion: 1990

GLP Compliance: Yes

QA- Reports: Yes

Drug Lot Number: Pseudo-Ephedrine: 2559013MR90,
Cetirizine: 2005,

Study Endpoint: Chromosomal damage – gaps, breaks, interchange, dicentric or acentric chromosomes, chromosomal fragments or rings, or complete metaphase pulverization.

Methodology:

Strains/Species/Cell line: Cultured human lymphocytes

Dose Selection Criteria:

Basis of dose selection: Non-precipitating concentration which was 10mM and also the limit dose for this assay.

Test Agent Stability: Not determined

Metabolic Activation System: S9 (from 1254-induced rats)

Controls

Vehicle: Water

Negative Controls: Water

Positive Controls: Ethylmethane sulphonate, cyclophosphamide.

Exposure Conditions:

Incubation and sampling times: -S9: 22 hr incubation with test article. +S9: 2hr incubation with test article followed by 22 hr incubation.

Doses used in definitive study: 1650, 825, 413, 206, 103, 51.6, 25.8, 12.9, 6.5, and 3.2 µg/ml. Final doses were 1650, 825 and 206 µg/ml.

Analysis:

No. slides/plates/replicates/animals analyzed: Duplicate

Counting method: ~100 metaphase figures were examined by light microscopy (160x and 1000X) from each culture (25 from each slide).

Cytotoxic endpoints: Mitotic Index.

Results:

Study Validity: Under –S9 conditions, cells were incubated with drug for 22 hr and then harvested. For the +S9 treatment, cells were treated for 2 hrs with S9 and drug, cells were resuspended in fresh medium and incubated for a further 22 hr before harvesting. Positive controls were appropriate and induced chromosomal aberrations. Reduction in mitotic index was to 27.7% of solvent control at the highest dose of test article under –S9 conditions, while no reduction in mitotic index was seen under +S9 conditions. A sufficient number of metaphases (100/culture or minimum 200/treatment) were examined. However, for +S9, cells should be incubated for 3-6 hr for a valid assay. This assay is not an issue for this NDA because clastogenicity testing of the combination product is not required for marketing.

Study Outcome The pseudo-ephedrine:cetirizine combination did not induce any chromosomal aberrations under + or – S9 conditions. Therefore this combination is negative for clastogenicity in this assay.

Study Title: **Mouse Micronucleus Test on D-Pseudo-Ephedrine HCl:Cetirizine 2HCl Mixture Ratio 120:5.**

Study No: [redacted] LE90K231/UCB345

Amendment #, Volume # and Page #: 000, Vol. 1.11, p. 3319

Conducting Laboratory: [redacted]

Date of Study Initiation/Completion: 7 March 1990 – 20 March 1990.

GLP Compliance: Yes

QA- Reports: Yes (√) No ( )

Drug Lot Number: Pseudo-Ephedrine: 900105,
Cetirizine: 2005, [redacted]

Study Endpoint: Increased incidence of micronucleated PCEs per 1000 cells in treated animals for at least one time point.

Methodology:

Strains/Species/Cell line: CD-1 mice of Swiss origin

Dose Selection Criteria:

Basis of dose selection: Preliminary toxicity study showed that 320 mg/kg was the MTD which caused no mortalities.

Test Agent Stability: Not determined

Metabolic Activation System: N/A

Controls

Vehicle: Water

Negative Controls: Water

Positive Controls: Mitomycin C

Exposure Conditions:

Incubation and sampling times: Animals were dosed once and then sampled at 24, 48 & 72hrs. Mitomycin C animals were sampled at 24 hr only.

Doses used in definitive study: 320 mg/kg PO. Use of only one dose is usually not acceptable since three doses are required for a definitive study. However, since the dose used was lethal and since the testing of the combination product is not required for marketing, this is acceptable.

Analysis:

No. slides/plates/replicates/animals analyzed: 5 mice/sex/time point. Two smears per animals were examined. However, some animals died and so for the 48 & 72 hr time points 6M and 4F per treatment were analyzed.

Counting method: Manual

Results:

Study Validity: CD-1 mice (15+5/treatment) were administered a single oral dose of vehicle (water), pseudo-ephedrine:cetirizine (120:5) mixture or Mitomycin C. 5 mice/sex were sacrificed at 24, 48 & 72 hr. Two thousand PCEs per animals were examined. The dose was selected from preliminary studies and was approximately 40% of the LD_{50} for mice from the acute toxicity studies. The positive control induced micronuclei and decreased the polychromatic to normochromatic erythrocyte ratio.

