CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-100

PHARMACOLOGY REVIEW(S)

10/25/05

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-100
DATE RECEIVED BY CENTER:	November 27, 2006
DRUG PRODUCT:	AZOR® Tablets
DRUG SUBSTANCE:	Amlodipine Besylate and Olmesartan Medoxomil
INTENDED CLINICAL POPULATION:	Hypertensive
SPONSOR:	Daiichi Sankyo Pharma Development
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Denise Hinton

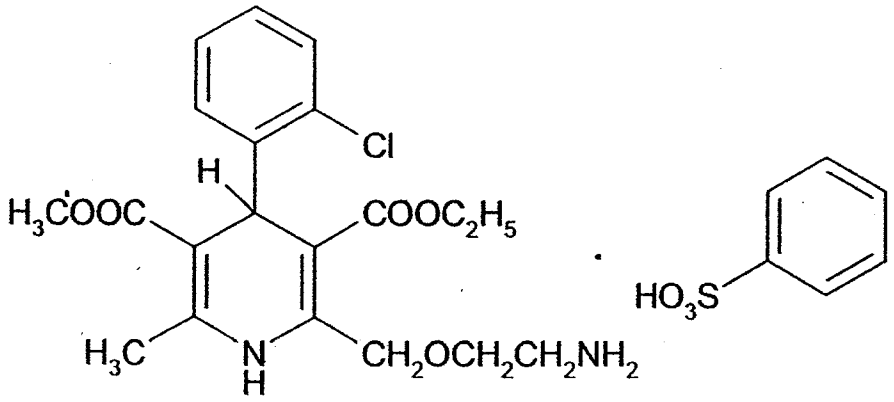
Date of review submission to Division File System (DFS): July 30, 2007

NDA number: 22,100
Date of Submission: 11-27-06
Center Receipt Date: 11-27-06
Sponsor: Daiichi Sankyo Pharma Development
Manufacturer of Drug Substance:
Olmesartan medoxomil is from Sankyo Co., Ltd., Kanagawa, Japan. b(4)
Manufacturer of Drug Product: Daiichi Sankyo Pharma Development
Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: July 30, 2007

Drug Product: AZOR® Tablets (CS-8663)

Drug Substances

Generic name: **Amlodipine Besylate**
Code name: LBT873-DMA.002
Chemical name: (*RS*)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.
Chemistry: Amlodipine is a racemic mixture (R and S isomers). It is a white to pale yellow crystalline powder slightly soluble in water and sparingly soluble in ethanol.
CAS registry number: 1114790-99-6 (besylate salt form)
88150-42-9 (free base form)
Molecular formula/molecular weight: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H$ / 567.06 (besylate)



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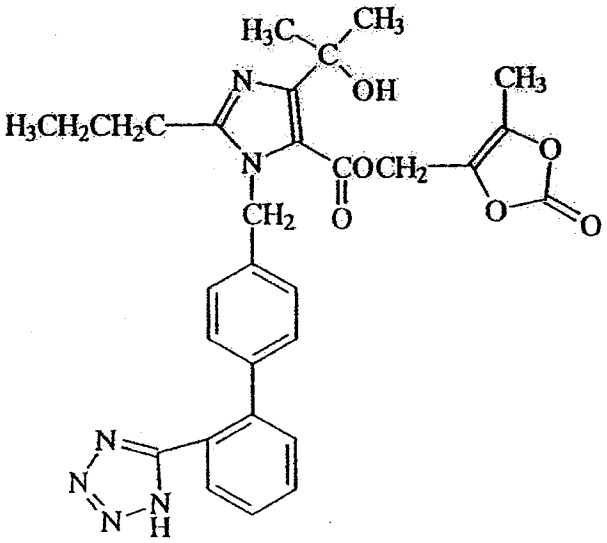
Generic name: **Olmesartan Medoxomil**
Code name: CS-866, RNH-6334
Chemical name: (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate
Chemistry: Olmesartan medoxomil is an imidazole with no chiral center. It is a white to pale yellowish white powder, practically insoluble in water and sparingly soluble in organic solvents such as methanol and acetone. It is not hygroscopic.
CAS registry number: 144689-63-4
Molecular formula/molecular weight: $C_{29}H_{30}N_6O_5$/ 558.59



Related Applications: Clinical trials supporting the current NDA were conducted under Daiichi Sankyo's IND 70,410. Pfizer's NDA 19,787 for racemic amlodipine besylate (Norvasc®) was approved for the treatment of hypertension, chronic stable angina and vasospastic angina in 1992. Sankyo's NDA 21,285 for olmesartan medoxomil (Benicar®) was approved for the treatment of hypertension in April 2002.

