♦ **Rat Embryo/Fetal Observations (1st Study):**

Reduced fetal weights were reported for the MD and HD CGP 63172 MD and HD groups vs controls ($p<.001$).

Remarkable fetal gross observations included 1 multi-malformed fetus was reported in the HCTZ group, and cleft palate and cleft lip were reported in one fetus each at MD CGP 63172.

Fetal visceral variations were reported in the kidney/ureters, and fetal skeletal observations included increased incidence of not ossified sternebrae at MD and HD CGP 63172. The drug sponsor considered these observations to be incidental to drug administration because of the single occurrence and lack of dose-response relationship.

Summary table, prepared by drug sponsor/edited by reviewer, of rat **fetal gross malformations/variations and visceral variations (by litter)** appears below.

CGP 63172: AN ORAL TERATOLOGY (SEGMENT II) STUDY IN RATS (MIN 944118)

8.9. Summary of fetal examinations (by litter)

Type/Parameter	Dose Level (mg/kg/day)				
	Control (0)	0:187.5	50:15.6	200:62.5	600:187.5
GROSS MALFORMATIONS:					
Amelia	0	1	0	0	0
Anotia	0	1	0	0	0
Ablepharia	0	1	0	0	0
Cleft palate/lip	0	0	0	2	0
Domed head	0	1	0	0	0
Eye bulge small/absent	1	0	0	1	0
Microagnathia	0	1	0	0	0
Oligodactyly	0	1	0	0	0
Protruding tongue	0	1	0	0	0
No. of Litters with Gross Malformations:	1	1	0	2	0
No. of Litters Examined Grossly:	26	25	26	21	13
GROSS VARIATIONS:					
Edematous	1	0	0	0	0
Filamentous tail	0	0	0	0	1
Fused placenta	1	0	0	0	0
No. of Litters with Gross Variations:	2	0	0	0	1
No. of Litters Examined Grossly:	26	25	26	21	13

Fetal skeletal observations were attributed by drug sponsor to random biologic variations in development an considered incidental to compound administration.

Skeletal malformations/variations (by litter) reported appeared unremarkable. Skeletal malformations reported in 1/13 litters at HD CGP 63172- short scapula, and bowed radius, and in 1/25 litters from the HCTZ group- misaligned centrum vertebrae, short scapula or irregular shape ulna.

Fetal skeletal variations reported included the increased incidence ($p<.005$ vs control) of wavy/angulated ribs in CGP 63172 but not dose-related; other increased incidences in fetal variations reported included not ossified centrum/vertebrae at the HD and two highest doses of CGP 63172 centrum/vertebrae at the HD.

In this 1st teratology study in rats treated with CGP 63172 (at doses ranging from 50:15.6 up to 600:187.5 mg/kg/day) or with HCTZ 187.5 mg/kg/day during the period of organogenesis, there was clear evidence of maternotoxicity at all doses of CGP 63172 which included mortality, decreases in food consumption and decreases in body weight (also noted with HCTZ). Signs of fetotoxicity were also associated with the treatment of CGP 63172 at the two highest doses as evidenced by reduced fetal weights and visceral variation of renal papillae absence and skeletal variations . However, there was no clear evidence of teratogenicity in the offspring from dams treated with CGP 63172 during organogenesis. The NOAEL for maternal toxicity could be determined for CGP 63172 in this study.

The following is a synopsis of the 1st rat oral developmental study (FDA Seg II) was prepared by drug sponsor (Study 944118)

Study type/ species data	Compound ID/regimen	Site, investigators, Tox/Path no., date	Findings and/or comments
Segment II; Sprague-Dawley rats (Crl:COBS CD(SD)BR); females - 26/group (216 to 292 g) approximately 12 weeks of age on gestation day 0.	CGP 63172, a 16:5 wt:wt combination of CGP 48933 (Lot 800194) and HCT (Lot 800188) at daily doses (CGP 48933:HCT) of 0:187.5, 50:15.6, 200:62.5 or 600:187.5 mg/kg administered orally by gavage, as suspensions in aqueous 3% corn starch, on gestation days 6 through 15 (dosing volume of 10 ml/kg). A control group received aqueous 3% corn starch in equivalent volumes (10 ml/kg) via gavage. Necropsies were conducted upon death, moribund sacrifice or on day 20 of gestation.	Ciba-Geigy Corporation Summit, New Jersey K Amemiya, SE Irwin and ET Yau T/P #95053 20 Oct 95	**≥ 50:15.6 mg/kg:** ↓ mean food consumption; ↓ mean body weight and body weight gain/body weight losses and corrected mean body weight gain (days 0-20); and skeletal variation of wavy/angulated ribs. **200:62.5 mg/kg:** Mortality (3/26); clinical sign of diarrhea. **≥ 200:62.5 mg/kg:** Clinical signs of salivation, decreased, no and soft stool and clinical signs (in animals that died) of stains on fur, lethargy and gasping/labored respiration; ↓ corrected mean body weight (day 20); ↓ fetal weights; ↑ visceral variation of renal papillae absent; and ↑ skeletal variation of not ossified sternebrae. **600:187.5 mg/kg:** Mortality (11/26); clinical signs (in animals that died) of ptosis, rales and unthriftyness; and ↑ skeletal variation of not completely ossified and not ossified centrum/vertebrae. **0:187.5 mg/kg (HCT):** ↓ mean body weight and body weight loss.

♦ **3.3.2.2 Follow-up study:** An Oral Teratology (Seg II) Study in Rat with **CGP 63172. (Study MIN 954068.** Study Report T/P (US) **# 95081.** GLP Study **No. 956049** conducted at drug sponsor's labs started on 03-08-95. v.20-21)

Mating period started on 03-13-95 and ended 03-21-95; dosing dates were from 03-20-95 (1st day of gestation) and ended 04-05-95 (gestation day 15) with in-life phase studies completed 04-10-95 (gestation day 20).

Drug sponsor asserted that since the 1st rat developmental study (summarized above) produced an insufficient number of litters secondary to excessive maternal mortality to allow for complete embryo/fetal assessments, the present "follow-up study" was conducted at lower doses of CGP 63172 and HCTZ expected to .

The following table was provided showing the rat dosing schedule.

Group	Number of female rats	Daily dose (mg/kg)	Dosing volume (ml/kg)	Dosing conc. (mg/ml)	Number of dose days
1 (Control)	26	0	10	0	10
2 (HCT)	26	0:31.3	10	0:3.13	10
3	26	10:3.1	10	1.0:0.31	10
4	26	25:7.8	10	2.5:0.78	10
5	26	100:31.3	10	10:3.13	10

Briefly, 5 groups of rats in this developmental study were treated with doses of CGP 63172 (valsartan: HCTZ) as LD- 10:3.1, MD- 25:7.8 and HD- 100:31.3 mg/kg in aq. 3% corn starch susp.; HCTZ group was treated with a susp. formulated to deliver 31.3 mg/kg and 2 control groups received the vehicle (3% aq. corn starch suspension).and .

The HD was selected based on the mortality observed in the 1st study at ≥ 200:62.5 mg/kg; the MD and HD selected were anticipated to produce slight to minimal maternal effects, and no-effect, respectively.

In this the follow-up rat developmental study, the daily drug treatments were calculated on the most recent body weight recorded on gestation days 6, 8 and 12.

In-life observations included- daily for mortality and clinical signs, and food consumption/body weight on gestation days 0, 6, 8, 12, 16 and 20. Treated rats received tap water ad libitum; consumption of food/water was monitored for contaminants, and maintained within the laboratories acceptable limits.

All dams were sacrificed on day 20 of pregnancy, and major viscera of all rats were examined grossly.

Similarly to 1st rat developmental study, after acclimation, animals were housed in a room at ~73°F, supplied with ~14 hrs of artificial light. Prior to mating, rats were assigned identification numbers, randomized to 5 treatment groups, and mated with stock male rats of the same strain in a 2:1 ratio until the presence of sperms were observed in vaginal washing; that day was designated day 0 of gestation. F rats at this time were ~ 12 weeks of age weighing from 229-302 on gestation day 0.

Reproductive parameters recorded included combined weight of uterus/ovaries/oviducts for pregnant-full term rats, the numbers of corpora lutea/resorption/implantation sites, dead/live fetuses, and fetal sex ratios and fetal gross visceral/skeletal parameters. Live fetuses were weighed/sexed/examined grossly and 1/3 placed in Bouin's fixative for visceral examination 2/3 placed in 70% ethanol and subsequently stained with alizarin red S for skeletal examination.

Statistical evaluation was conducted on the above listed parameters to detect differences between vehicle control and HCTZ groups, or the drug combination groups. An explanation of the statistical methods used was provided in the NDA submission.

RESULTS

♦ **Rat Maternal Observations (Follow-up Study)**

Mortality/Clinical Signs/Necropsy: All dams survived until gestation day 20 sacrifice. The only clinical observation reported was alopecia in ~ 1-3 rats from CGP 63172 treated groups.

Slight reductions in mean food consumption were reported for the LD and HD rats a various time periods during drug treatment.

Overall, treatment related decreases in mean body weight were observed during dosing period in LD/MD dams, but changes were not dose-related, and thus considered to be incidental by drug sponsor.

Group mean data of gestational parameters and fetal sex ratio are summarized below in table provided by drug sponsor.

A follow-up oral teratology (Segment II) study in rats MIN 954068

Summary of reproductive parameters
(Mean ± SD)

Parameter	Dose level (mg/kg/day)				
	Control (0)	HCTZ 0:31.3	LD- 10:3.1	MD-25:7.8	HD100:31.3
Number of females mated	26	26	26	26	26
Number of pregnant females	26	24	24	23	24
% of pregnant females	100	92.3	92.3	88.5	92.3
Number of corpora lutea	19.35 ± 3.41	18.67 ± 2.73	19.21 ± 2.83	18.74 ± 2.56	18.71 ± 3.00
Number of implantation sites	16.42 ± 1.94	16.79 ± 1.91	16.83 ± 2.57	16.52 ± 2.74	16.21 ± 3.96
Number of litters examined	26	24	24	23	24
Number of live fetuses	15.38 ± 2.53	15.79 ± 2.15	15.92 ± 2.89	15.39 ± 3.07	15.42 ± 4.02
Number of early resorptions	1.00 ± 0.94	1.00 ± 1.32	0.88 ± 1.12	1.13 ± 1.10	0.75 ± 0.68
Number of late resorptions	0.04 ± 0.20	0.00 ± 0.00	0.04 ± 0.20	0.00 ± 0.00	0.00 ± 0.00
Number of total resorptions	1.04 ± 0.96	1.00 ± 1.32	0.92 ± 1.14	1.13 ± 1.10	0.75 ± 0.68
Number of dead fetuses	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.04 ± 0.20
Postimplantation loss	1.04 ± 0.96	1.00 ± 1.32	0.92 ± 1.14	1.13 ± 1.10	0.79 ± 0.72
% postimplantation loss	6.78 ± 6.66	5.88 ± 7.87	5.79 ± 8.26	7.27 ± 7.94	8.67 ± 19.96
Fetal sex ratio (% males)	45.50	50.92	48.82	52.54	45.95

Necropsy observations

Group dose (mg/kg/day)	Dam number	Necropsy finding
1 (0)	20	Left kidney hollow
2 HCTZ - (0:31.3)	49	Thymus enlarged
CGP 62372 MD - 4 (25:7.8)	110	Left kidney, spleen and stomach engulfed in apparent connective tissue
HD- 5 (100:31.3)	148	Soft, fluid-filled mass on left axilla

♦ **Rat Embryo/Fetal Observations (Follow-up Study)**

No gross malformations or variations related to treatment with HCTZ alone or with CGP 63172 at any dose level were reported.

Summary table below prepared by drug sponsor and edited by reviewer shows findings of fetal examinations (by litter) from dams treated with CGP 63172 or HCTZ. Because of the lack of dose-response and low incidence of the findings these were considered by drug sponsor to be unrelated to treatment.

MIN 954068

Summary of fetal examinations
(by litter)

Type/parameter	Dose level (mg/kg/day)				
	Control (0)	0:31.3	10:3.1	25:7.8	100:31.3
Gross malformations					
Ablepharia	0	0	1	0	0
Agnathia	0	0	0	0	1
Cleft palate	0	0	1	1	1
Cleft lip	0	0	1	0	0
Conjoined twins	0	0	0	0	1
Craniorachischisis	0	0	1	0	0
Exencephaly	0	0	0	1	0
Eye bulge absent	0	0	0	0	1
Sympodia	0	0	1	0	0
Umbilical hernia	0	1	0	0	0
No. of litters with gross malformations:	0	1	1	1	2
No. of litters examined grossly:	26	24	24	23	23
Gross variations:					
Hematoma	0	0	0	0	1
Short tail	0	0	1	0	0
No. of litters with gross variations:	0	0	1	0	1
No. of litters examined grossly:	26	24	24	23	23
Visceral malformations					
Adrenals - agenesis	0	0	1	0	0
Bladder - agenesis	0	0	1	0	0
Ureters - agenesis	0	0	1	0	0
No. of litters with visceral malformations:	0	0	1	0	0
No. of litters examined viscerally:	26	24	24	23	23
Visceral variations:					
Lung - irregular	0	0	1	0	0
Liver - irregular	0	0	1	0	0
- reduced in size	0	0	1	0	0
Kidney - renal papillae short	12	18	10	13	14
- renal papillae absent	0	1	2	1	3
- reduced in size	0	0	1	0	0
Ureter(s) dilated	7	9	6	8	10
Nose - irregular	0	0	1	0	0
No. of litters with visceral variations:	14	19	13	15	14
No. of litters examined viscerally:	26	24	24	23	23

For fetal skeletal findings, were no malformations or variations reported that were considered treatment-related. There were significant ($p \leq 0.05$) increases in the incidence of bipartite centrum/vertebra from 3/23 litters each from MD/HD CGP 63172 treated dams, and not completely ossified metatarsals in 1/23 at MD and 3/23 at HD litters dams. The NOAEL may be <10:31 mg/kg.