Study Outcome: Treatment with the pseudo-ephedrine:cetirizine mixture produced clinical signs of pilo-erection, lethargy, increased movement, ptosis, hunched posture, increased or decreased respiratory rate, twitching, and coma. Ten animals died (3M & 7F).

There was no increase in micronucleated polychromatic erythrocytes, and no change in the polychromatic to normochromatic ratio. Therefore, the pseudo-ephedrine:cetirizine mixture was not clastogenic or toxic to bone marrow in this study.

Summary:
The mixture of pseudo-ephedrine and cetirizine in a ratio of 120:5 shows no evidence of mutagenic or clastogenic activities in the Ames, mouse lymphoma, chromosomal aberration, and mouse micronucleus tests.

Note:
An A-T conversion strain was not used in the Ames test.
In the chromosomal aberration test, an inadequate incubation time was used for the +S9 conditions (2 hr instead of 3-6 hr, as recommended by OECD guidelines).
Only a single (albeit lethal) dose was used for the micronucleus assay.

However, since genetic testing of the combination product is not required for marketing, these data are acceptable.

OVERALL SUMMARY AND EVALUATION:

Introduction: Cetirizine, a human metabolite of hydroxyzine (an anti-anxiety agent), is an antihistamine; its effects are mediated via selective inhibition of peripheral H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain and does not significantly occupy cerebral H_1 receptors. Pseudo-ephedrine hydrochloride is an orally active sympathomimetic amine and a nasal decongestant. Pseudo-ephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

In acute, single dose toxicity studies, the LD_{50}s for pseudo-ephedrine:cetirirzine (24:1) combination are as follows.

Species/Route	Dose (mg/kg)
Mouse-Oral	
M+F	813
Mouse-IV	
M+F	114
Rat-Oral	
M+F	1397
Rats-IV	
M+F	158

An acute, oral study in dogs given 5, 25 and 75 mg/kg of the pseudo-ephedrine:cetirizine combination indicates that 75 mg/kg is greater than the MTD since the two animals receiving that dose were sacrificed 4-hr post-administration, following chronic convulsions. Cmax and AUC increased in a greater than dose proportional manner. In cynomolgus monkeys administered 5, 25, 75 and 150 mg/kg PO, 75 mg/kg was the NOAEL based on marked appetite suppression and clinical signs. PK data suggests that the Cmax and AUC increased with dose in a greater than proportional manner.

Rats tolerated all the administered doses (10, 50 & 250 mg/kg) of pseudo-ephedrine/cetirizine combination for 4 weeks. Most of the findings were in the high dose group. These included post-dosing salivation, hypersensitive behavior, lower body weight gain, decreased food consumption, and alopecia. Although there was a slight decrease (~6%) in body weight gain at the MD, the effect was minimal and not statistically significant; therefore, 50 mg/kg was selected as the NOAEL.

In the 4-week rat study where the pseudo-ephedrine:cetirizine drug combination was administered via admixture with diet, expected levels of drug intake (10, 50 and 250 mg/kg) were achieved by admixture into the diet. Body weight gain was significantly lower at the highest dose. Thyroid weights were lower in males at the two higher doses. Based on the decreased body weight gain, the NOAEL in this study was determined to be 50 mg/kg. The levels of pseudo-ephedrine increased in a greater than proportional manner with dose and at the same dose, exposure was greater in females than males. Cetirizine was measurable in plasma only following the highest dose, and exposure appeared to be similar at this dose between males and females.

In the 26-week study with a 6-week recovery, rats were dosed at 30, 60, 120 and 240 mg/kg. For treated rats, clinical signs of salivation, forelimb paddling, & hyperreactivity are undesirable pharmacological effects of pseudo-ephedrine along with inappetance, which may account for the reduced body weight gain. No NOAEL was determined for this study based on the decreased body weight gain. Toxicity was seen in this study as hepatocyte enlargement & hemosiderosis in the spleen, primarily in the 240-mg/kg animals. The hepatocyte enlargement may account for the increased relative liver weight and minor increases in alkaline phosphatase and decreases in albumin. The splenic hemosiderosis may be due to the slightly increased Hb (high dose animals), RBC counts and packed cell volume (high dose females), but the background incidence of hemosiderosis was also fairly high.