Drug Class: Amlodipine: Dihydropyridine calcium channel blocker
Olmesartan: Angiotensin II receptor type 1 (AT_1 receptor) antagonist

Intended Clinical Population: Hypertensive subjects

Clinical Formulation: The tablets are formulated in six strengths with amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base combined with 10, 20 or 40 mg of olmesartan medoxomil. Four of these strengths (5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg (amlodipine/olmesartan medoxomil)) are proposed for marketing in the US. The following table lists proposed final commercial formulations.

COMPOSITION OF OLMESARTAN MEDOXOMIL AND AMLODIPINE BESYLATE (CS-8663) FILM-COATED TABLET

Component	Quality Std.	Function	10/5 mg	10/10 mg	20/5 mg	20/10 mg	40/5 mg	40/10 mg
Core Tablet (mg/tablet)								
Olmesartan medoxomil	DMF 14,953	Drug substance	10.000	10.000	20.000	20.000	40.000	40.000
Amlodipine besylate	EP	Drug substance	6.944[a]	13.888[a]	6.944[a]	13.888[a]	6.944[a]	13.888[a]
Starch, pregelatinized								
Silicified microcrystalline cellulose[b]								
Croscarmellose sodium								
Magnesium stearate								
[redacted]								
Total Tablet Weight (mg)	[redacted]		105	105	105	208	208	208

b(4)

[a] Equivalent to 5 mg (6.944 mg) and 10 mg (13.888 mg) amlodipine base

[b] Silicified microcrystalline cellulose is comprised of 98% microcrystalline cellulose (NF/ EP/JP) and 2% colloidal silicon dioxide (NF). Colloidal silicon dioxide is also referred to as Silica, Colloidal Anhydrous in the EP and Light Anhydrous Silicic Acid in the JP.

[c] The qualitative and quantitative composition statement are incorporated by reference Refer to Section 3.2.P.4.1.2

Route of Administration: Oral

Proposed Dosage Regimen: One tablet daily.

Disclaimer: Unless indicated otherwise, tables and graphs (some with editorial corrections by the reviewer) are taken directly from the sponsor's submission.

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EXECUTIVE SUMMARY

I. Background

The use of more than one drug to treat hypertension increases the chances of achieving a greater reduction in blood pressure in a short period and at lower doses of the component agents, thus resulting in fewer side effects. The seventh report (2004) of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends addition of a second drug from a different class when use of a single agent in adequate doses fails to achieve the goal.

CS8663 (Azor®) is a new combination tablet of amlodipine besylate (Norvasc®, Pfizer) and olmesartan medoxomil (Benicar®, Sankyo). Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle, which results in peripheral arterial vasodilatation, reduction in peripheral vascular resistance and reduction in blood pressure. Olmesartan medoxomil is a non-peptidic, orally effective, specific antagonist of angiotensin II, active at the AT-1 receptor. Both drugs have been extensively studied and are widely used as monotherapies for the treatment of hypertension. Daiichi Sankyo has submitted a 505(b)(2) application for the fixed-dose combination of amlodipine besylate and olmesartan medoxomil for the treatment of essential hypertension. Since these two classes of agents have different modes of action, their combination should provide an additive or synergistic antihypertensive effect when compared to single drug treatment.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

C. **Recommendations for Labeling:** Those sections of the proposed labeling (EDR version dated October 24, 2006) that deal with nonclinical studies covered by this review are considered satisfactory with the following exceptions.

1. Under NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility,
the sponsor's proposed text reads as follows:

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-_____

b(4)

b(4)

III. Summary of Nonclinical Findings

The sponsor has not performed pharmacology or ADME studies for the combination product.