In this "follow-up" teratology study in rats treated with CGP 63172 (at doses ranging from 10:3.1 up to 100:1.3 mg/kg/day) or with HCTZ 187.5 mg/kg/day during the period of organogenesis, no clear evidence of embryotoxicity, fetotoxicity or teratogenicity. Although 1 HD dam showed axillary mass filled with soft fluid, and 1 at MD showed spleen/stomach/kidney engulfed in connective tissue, and some dams showed alopecia, no other maternal observations were reported that were considered drug related. Therefore, the data suggest that the NOAEL for maternal toxicity could be below 10:3.1 mg/kg CGP 63172.

CGP 63172 ; A TERATOLOGY (SEGMENT II) STUDY IN RAT (MIN 954068)

SUMMARY OF FETAL EXAMINATIONS PARAMETERS

(BY LITTER)

TYPE/PARAMETER	DOSE LEVEL (MG/KG/DAY) CONTROL (0)	0:31.3	10:3.1	25:7.8	100:31.3
SKELETAL VARIATION :					
SKULL					
AUDITORY OSSICLES - NOT COMPLETELY OSSIFIED	2	1	1	2	0
AUDITORY OSSICLES - NOT OSSIFIED	2	2	6	3	1
BASISPHENOID - ADDITIONAL	0	1	5	0	3
BASISPHENOID - NOT COMPLETELY OSSIFIED	0	0	1	0	0
FRONTALS - NOT COMPLETELY OSSIFIED	3	3	0	1	2
FRONTALS - NOT OSSIFIED	0	0	0	1	0
HYOID - NOT COMPLETELY OSSIFIED	10	7	9	9	4
HYOID - NOT OSSIFIED	5	8	5	3	3
INTERPARIETALS - IRREGULAR SHAPE	0	0	0	1	0
INTERPARIETALS - NOT COMPLETELY OSSIFIED	11	14	14	12	10
MAXILLAE - NOT COMPLETELY OSSIFIED	3	3	3	4	0
NASALS - NOT COMPLETELY OSSIFIED	3	2	1	3	4
OCCIPITALS - BIPARTITE	0	0	0	1	0
OCCIPITALS - NOT COMPLETELY OSSIFIED	12	8	15	9	9
PALATINES - NOT COMPLETELY OSSIFIED	0	0	0	1	1
PALATINES - NOT OSSIFIED	1	0	0	1	0
PARIETALS - NOT COMPLETELY OSSIFIED	6	6	7	7	5
PARIETALS - WIDENED SUTURE	0	1	0	0	0
PRESPHENOID - NOT COMPLETELY OSSIFIED	0	1	3	0	0
PRESPHENOID - NOT OSSIFIED	0	0	1	1	1
SQUAMOSALS - NOT COMPLETELY OSSIFIED	4	3	3	3	1
TEETH - NOT COMPLETELY OSSIFIED	0	0	0	0	1
TEETH - NOT OSSIFIED	1	3	0	3	2
ZYGOMAS - NOT COMPLETELY OSSIFIED	3	2	2	3	0
CENTRUM/VERTEBRAE					
ADDITIONAL	1	1	1	0	1
AGENESIS	1	0	0	1	0
BIPARTITE	0	1	0	3*	3*
CERVICAL RIB	0	1	0	0	1
IRREGULAR SHAPE	1	2	3	2	3
NOT COMPLETELY OSSIFIED	15	19	10	13	13
NOT OSSIFIED	4	5	2	3	4
14TH RUDIMENTARY RIB	16	15	14	18	13
RIBS					
AGENESIS	0	0	0	1	0
LOCALIZED THICKENING	1	2	0	2	0
NOT COMPLETELY OSSIFIED	0	0	0	1	0
RUDIMENTARY RIB	1	0	0	0	0
WAVY/ANGULATED	1	1	0	2	0
STERNEBRAE					
BIPARTITE	0	1	1	1	1
IRREGULAR SHAPE ,	12	12	13	7	14
NOT COMPLETELY OSSIFIED	25	23	24	22	22
NOT OSSIFIED	25	20	20	20	19
FORELEG/FOREPAW					
DISTAL PHALANGES - NOT OSSIFIED	0	0	0	1	0
METACARPALS - NOT COMPLETELY OSSIFIED	22	23	20	17	20
METACARPALS - NOT OSSIFIED	25	20	20	22	19
PELVIC GIRDLES					
ILIUM - NOT COMPLETELY OSSIFIED	0	0	0	1	0
ISCHIUM - NOT COMPLETELY OSSIFIED	0	1	1	1	1
OS PUBIS - NOT COMPLETELY OSSIFIED	6	6	3	4	2
OS PUBIS - NOT OSSIFIED	0	1	1	1	2
HINDLEG/HINDPAW					
DISTAL PHALANGES - NOT COMPLETELY OSSIFIED	0	0	0	0	1
DISTAL PHALANGES - NOT OSSIFIED	0	3	0	3	0
METATARSALS - NOT COMPLETELY OSSIFIED	0	1	0	1	3*
METATARSALS - NOT OSSIFIED	1	3	0	2	2
TIBIA - IRREGULAR SHAPE	0	0	0	1	0
NO. LITTERS WITH SKELETAL VARIATIONS:	26	24	24	23	23
NO. LITTERS WITH SKELETAL VARIATIONS (EXCLUDING FOREPAW & HINDPAW):	26	24	24	23	23
NO. LITTERS EXAMINED SKELETALLY	26	24	24	23	23

* $P \leq 0.05$

The following synopsis of the "follow-up" rat oral developmental study (FDA Seg. II) was prepared by drug sponsor (**MIN 954068**)

A follow-up oral teratology (Segment II) study in rats — MIN 954068

Synopsis

Study type/ species data	Compound ID/regimen	Site, investigators, Tox/Path no., date	Findings and/or comments
Segment II; Sprague-Dawley rats (Crl:COBS CD[SD]BR); females - 26/group; approximately 12 to 13 weeks of age and weighing 229 to 302 grams on gestation day 0.	CGP 63172, a combination (16:5 wt:wt ratio) of CGP 48933 (Lot 800194) and HCT (Batch 800188), administered orally by gavage, as suspensions in aqueous 3% corn starch, at daily doses (CGP 48933:HCT) of 0:31.3, 10:3.1, 25:7.8 or 100:31.3 mg/kg (dose volume of 10 ml/kg) on gestation days 6 through 15. A control group received aqueous 3% corn starch in an equivalent volume. Necropsies were conducted on gestation day 20.	Ciba-Geigy Corporation Summit, New Jersey K Amemiya, SE Irwin and ET Yau T/P no. 95081 06 Feb 96	**0:31.3 mg/kg (HCT suspension only):** No significant findings. **10:3.1 mg/kg:** No significant findings. **25:7.8 mg/kg:** No significant findings. **100:31.3 mg/kg:** ↓ mean food consumption; ↓ mean body weight gain. Reproductive parameters, fetal weights and fetal gross, visceral and skeletal development were unaffected by treatment.

2.3.3 RABBIT (Hra:NZW-SPF)

♦ **2.3.3.1** Oral Teratology (Seg II) Study in Rabbit Treated with CGP 63172 (**MIN 944117**. Study Report T/P (US) # **95048**. GLP Study No. **946119** conducted at drug sponsor's labs started on 11-04-94. V. 22-23)

Insemination started on 11-06-94 (day 0 of gestation). Dosing (gavage) started on day 7 of gestation and ended 11-29-94 (gestation day 19) and in-life phase studies were completed 12-09-94. Dosing schedule for rabbits (gestation days 6-18) was advanced 1 day (gestation days 7-19) since artificial insemination was employed to established pregnancy.

The following table was provided showing the rabbit dosing schedule.

Group	Number of rabbits Female	Daily dose (mg/kg)	Dosing volume (ml/kg)	Compound concentration (mg/ml)	Number of dose days
1 (Control)	20	0	5	0	13
2* (Control)	20	0	5	0	13
3*	20	0.0:3.1	5	0:0.62	13
4*	20	1.0:0.3	5	0.20:0.06	13
5*	20	3.0:0.9	5	0.60:0.18	13
6*	20	10.0:3.1	5	2.0:0.62	13

*Animals received saline instead of tap water to drink during the dosing period.

The study report states that the above doses of CGP 63172 (valsartan:HCTZ) selected based on a previously conducted dose range-finding study (**MIN 944116** in v. 22) in 6 pregnant rabbits/group treated by gavage with 0, LD-1.0:0.3, MD-5.0:1.6 and HD-10.0:3.1 or HCTZ 3.1 mg/kg during gestational days 7 through 19 to provide data for the selection of appropriate doses for the definitive developmental study. The rabbit dose range-finding study was conducted in drug sponsor's labs in Summit, N.J. and is fully reported in the NDA (v22, p.1). No treatment related findings in the control or HCTZ groups. In the CGP 63172 groups, remarkable maternal toxicity reported was mortality (at MD- 2/6; HD- 1/6), and reductions in mean food consumption at all doses, with no evidence of embryotoxicity. For this study, the NOEL may be considered to be below 1.0:0.3 mg/kg/day CGP 63172.

The definitive developmental study was conducted to determine the potential maternal toxicity as well as the potential embryotoxic, fetotoxic, and/or teratogenic effect of CGP 63172 in pregnant rabbits.

Briefly, in this study, rabbits were ~ 4.5 to 5 months when received. After acclimation to the laboratory conditions, all rabbits were housed in a room at ~65°F, supplied with ~14 hrs of artificial light. Prior to artificial insemination, rabbits were assigned computer generated identification numbers, randomized to treatment groups, and then inseminated with semen from stock males of the same strain; that day was designated day 0 of gestation. On gestation day 0, rabbits body weights' ranged from 2.70 - 4.33 Kg.

Groups of 3 rabbits/group were treated by gavage (doses were calculated on the most recent body weight recorded on gestation days- 7, 10, or 14) with the both drugs as aq. 3% corn starch susp., and the 2 control groups each received the vehicle. The HCTZ susp. was formulated to deliver 3.1 mg/kg.

In-life observations included daily examinations for mortality/clinical signs, and food consumption/body weight on gestation days 0, 7, 10, 14, 20, 24 and 29. One control group (Group 2) and drug treated rabbits received physiologic saline instead of tap water during dosing period because, according to drug sponsor, the potentially **lethal hypotensive** effect of this class of drugs in pregnant of rabbits. Food/water were monitored for contaminants, and maintained within the lab acceptable limits.

All dams were sacrificed on day 29 of pregnancy, and major viscera of all rabbits were examined grossly (including those of 1 found dead on gestation day 18).

Reproductive parameters recorded included combined weight of uterus/placenta/ovaries/oviducts for pregnant-full term rabbits, the numbers of corpora lutea/resorption/implantation sites, dead/live fetuses, fetal weights/sex ratios. Following gross assessment, saved fetuses were cleared in potassium hydroxide and stained with alizarin red S for skeletal examinations.

Statistical evaluation was conducted on the above listed parameters (i.e., body weight, food consumption, fetal weight, fetal observations, etc.) to detect differences between vehicle control groups and individual drug dose groups and Group 2 control. References to and explanation of the statistical methods used was provided in the NDA submission.

RESULTS

Drug sponsor reported some dosing errors but in the opinion of drug sponsor, did not affect the quality or integrity of the study.

Rabbit Maternal Observations

Mortality/Clinical Signs/Necropsy: One MD doe died on gestation day 18; signs before death included decreased stool and body weight/food consumption during the dosing period. The cause of death was described as possibly related intraanimal sensitivity to this class of antihypertensive agents.

The incidence of clinical observations noted prior to death and mortality are listed in the table below summarized by drug sponsor.

CGP 63172: AN ORAL TERATOLOGY (SEGMENT II) STUDY IN RABBITS (MIN 944117)

7.1. Incidence of maternal mortality and clinical observations

Observations	Dose Level (mg/kg/day)					
	Control #1 (0)	Control #2 (0)	0.0:3.1	1.0:0.3	3.0:0.9	10.0:3.1
Stool						
decreased	3/20	7/20	5/20	4/20	4/20	5/20
soft	1/20	2/20	1/20	1/20	1/20	0/20
no stool	0/20	1/20	0/20	0/20	0/20	0/20
Blood in pan	0/20	0/20	1/20	1/20	2/20	1/20
Alopecia	4/20	1/20	3/20	3/20	4/20	1/20
Death	0/20	0/20	0/20	0/20	1/20[a]	0/20

[a]Animal #72 was found dead on day 18 of gestation.

Group mean data of the gestational parameters and fetal sex ratio are summarized below in table provided by drug sponsor.

CGP 63172: AN ORAL TERATOLOGY (SEGMENT II) STUDY IN RABBITS (MIN 944117)

Summary of reproductive parameters

(Mean ± Standard Deviation)

Parameter	Dose Level (mg/kg/day) Control #1 (0)	Control #2 (0)	0.0:3.1	1.0:0.3	3.0:0.9	10.0:3.1
Corpora lutea	12.21 ± 1.96 (19)	12.28 ± 2.42 (18)	11.67 ± 2.40 (18)	12.28 ± 2.19 (18)	11.56 ± 2.73 (18)	11.44 ± 2.18 (18)
Implantation sites	9.26 ± 2.33 (19)	8.94 ± 2.71 (18)	8.78 ± 2.44 (18)	9.33 ± 2.17 (18)	8.83 ± 2.71 (18)	8.72 ± 1.78 (18)
Early resorptions	0.47 ± 0.70 (19)	0.33 ± 0.84 (18)	0.50 ± 0.79 (18)	0.22 ± 0.43 (18)	0.50 ± 0.79 (18)	0.39 ± 0.61 (18)
Late resorptions	0.16 ± 0.50 (19)	0.00 ± 0.00 (18)	0.11 ± 0.47 (18)	0.56 ± 2.36 (18)	0.22 ± 0.55* (18)	0.94 ± 1.70** (18)
Total resorptions	0.63 ± 0.76 (19)	0.33 ± 0.84 (18)	0.61 ± 0.98 (18)	0.78 ± 2.34 (18)	0.72 ± 0.89 (18)	1.33 ± 1.91* (18)
Live fetuses	8.63 ± 2.31 (19)	8.61 ± 2.85 (18)	8.17 ± 2.33 (18)	8.56 ± 3.11 (18)	8.11 ± 2.54 (18)	7.39 ± 1.61* (18)
Dead fetuses	0.00 ± 0.00 (19)	0.00 ± 0.00 (18)	0.00 ± 0.00 (18)	0.00 ± 0.00 (18)	0.00 ± 0.00 (18)	0.00 ± 0.00 (18)
Postimplantation loss	0.63 ± 0.76 (19)	0.33 ± 0.84 (18)	0.61 ± 0.98 (18)	0.78 ± 2.34 (18)	0.72 ± 0.89 (18)	1.33 ± 1.91** (18)
% postimplantation loss	6.92 ± 8.45 (19)	3.95 ± 10.81 (18)	6.32 ± 10.41 (18)	8.26 ± 23.51 (18)	7.70 ± 8.82* (18)	13.48 ± 17.99** (18)
Fetal sex ratio (% males)	50.61	55.48	55.10	49.35	43.15	50.38

*Statistically different from control #2 ≤ 0.05.
**Statistically different from control #2 ≤ 0.01.