All treatment-related effects reversed in the high dose recovery group except for the slightly increased alkaline phosphatase and red cell parameters and decreased albumin. The decrease in body weight gain rebounded partially during recovery. Unlike the liver, the increased kidney and brain weights may not be toxicologically important since no histopathology was associated with them.

A study was conducted to determine the toxicity of the 24:1 combination of pseudo-ephedrine:cetirizine at doses of 10, 20 and 40 mg/kg, administered by oral gavage to cynomolgus monkeys for 13 weeks. Animals tolerated the drug combination well. Toxicity was seen mainly in the form of dose-dependent manifestations of clinical signs (repetitive behavior, unsteadiness/limb tremors, lethargy and salivation), body weight loss and inappetance; these changes were reversible upon discontinuation of treatment. Animals showed reduced spleen (38% at the high dose) and thymus weights (41% at high dose) and thymic involution. Based on the decreased body weight gain and thymic changes, the NOAEL for this study was not determined and appears to be below 10 mg/kg. The kinetics were almost linear and showed dose-dependence.

In a 29-week cynomolgus monkey study no target organ for toxicity was identified. The animals tolerated all administered doses of the combination product. The main adverse effects were monitorable clinical signs of toxicity such as altered behavior (agitation, lethargy etc), and inappetance (considered a pharmacological effect of pseudo-ephedrine) leading to a decrease in bodyweight. These reversed partially during recovery. Based on the decrease in body weight gain, the NOAEL was 10 mg/kg. The kinetics showed dose-dependent increases in exposure to both compounds, which were slightly greater than predicted by linear relationship. The data also suggest a greater exposure over time, which may be due to a time-dependent decrease in elimination or altered absorption.

Reproductive toxicity studies were done in both rats and rabbits (see IND [redacted]. Fertility and general reproductive performance of the rat were studied following treatment with 10, 40 or 160 mg/kg of the combination of pseudo-ephedrine:cetirizine mixture in a 24:1 ratio. Rats were dosed prior to mating (9 weeks for males, 2 weeks for females) and throughout gestation and lactation until weaning of the pups. The F0 animals treated with pseudo-ephedrine:cetirizine mixture, exhibited clinical signs of salivation, as well as decreased food intake for both sexes, decreased body weight gain in males and aggression in females prior to mating. These observations suggest that the doses used in this study were adequately high. Treatment with either 10, 40 or 160 mg/kg pseudo-ephedrine:cetirizine mixture in a 24:1 ratio had no effect on fertility and pregnancy index in CD

rats. The two lower doses did not appear to induce any changes in fetal morphology. The high dose was associated with changes in the skeleton, seen as an increased number of malformations (rib distortions) and skeletal variants (unossified sternebrae). In the F0 dams allowed to litter, treatment had no effect on litter and mean pup weight at birth in CD rats. However, the 160-mg/kg dose was associated with decreased litter size and pup viability (including the complete loss of 4/15 litters), as well as lower mean pup weights from day 4 onward. Reflex development was unaffected, except for a minor delay in attaining the startle reflex. The F1 pups culled for reproductive function analysis were also tested using the Rotarod®, Actimat® and passive avoidance tests and no differences were seen between groups. The body weight deficit observed preweaning persisted in these animals, particularly in males. Males also showed a delay (not statistically significant) in skin fold cleavage from 42.5 to 44.4 days. When tested for reproductive function, F1 offspring of parents treated with 160 mg/kg showed a slightly lower number of implants. This was reflected in smaller litter size (not significant) and weight. The doses used in the reproductive toxicology study in rats were 10, 40, and 160 mg/kg of a 24:1 combination of pseudo-ephedrine:cetirizine which are 0.3, 1.3, and 5.2X the maximum recommended daily human dose on a mg/m^2 basis. Embryofetal toxicity was seen in rats at the highest dose used, as was decreased pup viability and weight.

The mixture of pseudo-ephedrine and cetirizine in a ratio of 120:5 showed no evidence of mutagenic or clastogenic activity in the Ames test, human lymphocyte chromosomal aberration test, mouse lymphoma tk locus test and the mouse micronucleus test. It is noted, however, that a number of these assays did not follow the current guidelines; an A-T conversion strain was not used in the Ames test, the +S9 incubation period was only 2 hr for the chromosomal aberration test rather than the 3-6 hr recommended by OECD guidelines, and only a single (albeit lethal) dose was used for the micronucleus assay. Although there were deviations from the current genetic toxicity testing guidelines, genetic testing of the combination product is not required for marketing.