A. **Brief Overview of Toxicology:** To support the chronic administration of the amlodipine besylate and olmesartan medoxomil combination to adult hypertensive patients, a 13 week repeat dose toxicity study was performed in F344 rats. In this study, amlodipine besylate and olmesartan medoxomil were administered orally, by gavage, separately and together (at a ratio of 1:10). Clinically, it will be administered in a ratio of 1:2 to 1:8. Olmesartan (RNH-6270) is the active metabolite of olmesartan medoxomil. (All doses and dose ratios in this review are presented in terms of the amlodipine base.)

Daily administration of amlodipine besylate and olmesartan medoxomil at doses of 10:100 or 30:300 mg/kg/day for 13 weeks resulted in 3 deaths (an additional 3 in the group receiving amlodipine besylate alone), which were attributed to peristaltic motion disorder of the intestinal tract caused by an excessive pharmacological inhibitory effect of amlodipine on calcium channels. The target organs of toxicity in both sexes were stomach (minimal erosion in the fundus), intestine (luminal dilatation and diffuse mucosal thickening of the ileum and colon) and adrenal (hypertrophy of glomerular cortical cells) for amlodipine besylate, and kidneys (thickening of the

arterial wall of the afferent arterioles and increased thickness of the renal tubules) for olmesartan medoxomil. In addition, significant increases in BUN and creatinine were noted in animals of both sexes treated with combination doses, olmesartan medoxomil or amlodipine besylate alone. Olmesartan medoxomil-attributed significant decreases in erythroid parameters (erythrocytes, hemoglobin, hematocrit) were noted for both sexes receiving the combination drugs or olmesartan medoxomil alone. Additional findings included a dose-dependent and statistically significant decrease in mean body weight gain relative to concurrent control for both sexes at all doses, individual or combined, for the duration of the study. Reduced food consumption ($p < 0.05$) was also demonstrated in these groups. The combined administration of amlodipine besylate and olmesartan medoxomil at a ratio of 1:10 did not augment any existing toxicities of the individual agents, nor induce any new toxicities and resulted in no toxicologically synergistic effects.

Toxicokinetics demonstrated accumulation (week 13 *versus* day 1) of amlodipine and a significant increase in systemic exposure to olmesartan, the active metabolite of olmesartan medoxomil, with the co-administration of amlodipine besylate for either sex. The mean week 13/day 1 ratios of the $AUC_{0\text{-}24h}$ values for amlodipine and olmesartan were 3.4 and 2.0-fold at the low dose and 4.6- and 7.9-fold at the high dose combination, respectively. No accumulation was noted in the group receiving olmesartan medoxomil alone. The difference in exposure ($AUC_{0\text{-}24h}$) to olmesartan between the high dose combination and olmesartan medoxomil alone groups (animals in both groups had received 300 mg olmesartan medoxomil/kg/day) was 8.5-fold. This suggests that presence of amlodipine besylate in the combination dose group augments the plasma concentrations of olmesartan. By contrast, olmesartan medoxomil had no effect on the amlodipine toxicokinetic parameters, although a significant accumulation was noted for amlodipine. Follow-up mechanistic studies suggested that at a sufficiently high combination dose (10:100 mg (amlodipine:olmesartan medoxomil)/kg/day), amlodipine increased absorption (no effect on elimination kinetics) of olmesartan medoxomil in the gut as a result of an excessive relaxant effect on the gastrointestinal smooth muscle. The highly pronounced systemic exposure to olmesartan, however, did not translate into unexpectedly toxic effects when compared to changes produced by olmesartan medoxomil alone. The reason could be that the dosages employed in these studies were at or below a threshold level for triggering any toxicity.