$P < 0.009$ vs Control #2 (saline drinking water)
$P < 0.05$ vs Control # 2 (saline " ")

Slight reductions in mean food consumption were reported in the CGP 63172 treated rabbits during the dosing period. Rabbits treated with the HD when compared to Group 2 control (saline for drinking water), showed statistically significant ($p<0.005$) increased numbers of late/total resorptions, postimplantation losses and decrease number of live fetuses. Drug sponsor considered that the elevated number of late resorptions was related to the one rabbit with 100% resorption; however, this effect in 1 rabbit was considered by the drug sponsor to be an incidental finding.

A number of cysts adjacent to the ovaries were noted; however these tissues were not saved.

The incidence of necropsy observations in the dams are reported below in table prepared by drug sponsor.

CGP 63172: AN ORAL TERATOLOGY (SEGMENT II) STUDY IN RABBITS (MIN 944117)

Incidence of necropsy observations

Observations	Dose Level (mg/kg/day)					
	Control #1 (0)	Control #2 (0)	0.0:3.1	1.0:0.3	3.0:0.9	10.0:3.1
Cyst(s) - adjacent to ovary	2/20	2/20	1/20	0/20	2/20	2/20
Uterus - twisted and engorged w/blood	0/20	0/20	0/20	1/20	0/20	0/20

♦ **Rabbit Embryo/Fetal Observations :**

Fetal body weight was not affected by maternal treatment with the CGP 63172 or hydrochlorothiazide alone.

No treatment related effects were observed during fetal gross, visceral or skeletal examinations. Fetus from the HD groups showed an increased incidence of incomplete ossification of the os pubis; this skeletal variation was considered an isolated/minor change by drug sponsor because it occurred in 2 fetus from separate litters.

Summary of rabbit fetal gross malformations and variations (by litter) are reported in the table below prepared by the drug sponsor.

CGP 63172: AN ORAL TERATOLOGY (SEGMENT II) STUDY IN RABBITS (MIN 944117)

Summary of fetal examinations
(by litter)

Type/Parameter	Control #1 (0)	Control #2 (0)	Dose Level (mg/kg/day) 0.0:3.1	1.0:0.3	3.0:0.9	10.0:3.1
GROSS VARIATIONS:						
Red lesion lower back	1	0	0	0	0	0
No. of Litters with Gross Variations:	1	0	0	0	0	0
No. of Litters Examined Grossly:	19	18	18	17	18	18
VISCERAL MALFORMATIONS:						
Brain - dilated ventricles	0	0	0	1	0	0
- hydrocephaly	0	1	1	0	0	2
Gallbladder - absent	0	0	0	1	0	0
Kidney - malpositioned	0	1	0	0	0	0
Microphthalmia	0	0	0	0	1	0
No. of Litters with Visceral Malformations:	0	2	1	2	1	2
No. of Litters Examined Viscerally:	19	18	18	17	18	18
VISCERAL VARIATIONS:						
Bladder - coagulated blood	2	1	0	0	1	0
Gallbladder - coagulated blood	0	2	2	0	1	0
- enlarged	0	1	0	1	1	1
- reduced	0	2	0	1	0	0
Kidney - irregular shape	0	1	0	0	0	0
- pale	1	0	0	0	0	0
- renal papilla short	0	0	0	0	1	1
Liver - irregular shape	0	0	0	0	1	0
Ovary - dark red	0	0	0	1	0	0
No. of Litters with Visceral Variations:	3	6	2	2	3	2
No. of Litters Examined Viscerally:	19	18	18	17	18	18
SKELETAL MALFORMATIONS:						
Centrum/vertebrae						
Fused	1	0	0	0	0	0
Misaligned	1	0	0	1	0	2
Ribs						
Fused	0	0	0	0	0	1
Misaligned	0	0	0	0	0	1
No. of Litters with Skeletal Malformations:	1	0	0	1	0	2
No. of Litters Examined Skeletally:	19	18	18	17	18	18
SKELETAL VARIATIONS:						
Skull						
Frontals - additional	0	0	0	1	0	1
Frontals - fused	0	0	1	0	0	0
Frontals - not completely ossified	0	1	0	0	1	0
Hyoid - bowed	7	3	6	4	4	6
Hyoid - irregular shape	2	1	0	0	0	1
Hyoid - localized thickening	0	0	0	0	1	0
Hyoid - not completely ossified	9	8	4	11	10	8
Nasals - additional	0	0	0	0	0	1
Nasals - fused	0	0	1	0	0	0
Parietals - not completely ossified	0	1	0	0	0	0
Centrum/vertebrae						
Additional	2	0	0	0	1	1
Agenesis	0	0	0	0	1	0
Bipartite	0	0	0	0	0	1
Irregular shape	0	0	0	0	0	1

The following synopsis of the rabbit definitive oral teratology study was prepared by the drug sponsor.

An oral teratology (Segment II) study in rabbits — MIN 944117

Study type/ species data	Compound ID/regimen	Site, investigators, Tox/Path no., date	Findings and/or comments
Segment II; New Zealand White rabbits; females - 20/group (approximately 2.7 to 4.3 kilograms) and approximately 6 months of age on gestation day 0.	CGP 63172, a 16:5 combination of CGP 48933 (Lot No. 800194) and hydrochlorothiazide (Batch 800188) administered by gavage, as suspensions in aqueous 3% corn starch at daily doses of 1.0:0.3, 3.0:0.9 or 10.0:3.1 mg/kg. A fourth group received HCT alone (daily dose of 3.1 mg/kg). These animals received 0.9% saline as drinking water during the dosing period. Two additional groups received 3% corn starch and served as controls, one receiving tap water and the other 0.9% saline. All animals were artificially inseminated and received an equivalent dose volume of 5 ml/kg on gestation days 7 through 19. Necropsy was conducted upon early death or at terminal sacrifice on day 29 of gestation.	Ciba-Geigy Corporation Summit, New Jersey CL Smith and ET Yau T/P 95048 23 Oct 95	HCT alone: No effects. CGP 63172 ≥ 1.0:0.3 mg/kg: ↓ Food consumption. 3.0:0.9 mg/kg: Mortality in one female. 10.0:3.1 mg/kg: ↑ Late resorptions; ↑ total resorptions; ↑ mean and percent postimplantation loss; ↓ mean number of live fetuses.

3. **PHARMACOKINETICS** (V. 24)

The proposed tablet formulation for **Diovan HCTZ**™ contains 80:12.5 mg or 160:12.55 mg w/w combination of valsartan and HCTZ. The drug combination was given orally to rats or marmosets in repeat-doses studies lasting from 14 up to 6 months, and various pharmacokinetic parameters were examined for valsartan or HCTZ were reported.

All studies had a disclaimer that stated the "Contrary to the study protocol, these studies were conducted and reported in compliance with the "Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986" and not to the English GLP guidelines." For Study No. 1995/001 in marmosets, the plasma analysis was performed in France.

♦ **3.1. Rat** [Sprague Dawley derived Tif:RAIf (SPF) Albino]

♦ **3.1.1** Urinary Excretion of HCTZ in a **6-month** Toxicity Study with CGP 63172 (**Study No. 946116** summarized above under **TOXICOLOGY**.) Report BPK(CH) **1996/096** dated 01-29-97. V.24. p. 36)

The objective of this study was to evaluate the toxicity of the drug combination CGP 63172 in M/F rats treated daily repeated oral doses of controls 0, LD-39.37, MD-131.25 and HD-393.75 mg/kg/day for 26 weeks.

Urine samples were collected from 5M/5F of each group on 03-11-94 and on last day of dose on
27-04-95. Urinary concentrations of **HCTZ** were determined on day 1 and during week 26 (after the last dose). Mean conc. of HCTZ excreted within 0-24 hr at the start and end of the study appear in table below provided by drug sponsor.

RESULTS

The urine samples of controls animals were positive to small, but measurable amounts of HCTZ; this finding was not explicable by the investigators. Since drug sponsor stated that the amounts of HCTZ excreted in urine by LD F, and HD rats on day 1 were also inexplicable low, and no obvious errors in the determination were detected by investigators, no further evaluations of the urinary data for HCTZ were performed. A summary table with findings in this study appear below on following page.

Urinary Concentrations of Hydrochlorothiazide (Mean Values) Excreted Within 0-24 hr

Group no. (mg/kg)	Sex	Day 1 [µg]	Week 26 [µg]
1 (0)	Males	0.32±0.19	6.08±1.29
1 (0)	Females	0.46±0.10	3.04±0.59
2 (39.4)	Males	769.5±240.8	2724.3±1065.5
2 (39.4)	Females	0.99±0.81	1219.9±552.7
3 (131.3)	Males	3416.0±531.8	8183.3±5041.4
3 (131.3)	Females	3230.6±798.4	7078.3±3152.8
4 (393.8)	Males	2.57±1.92	19738.6±2337.8
4 (393.8)	Females	2.02±1.50	13297.8±2671.2

♦ 3.1.2 Plasma Concentration of **Valsartan** in Rats After Repeated Daily Oral Doses of CPG 63172 for 6 Months. (**Study No. 94-7907**; Report BPK(CH) **1996/156** dated 01-31-97 conducted on 08/09-11-94 and date of last treatment on 04/05-05-95- treatment day 178 of week 26. V.24.)

The objective of this study was to provide data on plasma concentration of **valsartan** in 21 M (362-426 g) and 21 F (235-282 g) rats (12 wks old) after repeated oral doses of CGP 63172 at 0, LD-39.375, MD-131.25 and HD-393.75 mg/kg/day for 7 days a week (corresponding to 30, 100 and 300 mg/kg **valsartan**). The drug combination was given at 24-hr intervals, as a suspension in 0.5% w/v aq. carboxymethylcellulose containing 0.5% v/v aq. polysorbate 80; vehicle was given to control rats.

Plasma samples were collected prior to dosing and 1, 2, 4, 8 and 24 hrs after dosing on days 1 and 178 (week 26) of treatment. Individual and mean plasma concentration of **valsartan*** in the rats were determined/reported in numerous tables by drug sponsor.

*The method of validation of **valsartan** in plasma was reported in the submission and consisted analyzing spiked human plasma samples with known amounts of valsartan (range of 0.15 to 12.9 µmol/L) analyzed 5 times on different days.

RESULTS

Briefly, drug sponsor submitted numerous tables reporting on various pharmacokinetic parameters of **valsartan** determined in this study. The table below was selected because it summarizes mean pharmacokinetic parameters of the drug at protocol required times.

Results reported indicate that there was no drug accumulation because the AUC values on days 1 and 178 were practically similar.

Data indicate that the absorption of **valsartan** from the drug combination was fast showing a T_{max} within 1 hr of dosing. C_{max} and $AUC_{0-24\ hr}$ tended to increase with the dose but not proportionally. C_{max} tended to be lower in week 26 when compared to day 1 of the study suggesting **no** accumulation of **valsartan**.

Drug sponsor reported that in this rat study there were no obvious sex differences in the pharmacokinetics of the drug.

The selected table and figure below (following page) summarize the findings in this pharmacokinetic study.

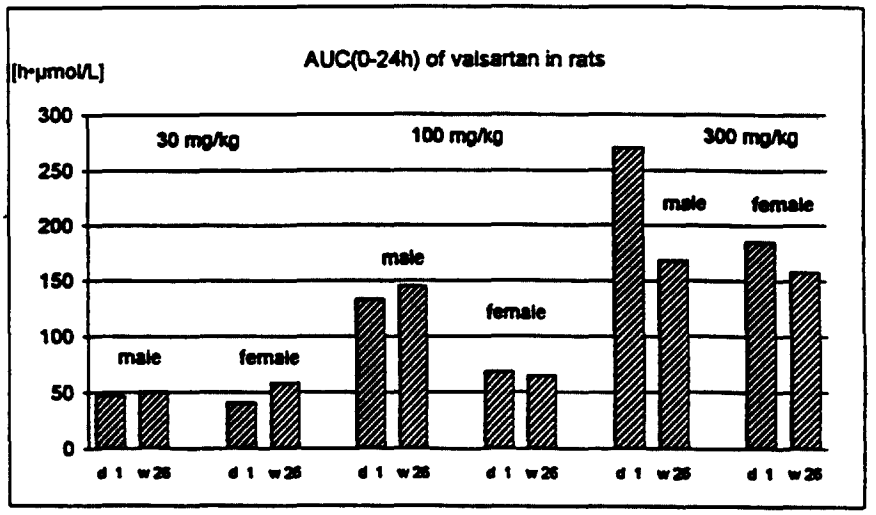
PHARMACOKINETIC PARAMETERS FOR VALSARTAN IN RATS ADMINISTERED THE DRUG COMBINATION DAILY FOR 6-MO BY ORAL ROUTE.

Dose of CGP 63172 (valsartan) [mg/kg]	Group	Sex	Date	tmax [h]	Cmax [µmol/L]	AUC(0-24h) [h·µmol/L]	R*
39.375	2	Male	Day 1	1	17.45	47.14	
(30)	2	Male	Week 26	1	8.58	50.41	1.07
39.375	2	Female	Day 1	1	11.03	41.06	
(30)	2	Female	Week 26	1	8.24	58.53	1.43
131.25	3	Male	Day 1	1	30.82	133.18	
(100)	3	Male	Week 26	1	22.35	145.01	1.09
131.25	3	Female	Day 1	1	17.41	68.14	
(100)	3	Female	Week 26	1	11.03	64.48	0.95
393.75	4	Male	Day 1	1	35.07	270.19	
(300)	4	Male	Week 26	1	16.45	168.10	0.62
393.75	4	Female	Day 1	1	35.99	185.25	
(300)	4	Female	Week 26	1	9.38	157.57	0.85

* R = accumulation factor: AUC(week 26) / AUC(day 1)

AUC(0-24h) of valsartan in male and female rats: all dose groups

Mean AUC(0-24h) in male and female rats after daily oral administration of 39.375, 131.25 and 393.75 mg/kg CGP 63172 (30, 100, and 300 mg/kg valsartan) on day 1 and in week 26. Each AUC(0-24h) is a mean of three concentration time profiles.