Safety Evaluation:

The combination of pseudo-ephedrine:cetirizine in a ratio of 24:1 is in general well tolerated in mice, rats and monkeys. The principle side effects appear to be loss of appetite leading to decreased body weight gain along with clinical signs of lethargy, huddled posture, salivation and altered behavior. The target organs for toxicity appear to be the liver (6-month rat study – hepatocyte enlargement and increased relative liver weight @ 240 mg/kg) and spleen (4-week rat study – decreased spleen weight in females @ 250 mg/kg; 6-month rat study – splenic hemosiderosis @ 240 mg/kg; 13-week monkey study – decreased spleen weight which was not seen in the 29-week study). Lower thyroid weights were also seen in male rats treated via the diet, but not by gavage for 4 weeks. In addition, lower thymus weights (~41% @ 40 mg/kg) and thymic involution were also seen in cynomolgus monkeys treated for 13 weeks, but not in monkeys treated for 29 weeks.

However, the combination of pseudo-ephedrine and cetirizine appears to have embryofetal toxicity in rats. The effects include skeletal malformations (rib distortions) and an increase in variations (unossified sternebrae) at a dose of 160 mg/kg (5X the MRDD – maximum recommended daily dose). This dose also decreased pup viability and pup weights. A smaller, not statistically significant effect on pup viability was seen at 40 mg/kg (which is equivalent to the MRDD).

Clinical Relevance of Safety Issues:

This combination exhibits reproductive toxicity in rats in the form of fetal skeletal defects, and decreased pup viability and weight at doses similar to the MRDD. In contrast, the label for cetirizine indicates that cetirizine alone does not cause skeletal defects or decrease pup viability at doses 40-220 times the MRDD. Decreased pup weight gain during lactation was observed with cetirizine at 40 times the MRDD; no NOAEL was identified.

Labeling Review:

The labeling should read as follows:

Carcinogenesis, Mutagenesis and Impairment of Fertility: There are no carcinogenicity studies of pseudo-ephedrine and cetirizine in combination.
Cetirizine: In a 2-year study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily dose in adults on a mg/m^2 basis). In a 2-year study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily dose in adults on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily dose in adults on a mg/m^2 basis). The clinical significance of these findings during long-term use of ZYRTEC-D is not known.
Pseudo-ephedrine: Two-year studies in rats and mice conducted under the auspices of the National Toxicology Program demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudo-ephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 1/3 and 1/2, respectively, the maximum recommended daily dose of pseudo-ephedrine in adults on a mg/m^2 basis).

Cetirizine was not mutagenic in the Ames test or mouse lymphoma test, and not clastogenic in the human lymphocyte assay or the *in vivo* rodent micronucleus test. Likewise, the combination of pseudo-ephedrine and cetirizine in a 24:1 ratio was not mutagenic or clastogenic in these tests. However, the Ames and mouse lymphoma assays did not strictly adhere to test standards.

In a reproductive toxicity study in rats, combination oral doses of pseudo-ephedrine/cetirizine up to 154/6 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis) had no effect on fertility.

Pregnancy Category C: In rats, the combination of pseudo-ephedrine/cetirizine caused developmental toxicity when administered orally at 154/6 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). When rats were dosed throughout pregnancy with oral doses of pseudo-ephedrine/cetirizine, 154/6 mg/kg increased the number of fetal skeletal malformations (rib distortions) and variants (unossified sternebrae). When dosing was continued through lactation, 154/6 mg/kg also decreased the viability and weight gain of offspring. These effects were not observed at 38/1.6 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). No embryofetal toxicity was observed when rabbits were dosed throughout organogenesis with oral doses of pseudo-ephedrine/cetirizine of up to 154/6 mg/kg

(approximately 10 times the maximum recommended daily dose in adults on a mg/m^2 basis). Because there are no adequate and well-controlled studies in pregnant women, ZYRTEC-D should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: In rats, the combination of pseudo-ephedrine/cetirizine decreased the viability and weight gain of offspring when administered orally to dams throughout pregnancy and lactation at 154/6 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). This effect was not observed at 38/1.6 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). For cetirizine administered alone, studies in dogs indicate that approximately 3% of the dose is excreted in milk, and cetirizine has been reported to be excreted in human breast milk. For pseudo-ephedrine administered alone, 0.4 – 0.7% of the dose has been reported to be excreted in human breast milk. Because cetirizine and pseudo-ephedrine are excreted in milk, use of ZYRTEC-D in nursing mothers is not recommended.

/S/ 9/28/00

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