♦ **3.2 Marmoset** (Callithrix jacchus)

3.2.1 Marmosets Treated With Daily Oral Doses of **Valsartan** for 3 Months: Pharmacokinetic Profile of **Valsartan**. (**Study No. 94-7905**; Report BPK(CH) **1995/001** dated 03-02-95 and conducted between 21-04-94 and 27-07-94. Analyses of plasma samples were performed in drug sponsor's laboratories in Rueil-Malmaison, France from 08-09-94 to 03-11-94. V.24, p.161.)

The objective of this study was to determine the pharmacokinetic profile of **valsartan** when given to 30M/30F marmosets (~1-3 y at the start of the study and weighing ~ 250 g). The oral doses (gavage) at 0, LD-60, MD-1 120, MD-2 200, and HD-400 mg/kg/day for 3 months were suspended was suspended in 0.5% w/v carboxymethylcellulose and 0.1% Tween 80. Briefly, marmosets (singly or as single sex pairs) were acclimatized to experimental quarters (kept at ~ 23-27 ° C) for at least 1 wk prior to starting study. Artificial lighting was controlled to provide 12 hrs of lighting followed by 12 hrs of dim night lights. Tap water was available freely.

Blood samples were collected from 3 animals/sex/group at week 0 (day 1), during weeks 4 and 13 at 0.5, 2, 4, 8, 12 and hrs after treatment. Plasma **valsartan** concentrations were measured by a validated HPLC method. The limit of quantitation (L0Q) for valsartan was reported as 11.5 nmol/L.

RESULTS

Variability of plasma pharmacokinetic parameters examined from animal to animal was high, thus drug sponsor stated that proportionality could <u>not</u> be demonstrated. In most cases the absorption was fast, mean exposure to **valsartan** increased with increasing dose and no sex differences were noted.

Ratios of AUCs at different times were calculated (but no T ½) to estimate accumulation of the drug, and <u>no</u> accumulation of valsartan was noted after repeat administration of the drug for 3 months.

Although no clinical chemistry or histopathologic reports were provided, drug sponsor stated that there "was no correlation of plasma urea or creatinine concentration or minimal arteriolar hypertrophy with Cmax..." after 13 weeks of treatment with valsartan.

The calculated pharmacokinetic parameters for the marmosets treated orally with valsartan for 3-months. The tables were prepared by drug sponsor.

Valsartan pharmacokinetic parameters in male marmosets.

Dose (mg/kg)	Cmax (µmol/l)	Tmax (h)	AUC(0-24h) (µmol.h/l)	Normalised AUC (µmol.h/l)/(mg/kg)
Week 0				
60	20.8	0.5	116	1.97
120	37.0	0.5	198	1.800
200	35.5	4	264	1.32
400	79.4	4	517	1.29
Week 4				
60	18.7	0.5	60.0	1.00
120	27.5	0.5	120	1.00
200	33.0	4	207	1.04
400	46.5	4	448	1.12
Week 13				
60	11.8	4	64.3	1.07
120	41.8	0.5	184	1.53
200	84.8	0.5	387	1.94
400	97.9	0.5	630	1.58

Valsartan pharmacokinetic parameters in female marmosets.

Dose (mg/kg)	Cmax (µmol/l)	Tmax (h)	AUC(0-24h) (µmol.h/l)	Normalised AUC (µmol.h/l)/(mg/kg)
Week 0				
60	41.1	0.5	144	2.40
120	27.2	0.5	115	0.958
200	27.5	0.5	207	1.04
400	68.3	4	732	1.83
Week 4				
60	36.3	0.5	104	1.73
120	47.8	2	227	1.89
200	23.9	2	122	0.61
400	124	4	569	1.42
Week 13				
60	30.7	0.5	71.5	1.19
120	40.2	0.5	121	1.01
200	48.1	0.5	261	1.31
400	102	0.5	696	1.74

AUC ratio between periods.

	Dose (mg/kg)	Males	Females
$R1 = \frac{AUC(0-24\ h)\ Week\ 4}{AUC(0-24\ h)\ Week\ 0\ (day\ 1)}$	60	0.51	0.72
	120	1.11	1.97
	200	0.78	0.59
	400	0.87	0.78
$R2 = \frac{AUC(0-24\ h)\ Week\ 13}{AUC(0-24\ h)\ Week\ 0\ (day\ 1)}$	60	0.54	0.50
	120	1.70	1.05
	200	1.47	1.26
	400	1.22	0.95
$R3 = \frac{AUC(0-24\ h)\ Week\ 13}{AUC(0-24\ h)\ Week\ 4}$	60	1.07	0.69
	120	1.53	0.53
	200	1.87	2.14
	400	1.40	1.22

3.2.2 Fourteen (14)-day oral pharmacokinetic study: Plasma concentration and urinary excretion of **HCTZ** by marmosets. (Study **No. 94-7909**; Report BPK(CH) **1996/087** dated 20-12-96. No dates of treatments were reported. V.24, p.56.) #2

The objective of this study was to evaluate the oral (gavage) toxicity of HCTZ in marmosets in 21 M (14-45 mo, 310-451 g), and 21 F (21-48 mo., weighing 316-542 g) treated with daily doses of the diuretic at LD-100, MD-300 and HD-1000 mg/kg/day/14 days; the drug was suspended in 0.5% w/v Klucel HF (generic name not identified).

Plasma and urinary concentrations of **HCTZ** were determined on day 1 and on day 14 (after the last dose) using a validated gas chromatography assay. Urine samples were collected prior to dosing and at 4, 8, and 24 hr post dosing. Blood samples were taken from 3M/3F, according to schedule below in the table prepared by drug sponsor, prior to, and post dosing.

RESULTS

The drug sponsor provided numerous tables with individual concentrations of **HCTZ** in urine fractions collected at 4, 8 and 24 hrs after treatment. However, since there was large variability among the individual amounts of the drug excreted and no clear dose-dependency could be discerned, the cumulative urinary excretion (0-24 hr) could not be accurately determined by the investigators.

Plasma AUCs values for **HCTZ** reported for these marmosets appear in table below prepared by drug sponsor. The AUC values for F tended to be lower than in the M marmosets.

Only slight accumulation of **HCTZ** in blood was reported in some marmosets. Plasma AUC values for the diuretic in F were reported to be lower (10-50% ↓) than for the M.

Some urine samples from control animals contained HCTZ (this contamination was also reported in the rat studies). Drug sponsor stated that the cumulative urinary excretion (0-24 hr) could not be determined.

Dose [mg/kg]	Sex	AUC [(ng/mL)h] Day 1	AUC [(ng/mL)h] Day 14	R_A
100	M	25977	34182	1.32
100	F	21982	23700	1.08
300	M	41433	48577	1.17
300	F	37414	35730	0.96
1000	M	123666	126560	1.02
1000	F	63046	101661	1.61

* R_A = AUC(day 14) / AUC(day 1)

Dose proportions		AUC proportion day 1	AUC proportion day 14
1.0	Males	1	1
3.0		1 60	1 42
10.0		4 76	3 70
1.0	Females	1	1
3.0		1 70	1.51
10.0		2.87	4.29

♦ **3.2.3** Pharmacokinetics of a 6-month study in marmosets: Urinary Concentration of **HCTZ** after Repeated Daily Administration of CGP 63172. (Study No. 94-7908; Report BPK(CH) **1996/132** dated 20-12-96 conducted between 24-01-95 and 01-08-95 V.24, p 123.) #4

The objective of this study was to evaluate the urinary excretion of HCTZ when administered in the proposed drug combination to 10 M (264-468 g) and 10 F (288-470 g) marmosets (~1 to 1.8 years) after repeated gavage dosing of CGP 63172 of 0, 39.4, 78.8 and 157.5 mg/kg/day/6-mo as a suspension in a vehicle of 0.5% w/v aq. carboxymethylcellulose containing 0.5% v/v aq. polysorbate 80; control animals received the vehicle.

Urine samples were collected (over a 0-24 hr period) from marmosets on day 1 and week 25 of study. The samples were analyzed for **HCTZ** using a validated gas chromatographic method. Validation method was described in the submission. The LOQ was estimated at 50 ng/ml and the limit of detection at ~ 5 ng/ml.

RESULTS

Total amounts of **HCTZ** excreted and concentrations in urine were reported in the NDA as part of numerous and detailed tables prepared by drug sponsor for day 1 and during week 25. The table below (on following page), prepared by drug sponsor, was selected to show mean amounts of **HCTZ** excreted within 0-24 hrs at the start and at the end of the study.

The bar graphs (on following page) were also prepared by drug sponsor show the total (0-24 hrs) amounts of HCTZ excreted by M and F marmosets.

Again, the investigators were unable to explain the reason for the appearance of HCTZ in urine of control animals.

Results showed that the excretion of HCTZ increased with the dose and the increase was only proportional at the LD/MD of the combination. Again, the amounts of HCTZ were higher in urine of F than in that from the M marmosets.

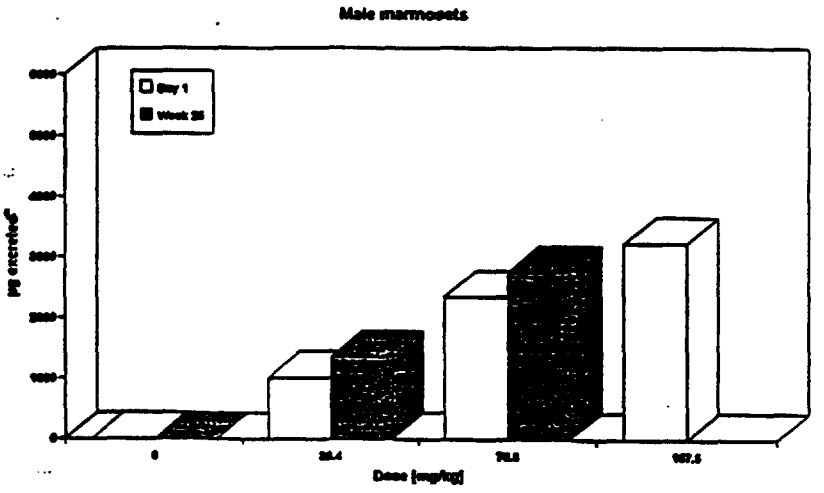
URINARY EXCRETION OF HCTZ: MARMOSETS TREATED ORALLY WITH CGP 63172 FOR SIX MONTHS.
(Study BPK(CH) 1996/132/Protocol 947908)

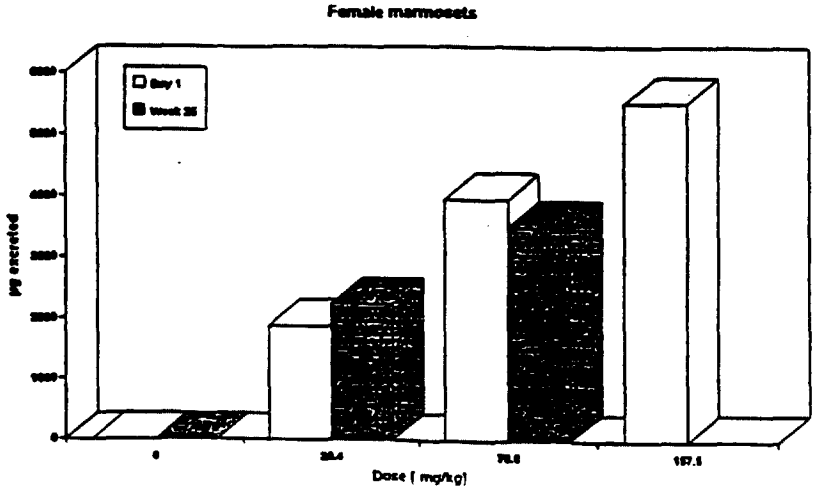
Group no. (mg/kg)	Sex	Day 1 [µg]	Week 25 [µg]
1 (0)	Males	2.03±1.27	0.67±0.17
1 (0)	Females	1.46±0.11	1.10±0.38
2 (39.4)	Males	1013.0±374.2	1358.0±399.4
2 (39.4)	Females	1871.2±371.5	2247.3±391.2
3 (78.8)	Males	2351.2±1345.1	2763.3±1978.9
3 (78.8)	Females	3954.7±1310.2	3511.6±727.7
4 (157.5)	Males	3234.0±1260.9	#
4 (157.5)	Females	5511.1±1794.4	#

(# no samples, all animals died)

Mean amounts of HCTZ excreted

Bar graph of total 0-24 h amounts of HCTZ excreted by male and female marmosets treated with daily oral doses of CGP 63172.





Again, the investigators were unable to explain the reason for the appearance of HCTZ in urine of control animals.

Results showed that the excretion of HCTZ increased with the dose and the increase was only proportional at the LD/MD of the combination. Again, the amounts of HCTZ were higher in urine of F than in that from the M marmosets.

♦ **3.2.4** Six-Month Oral Pharmacokinetics Study in Marmosets Treated with CGP 63172: Plasma Concentrations of Valsartan (Study No. **96-9003**; Report BPK(CH) **1996/136** dated 23-01-97 started with M on 24-02-96 and studies terminated on 12/09-96. V.24, p 140). #5

The objective of this study was to evaluate the pharmacokinetics of valsartan given the drug combination by gavage to groups of M and F marmosets (weighing M 305-502 g and F 321-497 g, and of ~26-33 months of age at the start of the study). Controls received 0 (the vehicle) and LD-3.938, MD-13.125 and 39.375 mg/kg/day/6 months (corresponding to ~ LD-3, MD-10 and HD-30 mg/kg valsartan, respectively) as a suspension in a vehicle of 0.5% w/v aq. carboxymethylcellulose containing 0.5% v/v aq. polysorbate 80.

Briefly, blood samples were collected from marmosets on day 1 and week 26 immediately prior to dosing, and at various time intervals (ranging from 1 up to 24 hrs).

The samples were analyzed for **valsartan** using a validated HPLC method. Validation method was described in the submission. The LOQ was 0.08 μmol/L and the limit of detection at 0.01 μmol/L.

RESULTS

Briefly, the data reported indicate that all marmosets were systemically exposed to **valsartan** after repeated once a day oral administration of the drug combination **CGP 63172** at doses ranging from 3.9 up to 39 mg/kg. Both C_{max} and $AUC_{0-24\ hr}$ increases appeared to proportional to the dose, and decreased during repeated daily dosing (as reported in previous studies). By week 26 the C_{max} and AUC values at all doses had ~60% when compared to day 1 values. Drug sponsor asserted that similar effect was seen in an earlier study in the marmoset with valsartan alone and affirmed that this decrease was not likely to be an effect of the coadministration of **HCTZ**. No obvious difference the pharmacokinetic parameters were noted in the present study between M and F marmosets.

The tables below (following page) were selected from numerous tables provided by drug sponsor comparing the Cmax and AUC 0-24 hr of the mean concentration-time curves in M and F marmosets of the higher doses vs lower dose groups on day 1 and wk 26 after daily doses of the drug combination corresponding to 3, 10 and 30 mg/kg/day of **valsartan**.

MARMOSETS TREATED ORALLY WITH CGP 63172 FOR SIX MONTHS: INFLUENCE OF DOSE or REPEATED DOSING PLASMA PHARMACOKINETICS OF VALSARTAN (Study BPK(CH) 1996/136/Protocol 969003)

Influence of dose on pharmacokinetics

Dose [mg/kg]	Day (week)	Animal* sex	C_{max} [µmo/L]	AUC(0-24h)† [h·µmo/L]	Ratio of 10 mg/kg vs 3 mg/kg group C_{max}	Ratio of 10 mg/kg vs 3 mg/kg group AUC	Ratio of 30 mg/kg vs 3 mg/kg group C_{max}	Ratio of 30 mg/kg vs 3 mg/kg group AUC
3	1	M	2.76	9.54				
		F	1.22	4.31				
10		M	9.91	35.19	3.6	3.7		
		F	5.50	19.45	4.5	4.5		
30		M	29.03	97.07			10.5	10.2
		F	16.72	64.66			13.7	15.0
3	(26)	M	2.22	5.14				
		F	0.67	2.17				
10		M	3.60	15.09	1.6	2.9		
		F	4.07	14.20	6.0	6.5		
30		M	9.22	39.21			4.2	7.6
		F	10.35	39.04			15.4	18.0
Mean	both time	M+F			3.9	4.4	10.9	12.7
SEM	points				0.9	0.8	2.5	2.3

* 2-3 animals per sex and time point

† equal to AUC in Week 26 (steady-state conditions)

Influence of repeated dosing on pharmacokinetics

Day (Week)	Dose [mg/kg]	Animal* sex	C_{max} [µmo/L]	AUC(0-24h)† [h·µmo/L]	Ratio Week 26 vs Day 1 C_{max}	Ratio Week 26 vs Day 1 AUC*
1	3	M	2.76	9.54		
		F	1.22	4.31		
	10	M	9.91	35.19		
		F	5.50	19.45		
	30	M	29.03	97.07		
		F	16.72	64.66		
(26)	3	M	2.22	5.14	0.80	0.54
		F	0.67	2.17	0.55	0.50
	10	M	3.60	15.09	0.36	0.43
		F	4.07	14.20	0.74	0.73
	30	M	9.22	39.21	0.32	0.40
		F	10.35	39.04	0.62	0.60
Mean	3-30	M+F			0.57	0.53
SEM					0.08	0.05

* 2-3 animals per sex and time point

† equal to AUC in Week 26 (steady-state conditions)

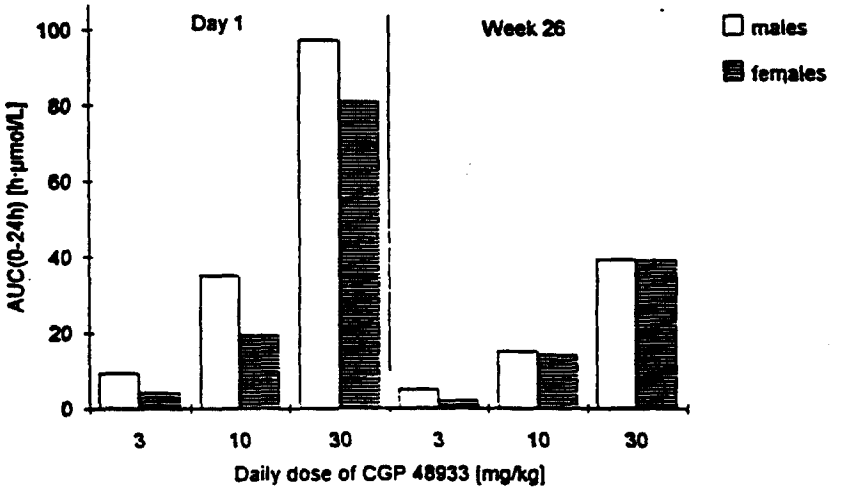
MARMOSETS TREATED ORALLY WITH CGP 63172 FOR SIX MONTHS: INFLUENCE OF GENDER ON PLASMA PHARMACOKINETICS OF VALSARTAN (Study BPK(CH) 1996/136/Protocol 969003)

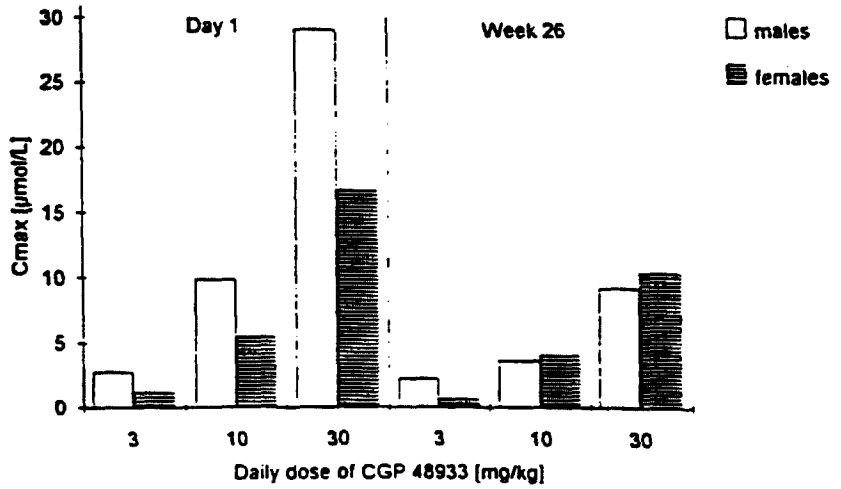
Influence of sex on pharmacokinetics

Day (Week)	Dose [mg/kg]	Ratio males vs females C_{max}	Ratio males vs females AUC(0-24h)*
1	3	2.27	2.21
1	10	1.80	1.81
1	30	1.74	1.50
(26)	3	3.30	2.37
(26)	10	0.88	1.06
(26)	30	0.89	1.00
Mean		1.81	1.66
SEM		0.37	0.23

* Equal to AUC at Week 26 (steady-state conditions)

Effect of sex, dose and repeated administration on pharmacokinetics





♦ 3.2.5 Oral Pharmacokinetics of a 6-month Study in Marmosets: Urinary Excretion of HCTZ Given in CGP 63172.
(Study No. 964-9003; Report BPK(CH) **1996/154** dated 30-01-97 conducted between 28-02-96 and 05/09-96 V.24, p.216) #6

The objective of this study was to evaluate the urinary excretion of HCTZ by marmosets when given in the proposed drug combination CGP 63172 to 10 M/10 F (≈ 250 g; ≈1 to 1.98 years) by gavage at 0, LD-3.938, MD-13.125 and HD-39.375 mg/kg/day/6-mo, suspended in 0.5% w/v aq. carboxymethylcellulose containing 0.5% v/v aq. polysorbate 80; vehicle was given to control marmosets.

Urine samples were collected from 3 marmosets/sex from control and up to 6/sex from drug treatment groups on day 1 and week 26 of the study for a collection period of 0-24 hr.

The volume of samples collected for the analysis were recorded and samples stored at 18° C until analyzed for HCTZ using a validated gas chromatographic method. Validation method was described in the submission, and the LOQ was estimated at 50 ng/ml with a limit of detection of ≈ 5 ng/ml.

RESULTS

Individual concentrations and amounts of **HCTZ** in urine after oral treatment with doses of the drug combination CGP 63172 were reported for each animal in numerous and detailed tables in the NDA. For brevity, a table was selected that shows mean amounts of **HCTZ** excreted in urine are presented below in table submitted by drug sponsor.

Briefly, the data show that all marmosets were exposed to HCTZ after once daily oral administration of CGP 63172 for 6 months as evidenced by the excretion of the diuretic. Again, as in previous reports, the drug sponsor had no explanation for the appearance of HCTZ in the urine of 2 controls marmosets.

In the drug treated marmosets, the exposure to **HCTZ** appeared proportional to the dose, and there was a proportional increased in the excretion of HCTZ except for M by week 26. As previously reported, no sex-dependent effects on the systemic exposure of the drug were reported.

Group no. (mg/kg)	Sex	Day 1 [µg]	Week 26 [µg]
1 (0)	Males	0.24±0.41	blq
1 (0)	Females	blq	0.11±0.19
2 (3.938)	Males	133.77±42.46	290.44±133.24
2 (3.938)	Females	128.71±15.69	213.97±102.37
3 (13.125)	Males	413.61±155.04	657.02±108.80
3 (13.125)	Females	536.53±072.54	395.00±127.02
4 (39.375)	Males	1414.59±428.61	2320.70±703.22
4 (39.375)	Females	1196.77±407.03	1261.77±591.44

blq : below limit of quantitation

♦ 3.2.6 Pharmacokinetics Study with Marmosets Treated Orally with **Valsartan** (CGP 48933) for 6 months. (Study No. 94-7908; Report BPK(CH) **1996/155** dated 23-01-97 conducted between 20-03-96 and 24-08-95. V.24, p.90). #7

The objective of this study was to evaluate the pharmacokinetics of **valsartan** given in the proposed drug combination to 3M (264-468 g) and 3F (288-470 g) marmosets (~1 to 1.8 y). Animals were treated with CGP 63172 at 0 (vehicle), and at higher doses than tested before LD-39.4, MD-78.8 and HD-157.5 mg/kg/day/gavaged for 6-mo given as a susp. as previously described.

Briefly, blood samples were collected at protocol designated time intervals from the animals from all treatment groups following various different schedules, on day 1 and during week 26 of the study, immediately prior to/postdosing at various time intervals ranging from 1 up to 24 hrs. All marmosets in the HD group were killed on 17-03-95 after being on the study for 1 months because of "severity of signs" seen in this group. (There was **no** report on what the severe signs were.)

The blood samples were analyzed for **valsartan** using a validated HPLC method; the validation method was described. The LOQ was 0.08 μmol/L and the limit of detection at 0.01 μmol/L.

RESULTS

Briefly, the data reported indicate show that all marmosets were exposed to **valsartan** after repeated once a day oral administration of the drug combination CGP 63172. As in previous studies with marmosets, both Cmax and AUC for valsartan increased appeared to be less than proportional to the dose and decreased during repeated daily dosing as reported in previous studies; by week 26 the AUC values for the MD/HD animals had dropped between 16 and 51% vs day 1 of study. Due to large variability, no obvious difference between M and F marmosets in Cmax and AUC could be detected.

Pharmacokinetic parameters calculated from mean plasma concentrations of valsartan collected from marmosets appear below in table prepared by drug sponsor.

One remarkable finding reported- "None of the plasma samples of the controls animals contained measureable concentrations of valsartan." **Pharmacokinetic parameters**

Dose [mg/kg]	Animal Sex	Day 1 C_{max}	Day 1 t_{max}	Day 1 AUC	Week 26# C_{max}	Week 26# t_{max}	Week 26# AUC	R
39.375	M	20.43	1	67.68	10.46	1	48.48	0.72
	F	25.03	1	70.80	10.74	1	34.95	0.49
78.75	M	43.16	1	114.45	11.49	1	87.16	0.76
	F	18.19	2	119.86	14.24	2	70.06	0.58
157.5	M	56.39	1	172.33	14.68	2	*154.36	0.90
	F	30.57	2	235.91	**29.40	2	*96.64	0.41

C_{max}: [μmol/L]; t_{max}: hours; AUC: [(μmol/L)h]
highest dose group, males 31 days, females 29 days;
* AUC(1-24h);
** without high 8h Cmax value (considered an outlyer)

♦ **3.3 Human**: Normal Volunteers Bioavailability Studies.

Reports state that monotherapy with **valsartan** has been shown to be both safe/effective in the treatment of hypertension, however; some patients may require the added antihypertensive effect of a diuretic. Drug sponsor asserts that a fixed combination of these two approved/marketed drugs into one formulation will simplify the combined treatment with both drugs.

Briefly, reports from the literature submitted on the human (healthy volunteers) pharmacokinetics of **HCTZ** and **valsartan,**

Using **iv** ^{14}C-labeled drug, ~90-93% of the dose is recovered within 12 hr of dosing (in feces up to ~4%). Circulating **HCTZ** is reported bound serum proteins (mainly to albumin) in the range of 40-70%

For **valsartan**, the oral absorption of valsartan is highly variable (mean bioavailability of ~23% from capsule relative to an iv dose). Mean systemic availability may be reduced with a high fat meal resulting in ~ 59% decrease in CGP 63172 C_{max} and ~48% in AUC values; however, the response is less marked, and valsartan may be given with or without food.

Valsartan undergoes little in the way of metabolic conversion(81% is excreted unchanged and the remainder as metabolites and unidentified compounds). A minor metabolite (9% of administered drug is excreted as metabolites) is valeryl-4-hydroxy valsartan which is reported as having a ~200 X lower affinity with the angiotensin II receptor than valsartan, the parent compound. Circulating valsartan is bound 94-97% to serum proteins (mainly albumin); there is minimal binding to erythrocytes.

Using **oral** ^{14}C-labeled drug, ~96% of the dose is recovered within 72 hr of dosing (mostly in feces and a smaller fraction in urine). **Valsartan** undergoes little in the way of metabolic conversion

For **HCTZ**, the oral absorption is rapid (T_{max} is ~2 hrs), distribution and elimination kinetics have been described by a bi-exponential decay function with T½ 6-15 hr. The absolute bioavailability is within 60-80% with >95% of the absorbed dose excreted in urine unchanged and ~ 4% as the metabolite 2-amino-4-chloro-m-benzenedisulfonamide with food having no remarkable impact on the pharmacokinetics of **HCTZ.** Absolute bioavailability is reduced by ~30% when co-administered with valsartan*, but the kinetics of valsartan are not markedly affected by the co-administration of HCTZ. However, drug sponsor asserts that this observed interaction "has no impact on the combined use of valsartan and HCTZ" because controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either drug given alone.

* The structurally related losartan (an angiotensin II antagonist) also reduced the availability of HCTZ by ~17%; but this effect is clearly less marked.

The tables below prepared by drug sponsor, show that the mean $AUC_{0 \text{ to } 24}$ and C_{max} of **valsartan** when administered alone vs in combination with **HCTZ**. The drug combination slightly reduced these two last mentioned parameters plus T_{max} but increased the plasma T ½ and the amount of HCTZ excreted in the urine, drug sponsor forwarded no hypothesis to explain the observed interaction.

Valsartan AUC, Cmax, tmax and t½ after administration of 160 mg valsartan and 160 mg valsartan together with 25 mg HCTZ (in free combination)

valsartan kinetics Mean ± SD (n=12)	valsartan alone	HCTZ + valsartan	confidence interval (90%)
AUC(0-∞) - h.mg/L	24.25±9.63	21.14±9.69	0.72-1.04
Cmax - mg/L	3.32±0.99	2.78±1.01	0.63-1.05
tmax - h (median)	2.0	2.5	
t½ elimination - h	6.59±0.64	6.47±3.14	

HCTZ AUC, Cmax, tmax, t½ and the amount excreted in the urine (Ae), after administration of 25 mg HCTZ and 25 mg HCTZ together with 160 mg valsartan (in free combination)

HCTZ kinetics Mean ± SD (n=12)	HCTZ alone	HCTZ + valsartan	confidence interval (90%)
AUC(0-∞) - h.mg/L	1.10±0.27	0.79±0.27	0.56-0.85
Cmax - mg/L	0.14±0.04	0.10±0.03	0.61-0.91
tmax - h (median)	2.3	2.0	
t½ elimination - h	12.4±4.1	8.1±1.7	
Ae (24 h) - %dose	63±15	54±14	0.73-1.02

In drug interaction studies, it was reported that oxidative metabolic clearance of both drugs has only a minor role, therefore the drug sponsor considered drug-drug interaction via metabolic induction or inhibition of the cytochrome P450 system is not expected.

As stated before, valsartan is bound ≈94-97% to serum proteins and HCTZ is not highly bound to serum proteins (≈40-70%). Although this could be considered a potential source of drug-drug interaction, in vitro studies showed no interaction of valsartan with a range of compounds (e.g., warfarin, furosemide).

Since preclinical studies had indicated a low potential for drug-drug interactions at the kinetic level, single doses of each of the drugs and in combinations were administered to healthy volunteers in a 3-way crossover study to detect a gross effect of the concomitant medication on the pharmacokinetics of valsartan and no interaction with HCTZ on the pharmacokinetics of valsartan was noted. However, with drug combination the HCTZ pharmacokinetic values determined were reduced; the mean AUC_{0-24h} (↓22%), C_{max} (↓26%) and t½ (↓ 31%) as well as the amount of HCTZ excreted in the urine

(↓≈15%). The drug sponsor stated that no one hypothesis (e.g., slight reduction in the amount absorbed; slight increase in plasma clearance) could be forwarded to explain the observed interaction, and reported that a structurally related AII antagonist losartan also reduces the availability of HCTZ but to a less marked effect.

As for bioequivalence clinical trials (Protocols 302 with 160/12.5 mg valsartan/HCTZ and Protocols 303 with 80/12.5 mg, respectively of the 2 drugs at different ratios) with the two formulations of the proposed drug combinations in capsules were compared with single oral doses of valsartan and HCTZ (commercially available as a tablet) formulated also as capsules for this study. In the summary tables submitted with results of the study, based on the pharmacokinetic parameters reported, the fixed combination tablets can be considered bioequivalent.

Valsartan pharmacokinetic parameters for the fixed combination tablet (valsartan:12.5 mg HCTZ, FMI) and the free combination [Protocols 302 (160 mg valsartan) and 303 (80 mg valsartan)]. * - median value, ** - 90% confidence interval for log transformed data with the free combination capsules as reference material.

Protocol 302 Mean ± SD, (n=50-52)	AUC (0-48) (h.mg/L)	Cmax (mg/L)	tmax * (h)
1x160 mg free capsule	20.5 ± 10.0	3.29 ± 1.80	3.0
1x160 mg FMI tablet 90% CI vs capsule**	22.4 ± 11.4 1.04 - 1.24	3.60 ± 1.83 0.99 - 1.24	3.0

Protocol 303 Mean ± SD, (n=51-54)	AUC (0-48) (h.mg/L)	Cmax (mg/L)	tmax * (h)
1x80 mg free capsule	9.39 ± 4.8	1.45 ± 0.8	2.5
1x80 mg FMI tablet 90% CI vs capsule**	10.6 ± 5.2 0.91 - 1.12	1.64 ± 0.8 0.87 - 1.12	3.0

HCTZ pharmacokinetic parameters for the fixed combination tablet (valsartan:12.5 mg HCTZ, FMI) and the free combination [Protocols 302 (160 mg valsartan) and 303 (80 mg valsartan)]. * - median value, ** - 90% confidence interval for log transformed data with the free combination capsules as reference material.

Protocol 302 Mean ± SD, (n=50-52)	AUC (0-48) (h.ng/mL)	Cmax (ng/mL)	tmax * (h)
1x12.5 mg free capsule	483 ± 87	69 ± 14	1.8
1x12.5 mg FMI tablet 90% CI vs capsule**	482 ± 93 0.96 - 1.04	69 ± 20 0.96 - 1.07	1.5

Protocol 303 Mean ± SD, (n=51-54)	AUC (0-48) (h.ng/mL)	Cmax (ng/mL)	tmax * (h)
1x12.5 mg free capsule	467 ± 14	72 ± 20	2.0
1x12.5 mg FMI tablet 90% CI vs capsule**	451 ± 118 0.92 - 1.00	69 ± 21 0.86 - 0.96	1.5

Since preclinical studies had indicated a low potential for drug-drug interactions at the kinetic level, single doses of each of the drugs and in combinations were administered to healthy volunteers in a 3-way crossover study to detect a gross effect of the concomitant medication on the pharmacokinetics of valsartan and no interaction with HCTZ on the pharmacokinetics of valsartan was noted. However, with drug combination the HCTZ pharmacokinetic values determined were reduced; the mean AUC_{0-24h} (↓22%), C_{max} (↓26%) and $t_{½}$ (↓ 31%) as well as the amount of HCTZ excreted in the urine (↓~15%). The drug sponsor stated that no one hypothesis (e.g., slight reduction in the amount absorbed; slight increase in plasma clearance) could be forwarded to explain the observed interaction, and reported that a structurally related AII antagonist losartan also reduces the availability of HCTZ but to a less marked effect.

As for bioequivalence clinical trials (Protocols 302 with 160/12.5 mg valsartan/HCTZ and Protocols 303 with 80/12.5 mg, respectively of the 2 drugs at different ratios) with the two formulations of the proposed drug combinations in capsules were compared with single oral doses of valsartan and HCTZ (commercially available as a tablet) formulated also as capsules for this study. In the summary tables submitted with results of the study, based on the pharmacokinetic parameters reported, the fixed combination tablets can be considered bioequivalent.

artan pharmacokinetic parameters for the fixed combination tabl
artan:12.5 mg HCTZ, FMI) and the free combination [Protocols 302 (160 n
alsartan) and 303 (80 mg valsartan)]. * - median value, ** - 90% confidence interv
for log transformed data with the free combination capsules as reference material.

Protocol 302 Mean ± SD. (n=50-52)	AUC (0-48) (h.mg/L)	Cmax (mg/L)	tmax * (h)
1x160 mg free capsule	20.5 ± 10.0	3.29 ± 1.80	3.0
1x160 mg FMI tablet	22.4 ± 11.4	3.60 ± 1.83	3.0
90% CI vs capsule**	1.04 - 1.24	0.99 - 1.24	

Protocol 303 Mean ± SD. (n=51-54)	AUC (0-48) (h.mg/L)	Cmax (mg/L)	tmax * (h)
1x80 mg free capsule	9.39 ± 4.8	1.45 ± 0.8	2.5
1x80 mg FMI tablet	10.6 ± 5.2	1.84 ± 0.8	3.0
90% CI vs capsule**	0.91 - 1.12	0.87 - 1.12	

HCTZ pharmacokinetic parameters for the fixed combination tablet (valsartan:12.5 m
HCTZ, FMI) and the free combination [Protocols 302 (160 mg valsartan) and 30
(80 mg valsartan)]. * - median value, ** - 90% confidence interval for log transforme
data with the free combination capsules as reference material.

Protocol 302 Mean ± SD. (n=50-52)	AUC (0-48) (h.ng/mL)	Cmax (ng/mL)	tmax * (h)
1x12.5 mg free capsule	483 ± 87	69 ± 14	1.8
1x12.5 mg FMI tablet	482 ± 93	69 ± 20	1.5
90% CI vs capsule**	0.96 - 1.04	0.96 - 1.07	

Protocol 303 Mean ± SD. (n=51-54)	AUC (0-48) (h.ng/mL)	Cmax (ng/mL)	tmax * (h)
1x12.5 mg free capsule	467 ± 14	72 ± 20	2.0
1x12.5 mg FMI tablet	451 ± 118	69 ± 21	1.5
90% CI vs capsule**	0.92 - 1.00	0.86 - 0.96	

LABELING (V. 1)

Diovan HCT oral tablets are formulated in a combination of 80 mg or 160 mg of valsartan, and 12.5 mg HCTZ. The proposed label under the section **DOSAGE AND ADMINISTRATION** and subsection **Dose titration by Clinical Effects** states on Lines 894-900 that **"The usual dose of Diovan HCT is one tablet once daily. Doses higher than valsartan 160 mg/hydrochlorothiazide 25 mg have not been studied. The maximal antihypertensive effect is attained about 4 weeks after initiation therapy."** From this statement reviewer considers that the maximum human recommended dose (**MHRD**) for Diovan HCT would be two tablets of the valsatan 80 mg + HCTZ 12.5 mg formulation (or a total dose of 160 mg valsartan + 25 mg HCTZ). Reviewer has used this last mentioned **MHRD** assuming a 60 kg patient to calculate the animal developmental doses multiples.

The drug sponsor contends that the need for the proposed drug combination formulation is for the convenience of taking both drug ingredients in one formulation and thus control compliance.

The following minor changes are recommended for the text of the proposed label:

1.- Under the section **WARNINGS**/subsection **Valsartan-Hydrochlorothiazide**, the doses of the drug ingredients showing no evidence of teratogenicity in mice, rat or rabbits be changed based on our evaluation of the nonclinical studies, starting on line 342, to read "....at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 188, 31 and 3 mg/kg/day. These non-teratogenic doses in mice, rats and rabbits, respectively, represent approximately 18, 7 and 2 times the maximum recommended human dose (MRHD) of valsartan and approximately 36, 14 and 3 times the MRHD of hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 160 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)"

2. Under the section **PRECAUTIONS**:/subsection **Carcinogenesis, Mutagenesis, Impairment of Fertility** please insert on line 627 the words "drug" and "adverse" the word "interaction".

3. Under the section **OVERDOSAGE** /subsections **Valsartan and Hydrochlorothiazide**, delete lines 840 to 846 and lines 848 to 852.

EVALUATION:

Diovan HCT™ (CGP 63172) is a fixed dose drug combination of two orally active and approved drugs formulated as film-coated tablets proposed by Novartis* for management of hypertension.

The absence of clear guidance on what studies are necessary for the approval of a drug combination of previously marketed drug ingredients in the proposed combination, allows drug firms the flexibility to conduct limited number of nonclinical studies.

An in-house report** available to pharmacologists states that a review of FDA files have shown that the types of pharmacologic/toxicologic studies supporting approval of a drug combination have frequently dictated by the approval status of the individual drugs and the therapeutic indication. Further that "approvals where possible toxicological interaction" or an adverse effect was anticipated, "[nonclinical] studies would have been conducted on the combination to support safety [in humans]" of the pharmaceutical.

The proposed drug combination CGP 63172 will contain the nonpeptide and specific angiotensin II (AII) receptor antagonists **valsartan** (CGP 48933; an S-enantiomer*** marketed as 80 or 160 mg capsules), and thiazide-type diuretic that acts on the renal convoluted tubule distal to the macula densa **hydrochlorothiazide (HCTZ;** marketed as 25 or 100 mg tablets). Each of these drugs are indicated in the management of hypertension. The CGP 63172 finished formulation (Diovan HCT 80 mg/12.5 and 160 mg/12.5 tablets, respectively, of **valsartan/HCTZ**) will be manufactured in Switzerland (valsartan chemically manufactured in Switzerland and HCTZ in Croatia).

Although in the management of hypertension, monotherapy with valsartan is considered safe/effective, drug sponsor affirms that some patients may require the added antihypertensive effect of a diuretic, and asserts that CGP 63172 is being developed to simplify the dosage and aid patient compliance.

* In 1996 Sandoz and Ciba-Geigy merged under the name of Novartis, thus some of the nonclinical studies reported appear under the rubric of Ciba-Geigy.

** Combination Drugs: Evaluation of Existing Information; Pharmacologic Considerations; Toxicologic Considerations and Combination Drugs Committee. September 1991, Pharmacology/Toxicology "Go Away", Harper's Ferry, West Virginia.

*** Manufacture of valsartan is controlled so that the total amount of the R-enantiomer does not exceed 1.5%. In vitro studies reported indicate that the R-enantiomer (CGP 49 309)_is less active at the AT_1 receptor subtype with an IC_{50} of ~ 179 ng/ml vs that of valsartan of ~ 1.03 ng/ml.

Briefly, angiotensinogen is a circulating protein from which renin cleaves angiotensin I (AI); AI is converted to the biologically active and potent pressor octapeptide **AII** by the action of dipeptidase angiotensin converting enzyme (**ACE**), and converting enzymes are widely distributed in the body. AII exerts actions at several sites in the body (i.e., on vascular smooth muscle to contract especially the arterioles smooth muscle thus increasing blood pressure; on brain which resets the baroreceptor reflex control of heart rate to higher pressure; on adrenal cortex to stimulate aldosterone biosynthesis and, on renal artery, human uterus, etc).

AII receptors are also widely distributed in the body, and two distinct subtypes have been identified and termed AT_1 * (which predominate in vascular smooth muscle), and AT_2. These receptor subtypes are differentiated on the basis of their affinity for CGP 42112A and losartan; losartan and valsartan have a high affinity for AT_1 receptors, and AII is reported as binding equally to both receptor subtypes.

Non-clinical Studies:

In absence of clear guidance for suggested nonclinical studies to support the clinical trials with this drug combination CGP 63172, drug sponsor submitted a limited number of nonclinical studies. To support the need for more nonclinical studies, the firm based its case on the human experience with each of the marketed drug ingredients in **CGP 63172.**

In this NDA, the oral route studies (the proposed human route of administration) was used to characterize the toxicity potential of CGP 63172. Nonclinical studies reported included single and repeat dose, and pharmacokinetics in 2 animals species (rat and marmoset) and developmental in 3 animal species (mouse, rat, and rabbit).

No **carcinogenicity** studies were conducted with the drug combination. Neither were there any genotoxicity studies conducted in spite that one drug ingredient CGP 63172- HCTZ has shown evidence of mutagenicity and clastogenicity in some assays. Further, in a National Toxicology Program study, HCTZ was also reported as showing equivocal evidence for hepatocarcinogenicity in male mice.**

*** Since the AT_1 receptor subtype is considered responsible for the effects of AII (i.e., vasoconstriction, aldosterone and adrenaline release, water intake and cellular proliferation), valsartan inhibits the renin-angiotensin-aldosterone system (RAAS) cascade by blockade of AII receptors. Blockers of the RAAS also lower BP in normotensive animals and, in normal volunteers after prolonged administration. The magnitude of the hypotensive response in normotensive individuals is reported as being less than in hypertensives patients and depends on the Na^+ and volume status of the individual and the degree of activation of the RAAS.**

** HCTZ tablets, Physicians Desk Reference, 51th ed., p.1717, 1997

♦ **Pharmacology**: To examine the pharmacologic effects of the drug combination, conscious telemetered SHR were coadministered the diuretic HCTZ (10 mg/kg) with valsartan (2 mg/Kg) and the combination potentiated the BP lowering effect when compared to the monotherapy. The responses varied in magnitude (additive to synergistic) depending on the doses of the individual drugs, and the changes in HR were not sustained.

In separate series of studies with telemetered SHR, valsartan (1 and 3 mg/kg) the subacute effect of the combinations given sc for 2 weeks, an additive to synergistic antihypertensive effect was reported. The degree to which enhanced BP was lowered depended on the doses. At low doses of valsartan (1 mg/kg/day) + HCTZ (3 or 10 mg/kg) additive effects were reported while with a higher dose of valsartan (3 mg/kg/day) combined with 10 mg/kg/day HCTZ resulted in a synergistic effect on BP. In the same rat model as above, two week infusions of valsartan produced minimal and transient changes in HR, while HCTZ at 3 or 10 mg/kg/day evoked mild/persistent bradycardia. When valsartan and HCTZ were combined (3 + 10 mg/kg) resulted in an increase in HR that gradually diminished with time.

In conscious normotensive Na^+ replete marmosets, daily oral doses of valsartan (60, 120 and 200 mg/kg/day) reduced the BP; 200 mg/kg reduced diastolic BP; increased tubular lesions and plasma urea/creatinine levels were reported. The continuous reductions in BP at 200 mg/kg valsartan is believed to contribute to the renal lesions observed in the toxicology studies in normotensive and Na^+-replete marmosets.

In telemetered-marmosets using a high dose of valsartan + HCTZ (3:1 ratio at doses of 120:37.5, 30:9.3, 10:3.1 and 3:1 mg/kg/day once a day, resulted in dose-related fall in diastolic BP; however, one HD died after 2 weeks of drug treatment. Although there were reported increases in HR in these marmosets, this effect lasted ~ 2 hrs even when the reduction in BP was sustained throughout 24 hrs. Plasma urea and creatinine values rose after 2 wks of treatment.

No nonclinical pharmacology studies could be identified that were conducted to define the optimal therapeutic ratio of valsartan to HCTZ.* Thus, the selection of the proposed ratio of the individual drugs appears <u>not</u> to have based on nonclinical studies.

* No nonclinical studies with the drug combination could be identified that had been reviewed at the IND level.

♦ **TOXICOLOGY:**

In the nonclinical studies the drugs were administered as suspension using as a vehicle various suspending agents; control animals always received the vehicle used for the drugs. In the single/repeat dose toxicity studies, CGP 63172 (16:5 w/w valsartan:HCTZ) or HCTZ were given orally (gavage) as a suspension in 0.5% w/v Carboxymethyl cellulose and 0.5% v/v Tween 80.

♦♦ **RAT (Sprague-Dawley, Tif:If[SPF])**

♦ Single dose studies in rats treated with CGP 63172 (1523.8:476.2 mg/kg) and observed for 14 days showed that the drug combination was well tolerated by these animals and none died. Thus, the LD_{50} of this drug combination (3:2 valsartan:HCTZ) was estimated to be ≈2000 mg/kg/po.

♦ In a 1-mo repeat dose in rats treated with CGP 63172 (at 16:5 w:w ratio of valsartan:HCTZ) Doses of the combination tested were 50:15.6, 200:62.5 or 600:187.5 mg/kg/day, and HCTZ 187.5 mg/kg/day. CGP 63172 related effects were reported at all doses (↓ body weight/food consumption, ↑ urinary excretion of Na+ and K+, ↑ plasma urea, creatinine, cholesterol, K+ and Mg++, ↓ total plasma protein, erythrocytic parameters and ↑ reticulocytic counts). A notable histopathologic change reported was hypertrophy of the renal glomerular afferent arterioles. HCTZ treated rats showed ↑ kidney weights, urinary K+/Na+ excretion, plasma urea and cholesterol. These were not considered to be signs of toxicity but dose-related pharmacologic changes induced by the drugs.

♦ In a 6-mo repeat dose study in the same strain of rats treated with daily doses of the drug combination (at ≈ 39.375 up to 393.75 mg/kg/day containing 30 up to 300 mg/kg valsartan, and ≈9.3 up to ≈93.7 mg/kg HCTZ) was associated with reversible (after 1 month without treatment) reduction of bodyweight, slight reduction in food consumption and dose-related increases in plasma urea and increases in plasma lipid levels, slight reduction in Hgb, RBC and Hct, minimal decrease in heart absolute/relative weights, and dose-related increases in urinary volume and in K^+ output, and decreases in specific gravity. Although no abnormalities were reported in ophthalmology, and hearing test (ECG recordings interpretation could not be done by investigators), no recovery was noted from tubular basophilia.

Remarkable histopathologic changes were reported in the kidney of these rats drug-treated (CGP 63172 or HCTZ) and controls and consisted of tubular basophilia; this histopathologic change was accompanied by thickening of the basement membranes and occassional lymphoid cell infiltration. The incidence and severity to the tubular basophilia was increased in M treated with GP 63172.

No full recovery from tubular basophilia was noted. Regarding tubular basophilia seen in both control and treated rats, drug sponsor asserted that it is often present as part of regenerative process necessary to replace tubular cells after necrosis but it is also a component of chronic progressive nephropathy whose onset commences before rats reaches 6 months of age, and is more common males than in female rats. Further, that the onset of this pathologic change can be accelerated by an increased renal demand and/or hypotension.*

♦ Toxicokinetics

From the rats treated with CGP 63172, the plasma concentrations of valsartan were measurable in all treated groups from 1 to 24 hr after dosing but a large interanimal variability in levels were reported. AUC_{0-24h} values were about the same on day 1 and week 26 of study. Cmax values of the drug increased with increasing doses but not proportionally and were lower by week 16 of study. No accumulation was reported for valsartan was reported.

Urinary excretion of HCTZ were detected in both CGP 63172 treated and control animals (suggesting some error in dosing or contamination of the samples.) Since drug sponsor was not able to detect the source of the error, it was decided not further evaluate the urinary HCTZ data.

♦♦ MARMOSET (Callithrix jacchus)

♦ Single dose studies in 1 M marmoset treated with CGP 63172 (320:100 valsartan: HCTZ mg/kg) and both M and F marmosets with 761.9:238.1 mg/kg) and observed for 14 days showed that both drug combination ratios were well tolerated by these animals and none died. Thus, the LD_{50} of this drug combination (3:2 valsartan:HCTZ) was estimated to be ~1000 mg/kg/po and above.

♦ In a 1-mo repeat dose study, marmosets were treated with CGP 63172 (at 16:5 w:w ratio of valsartan and HCTZ) Doses of the combination tested were 30:9.4, 120:37.5 or 400:125 mg/kg/day, and HCTZ 125 mg/kg/day. Two HD F animals were sacrificed each on days 6/19 because of deteriorating conditions/severe clinical signs (body weight loss; vomiting) and the remaining F died on day 11 of study. Remarkable treatment related signs included increase plasma urea, creatinine and changes in some plasma electrolytes (↑ phosphates, ↓ in Na+ and K+) and the histopathologic showed tubular nephropathy. HCTZ marmosets also showed changes in plasma electrolytes and renal tubular basophilia. The NOAEL may have fallen below the lowest dose tested based on some clinical chemistry changes noted.

* "Acute Tubular Necrosis in the Rat Kidney Following Sustained Hypotension" in Lab Investig : 37(4) p. 411 (1977)

♦ In a 6-mo repeat dose study (No. 946117), marmosets were treated with CGP 63172 (at the same ratio of valsartan/HCTZ as above) at doses of 30:9.4 (was associated with mortality), 60:18.75, 120:37.5 or, 240:75 dose (reduced to 120:37.5 mg/kg/day) was also associated with mortality), and 75 mg/kg/day HCTZ. Animals were allowed to recover without drug treatment for 1- mo. Remarkable CGP 63172 treatment related signs included mortality, uremic gastritis, intestinal lesions and changes in plasma electrolytes (↑ Mg), clinical chemistry (↑ alkaline phosphatase and plasma urea), decreased erythrocytic parameters, and histopathologic changes (tubular nephropathy and renal arterial/arterioral hypertrophy). The HCTZ animals showed decreased liver/kidney weights. The reports indicated that all the changes were reversible. The **NOEL** could not be determined in this study because of death even at the lowest dose tested, and a follow-up 6-mo study was conducted at lower doses of CGP 63172.

Toxicokinetics

In a separate study (No. 94-7908), the pharmacokinetics (not toxicity) of CGP 63172 was studied in 1 and <2 year old M and F marmosets were treated by gavage at LD-39.4, MD-78.8 and HD-157.5 mg/kg/day CGP 63172 for 26 weeks.

Plasma pharmacokinetic parameters (C_{max}; t_{max}; AUC_{0-24hr} and accumulation factor calculated by AUC(day 26)/AUC(day 1) for valsartan were determined on day 1 and during week 26 (after the last dose).

From the summary table of findings prepared by drug sponsor, the data indicated that no obvious differences between the sexes were noted in terms of C_{max} and AUC values, due to large variability. Both Cmax and AUC values increased less than proportionally with doses. At all dose levels of CGP 63172, AUCs were reduced between 16-51% by the end of the study.

Urinary concentration of HCTZ were also determined on day 1 and during week 25 (after the last dose).

From the data reported show that urinary excretion of HCTZ increased with the dose, but not proportionally at the LD. Unexplained was the appearance of small amounts HCTZ in the urine of the control animals. F consistently excreted higher concentrations of HCTZ in urine that the M marmosets.

♦ In the follow-up 6-mo repeat dose study (with 1-mo recovery period) in marmosets treated with daily doses of the drug combination at the same ratio with doses ranging from ~ 3.9:0.93 up to 30:9.4 mg/kg/day) showed again vomiting at HD and so-called pharmacologically-induced microscopic changes in the kidney comprising glomerular arteriolar hypertrophy in the vasculature and nephropathy with mineralization in the proximal convoluted tubules at HD and MD only. The **NOEL** may be considered the drug combination at the LD (3.9:0.93 ratio of valsartan/HCTZ) for glomerular arteriolar hypertrophy in the vasculature and nephropathy with mineralization. In the absence of a conversion factor for the marmosets to calculate the dose by m2, only dose by kg body weight is given here.

From the reports of these repeat dose studies it may be concluded that administration of CGP 63172 to rats and marmosets was associated with remarkable histopathologic changes in the kidneys (i.e, renal basophilia in both species and tubular nephropathy in marmosets), changes in clinical chemistry which included increased plasma urea, creatinine and, cholesterol (in rats), increased urinary excretion of electrolytes (K+ and Na+). Marmosets treated with the drug combination vomited and some showed uremic gastritis, intestinal lesions and intestinal lesions. Drug sponsor asserted that most signs were to be considered as exaggerated pharmacologic effects of CGP 63172.

DEVELOPMENTAL STUDIES

In the developmental studies in mice, rats and rabbits evaluated below, CGP 63172 (16:5 w/w valsartan:HCTZ) or HCTZ were administered orally (gavage) as a suspension in 3% corn starch.

No fertility or postnatal development studies were conducted with CGP 63172.

MICE (Crl:CD-1[ICR] BR)

♦ Oral administration of CGP 63172 (from 78.8 up to 787.5 mg/kg/day) or HCTZ (187.5 mg/kg/day) on gestation days 6-15 and sacrificed on gestation day 18 showed no evidence of treatment-related maternal toxicity. Reproductive parameters, fetal weights and fetal gross, visceral and skeletal development appeared unaffected by either of the drugs tested. Since there were problems formulating the CGP 63172, the maximum attainable dose in this mouse developmental study was 600:187.5 = 787.5 (valsartan:HCTZ) mg/kg. A clear **NOAEL** for CGP 63172 for the pregnant mice or the conceptus could not determined in this study based on the appearance of cleft palate in 1 fetus from the LD-78.8 mg/kg litter, and from the HCTZ group; no cleft palates were reported in the control group, and no dose-relationship in the drug combination

treated groups. Further, reviewer notes that cleft palate is commonly reported in mice. Thus, this study did not show teratogenic potential for CGP 63172.

RAT [Sprague-Dawley, Crl:COBS CD(SD)BR]

♦ Two **oral** dose developmental studies in were conducted in rats treated with CGP 63172 or HCTZ. In the first study (No. 95053), oral administration of HCT (187.5 mg/kg) or the drug combination CGP 63172 (at doses ranging from 60:18.8 up to 600:187.5 mg/kg/day valsartan:HCTZ) to pregnant rats during the period of organogenesis (gestation days 6-15 and sacrificed on day 20 of gestation) showed evidence of maternal toxicity, and fetotoxicity but no evidence of teratogenicity. Signs of maternal toxicity included mortality at the MD (3 out of 26) and HD (11/26) of CGP 63172 with signs prior to death which included lethargy, gasping/labored respiration; other maternal toxic signs reported for both CGP 63172 and HCTZ dams included decreased in food consumption/mean body weight/body weight gain. Fetotoxic signs included reduced fetal weights, skeletal and viscera variations at the two highest doses of CGP 63172 which were considered related to the decrease in fetal weights. Thus the **NOAEL** for CGP 63172 for the pregnant rats or conceptus (since there was a high number of dams dying and an small number of litters) was not be determined and thus a follow-up study was conducted.

♦ In the **follow-up developmental study** (No. 95081) in the same strain of rats, these were treated with a lower doses of the CGP 63172 (ranging from 10:3.1 up to 100:31.3 mg/kg) and HCTZ (31.3 mg/kg) on gestation days 6-15 and sacrificed on day gestation day 20. The HD of CGP 63172 was associated with moderate maternal toxicity such as reduction of mean food consumption/body weight and 1 dam showed at necropsy some organs engulfed with connective tissue, but there was no clear evidence of embryotoxicity at the doses tested. In this study the **NOAEL** appears to be below the LD of 10:3.1 mg/kg CGP 63172 (valsartan:HCTZ representing 70:22 mg/m2) for dams and fetuses because fetal examination revealed 1 litter with cleft palate in all drug treated groups). However, the drug sponsor reported that although cleft palate is rare, it has been observed in untreated control rats of this strain.* Reviewer considers this 2nd study to be the most reliable of the two rat developmental studies. Thus, the non-teratogenic dose is considered to be 100:31.3 mg/kg CGP 63172 in this study and should be used in the label to estimate human risk.

* Historical control data for development and reproductive toxicity studies using Crl:CD BR rat. Compiles by Middle Atlantic Reproduction and Teratology Association (MARTA). Lang Pl. editor, Charles River Laboratories publication, Sept. 1993.

There was no evidence of teratogenicity even when the animals were treated during the period of organogenesis at HD of 100:31.3 (valsartan:HCTZ) mg/kg (representing ~ 700:219 mg/m^2); these doses represent ~ 7 and ~ 27 X, respectively, the MRHD of 160:25 mg/kg CGP 63172 (or valsartan:HCTZ of ~ 98:8 mg/m^2).

RABBIT (New Zealand white)

♦ An oral dose-rangefinding study in pregnant rabbits (artificially inseminated) was conducted to aid in the selection of doses of CGP 63172 and HCTZ for the definitive developmental study in rabbits. In the dose-rangefinding study, rabbits were treated with HCTZ (3.1 mg/kg/day) or CGP 63172 (at 1.3, 6.6 and 13.1 mg/kg/day) on gestational days 7-19, The treatment with CGP 63172 was associated with slight maternal changes (slight ↓ mean food consumption/body weight in rabbits that died at the MD/HD doses, but no evidence of embryotoxicity. HCTZ produced no apparent effects.

From that study, the oral doses selected for the definitive study with CGP 63172 were LD-1.3, MD-3.9 and HD- 13.1 mg/kg/day and for HCTZ- 3.1 mg/kg/day (controls received saline) were administered to artificially inseminated pregnant rabbits on days 7-19 of gestation during organogenesis. Treatment with CGP 63172 induced slight maternal toxicity as evidenced by slight reduction in food consumption at all dose levels during dosing period with CPG 63172, and mortality in 1 MD-3.9 mg/kg dam on day 18 of gestation. Necropsy of dams showed cysts in MD and HD groups (reported as being a common occurrence in rabbits).

Slight fetotoxicity was noted at HD- 13.1 mg/kg CGP 63172 when compared to saline controls (not vehicle) and statistically significant increases in the numbers of late resorptions with resultant increases in total resorptions and % post implantation loss and, slight decrease in the mean number of live fetuses.

The maternal **NOAEL** in this rabbit developmental study appears to be the LD ratio of 1.0:0.3 (valsartan:HCTZ) mg/kg/day based on the slight reduction of food consumption/body weight representing ~ 13.5/4 mg/m^2; these doses represent ~ 0.13 X and ~ 0.5X the MRHD of valsartan:HCTZ of 160:25 mg/kg (or ~98:8 mg/m^2 assuming a 60 kg patient).

However, in this rabbit study there was no evidence of teratogenicity even when the animals were treated during the period of organogenesis at HD of 10:3.1 (valsartan:HCTZ) mg/kg (representing ~ 135:42 mg/m^2); these doses represent ~ 1.3 and ~ 5.25 X, respectively, the MRHD of 160:25 mg/kg CGP 63172 (or valsartan:HCTZ of ~ 98:8 mg/m^2).

PHARMACOKINETICS

Numerous studies were conducted in rats and marmosets dosed orally and daily with CGP 63172, or each the ingredients separately. A remarkable finding in both animal species, was that there appears to be little sex difference in the handling of the drug combination, there is large variability in the excretion of the drug ingredients, and there was no remarkable accumulation of the drugs.

No data was found regarding the metabolites of the drug ingredients. In these pharmacokinetic studies, the sample analysis from control animal often showed contamination, mainly with HCTZ.

In rats after 6 months of daily administration of valsartan, the AUC values were approximately equal on day 1 and at the end of the study. Rats treated for 6 months with the CGP 63172, M tended to excreted more HCTZ than F rats.

Marmosets treated with HCTZ for 14 days, showed a great variability in the urinary excretion of the drug. When the animals were treated with CGP 63172 for 6 months, the amounts of HCTZ excreted by F were only slightly higher than that of the M, or no difference.

When marmosets were treated with CGP 63172 for 6 months, the marmosets were exposed to valsartan in dose-proportional way but exposure decreased during repeated dosing. No sex difference was noted in plasma pharmacokinetic parameters.

Notable for their absence were pharmacokinetic studies in pregnant mice, rats and rabbits.

In conclusion, reviewer recognizes that valsartan and HCTZ are approved/marketed and considered safe and effective for their intended therapeutic indication with different mechanisms of action. Limited nonclinical studies related to the proposed therapeutic indication for the management of hypertension showed that the combination of these two marketed drugs reduces blood pressure in SHR without increasing the heart rate no more that when HCTZ was given alone. In telemetered SHR treated sc for two weeks with the drug combination in a 3:1 and 1:1 ratio of valsartan: HCTZ, the blood pressure and heart rates appeared to be reduced in an additive to synergistic manner. However, at least in these reports of only two different dose levels, no individual dose-response curves (more than 2-3 doses) were found showing that smaller amounts of the drugs in the combination produced a greater antihypertensive effect indicating synergism. In marmosets, prolonged oral administration of CGP 63172 (at a ratio of 3:1 valsartan:HCTZ for 4 weeks) induced a dose-dependent reduction of

diastolic blood pressure. In single and repeat dose toxicology studies, the toxicity of appear to have been unremarkable because the rats and marmosets showed no treatment related effects with high doses of the combination and no animals died. The acute oral lethal dose of the drug combination **16:5 ratio in** rat or marmosets, respectively, was reported to be > 2000 mg/kg (1523.8:476.2, valsartan: HCTZ) and > 1000 mg/kg (761.9:238.1, valsartan: HCTZ.

Developmental studies with the combination of the two drugs **at a ratio of 16:5 (valsartan:HCTZ)** administered to 3 species of animals (mice, rat and rabbits) orally (gavage) during the period of organogenesis, revealed **no** evidence of teratogenicity associated with the treatment of CGP 63172 at oral doses of 600:187.5 ratio (mice), 100:31.3 ratio (2nd and more reliable study in rat) or 10:3.1 ratio (rabbits); neither was teratogenicity reported for HCTZ treated animals. Although no evidence of teratogenicity was reported in animals treated with the CGP 63172, the approved label for **HCTZ** advises that against the routine use of diuretics during normal pregnancy as inappropriate.

No data were provided on blood or tissue distribution of the ingredients in CGP 63172 in the pregnant mice, rat or rabbit.

In the developmental study, maternal toxicity was noted in 2 species (rat -slight reductions in food consumption/body weight, and rabbits -death at 3.0:0.9 ratio) was associated with fetotoxicity at some doses of CGP 63172.

The **NOAEL** for maternal toxicity in pregnant mice treated with CGP 63172 during the period of organogenesis could not be clearly determined because there were difficulties formulating the drug above 60 mg/ml, and investigators did not recommend the use of doses higher than 600:187.5 ratio (valsartan:HCTZ). In pregnant rat (data used from the follow-up study), the dose inducing maternal toxicity appears to be < 10:3.1 ~13.1 mg/kg CGP 63172 equivalent to ~92 mg/m^2 (70 for valsatan and ~ 22 for HCTZ mg/m^2) for 250 g rat using a km=7. In pregnant rabbit, the materno-toxic dose appears to be ~ 3.0 + 0.9= 3.9 mg/kg CGP 63172 equivalent to ~ 53 mg/m^2 (40 for valsartan and ~ 12 mg/m^2 for HCTZ) for a 2.5 rabbit using a km=7.

As for the NOAEL for fetotoxicity, for the rat (based on cleft palate findings in 1 litter of all CGP 63172 dosed groups and none in the HCTZ group in the rat follow-up study) this appears to be below the lowest dose of LD-13.3 mg/kg (~93 mg/m^2), and for the rabbit (based on death) at 3.9 mg/kg (~53 mg/m^2) CGP 63172.

Previously reported nonclinical studies with **valsartan** alone have not shown evidence of mutagenic or carcinogenic potential at the doses tested. As for **HCTZ**, the second ingredient in CGP 63172, both the **FDA** and the drug industry have accepted National Toxicology Program (NTP) reports of equivocal evidence for hepatocarcinogenicity in M mice (and no evidence of carcinogenicity potential in F mice or M/F rats in 2-year feeding studies with HCTZ). Also, that HCTZ although not genotoxic in vitro Ames assay, in Chinese Hamster Ovary (CHO) test for chromosomal aberrations, in in vivo assays using mouse germinal cell chromosomes, or in the Drosophila sex-linked recessive lethal trait gene, it was positive for clastogenicity in vitro CHO Sister Chromatid Exchange, and was mutagenic in the Mouse Lymphoma Cell assays using concentrations of the drug ranging from 43 up to 1300 μg/ml, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration. Although this data presently appear on the label of HCTZ and on marketed drug combinations containing this diuretic, several of those assays showing positive results are not included in the battery of tests recognized by FDA in genotoxicity guidances.

Since the time those genotoxicity assays with HCTZ alone were conducted, attempts have been made to harmonize regulatory guidelines for genotoxicity testing. As a result a standard battery for testing is recommended which includes the mouse lymphoma tk assay. The mouse lymphoma tk assay detects both gene mutations and clastogenic effects. The FDA guidance to industry (**62 FR 16026-16030 of April 3, 1997**) suggests that the mouse lymphoma tk assay is an acceptable alternative for the direct analysis of chromosomal damage in vitro, and that this assay has also shown the ability to detect some clastogens/aneuploidy inducers under some treatment protocols. The NTP studies using the mouse lymphoma assay, HCTZ gave a positive response for mutagenicity.

Even tough valsartan alone (See NDA-20,665 dated 09-30-96, by G. Jagadeesh, Ph.D. reviewing Pharmacologist) has not shown potential for genotoxicity in the assays performed, it is not unreasonable to ask the drug sponsor to confirm the positive findings of HCTZ in the mouse lymphoma cell assay, and determine whether valsartan interacts with HCTZ to yield stronger positive evidence of mutagenicity than HCTZ alone.

It should be noted out that some firms have conducted genotoxicity studies with their drug combinations.

Prior to the first human exposure with a drug, in vitro tests for the evaluation of mutations and chromosomal damage are usually needed. However, since the IND for **Diovan HCTZ** was not reviewed the possible need for genotoxicity studies with the drug combination was not discussed with the drug sponsor. Thus, this reviewer does not consider it unreasonable at this time to suggest that the drug sponsor might consider conducting at some point at least the mouse lymphoma assay with the drug combination CGP 63172.

Based on the limited nonclinical data provided it may be concluded that **CGP 63172** does not represent a significant therapeutic advancement in the treatment of hypertension but may, as the drug sponsor suggests, be convenient formulation for patients whose blood pressure is not adequately controlled with valsartan monotherapy as is approvable on this basis.

RECOMMENDATIONS:

1. CGP 63172 is approvable with the recommended labeling changes described under LABELING on page 82, above.

2. Reviewer considers that the firm should be encouraged to conduct the genotoxicity mouse lymphoma tk assay of the drug combination CGP 63172 as well as of the drug ingredient HCTZ.

Estela A. González Barry, M.S.

cc
Original NDA 20-818
HFD-110
HFD-110/CSO KBongiovanni
HFD-110/EGBarry
HFD-024/JDeGeorge
HFD-345

egb:10-21/22-97//11-03-97//11-05-97

11/5/97

Since the equivocal/positive prior genotoxicity findings of HCTZ per se will be fully retained in the labelling for this combination, I see no compelling need for additional genotoxicity testing

Noted EB 2-17-98 ADeS 2/17/98