B. Nonclinical Safety Issues Relevant to Clinical Use

In the 13 week toxicity study with rats, a 1:10 amlodipine: olmesartan medoxomil combination was associated with findings in the stomach, intestine, adrenal cortex and kidneys. Each of these effects could be attributed to known effects of amlodipine and/or olmesartan medoxomil. All of them were associated with exaggerated pharmacological effects of amlodipine or olmesartan medoxomil. Deaths of rats receiving the highest combination dose or amlodipine besylate alone were attributed to an excessive relaxant effect of amlodipine on the gastric smooth muscle. This property of amlodipine may have been responsible for increasing the absorption and

elevating the systemic exposure to olmesartan by several fold relative to animals receiving olmesartan medoxomil alone. However, this did not translate into unexpectedly exaggerated pharmacologic or toxic effects when compared to changes produced by olmesartan medoxomil alone. Additionally, findings from human PK studies indicated no pharmacokinetic drug-drug interactions between amlodipine besylate and olmesartan medoxomil. Thus, it is concluded that the observed large increase in systemic exposure to olmesartan resulting from co-administration of amlodipine besylate is primarily related to the repetitive daily administration of high multiples of the pharmacologic dose in rats and not a concern for humans.

In conclusion, the combined administration of amlodipine besylate and olmesartan medoxomil to rats did not augment any existing toxicities of the individual agents, nor induce any new toxicities and resulted in no toxicologically synergistic effects. The combination product can be used safely in humans for the treatment of hypertension because the target organ toxicities noted in the toxicity study are monitorable and attributable to the individual drugs of the combination which are currently approved for use in this patient population and have often been used concomitantly.

IV. Administrative

Reviewer's Signature

Supervisor Signature: Concurrence

PHARMACOLOGY/TOXICOLOGY REVIEW

1.0. PHARMACODYNAMICS: NO STUDIES CONDUCTED

2.0. DRUG DISPOSITION: NO STUDIES CONDUCTED

3.0. TOXICOLOGY

3.1. Repeat Dose Toxicity

3.1.1. 3 Month Oral Gavage Study in F344 Rats

Key Study Findings: Six rats (a male and two females at 30:300 and three females at 30:0 mg/kg/day amlodipine:olmesartan medoxomil) died during the study. Principal drug-related findings in both sexes for all treated groups were a statistically significant reduction in mean body weight gain relative to control, reduced food intake, decline in erythroid parameters (amlodipine besylate alone group excluded), and increases in BUN and alkaline phosphate. Test substance related microscopic pathology was observed in intestinal tract (luminal distention), adrenal (hypertrophy of the glomerular cells), uterus and vagina (atrophy) in animals given amlodipine besylate alone or in combination with olmesartan medoxomil. In kidneys, thickening of the arterial wall and tubular regeneration were noted in both sexes treated with olmesartan medoxomil alone or in combination with amlodipine besylate. Toxicokinetics analysis showed that $AUC_{0\text{-}24h}$ values for olmesartan, the active metabolite of olmesartan medoxomil, in the combination group were several fold higher than in the olmesartan medoxomil alone group, suggesting enhancement of effects of olmesartan medoxomil by co-administration with amlodipine besylate.

Study No.: B-5681, Report #APS-152-088 and APS-152-095 (TK)
Location of Report: EDR
Conducting Laboratory and Location: b(4)

Dates of Study: The animals were initially dosed on November 30 (males) and December 1 (females), 2005 and necropsied on March 1 (males) and March 2 (females), 2006.
GLP Compliance: Yes
QA'd Report: yes (X) no ( )
Drug, Lot #: Amlodipine besylate, lot #F40456, 101.2% pure; Olmesartan medoxomil, lot #0001, 99.2% pure
Formulation: The drugs were suspended in 0.5% (w/v) methylcellulose aqueous solution, once every 7 days, and used within 10 days of preparation (stored at 2 to 10°C). All of the investigational drugs were stable for 1 day at 23°C and for 16 days at 4°C. The homogeneity and concentration of each dose suspension prepared in weeks 1, 4 and 13 were analyzed by taking 3 samples per concentration.
Animals
Species/Strain: Rats, F344/DuCrlCrlj SPF (from Charles River)

#/Animals/Group: 15/sex for toxicology; 5/sex (3/sex in case of control group) for toxicokinetics (see Table 3.1.1.1).
Age: 6 weeks old at initiation of dosing
Weight: Males: 114-136 gm, Females: 100-112 gm, at initiation of dosing
Husbandry: Animals were housed individually in cages. Food and water were available *ad libitum* except for study defined fasting procedures

TABLE 3.1.1.1
STUDY DESIGN

Test group	Dose (mg/kg/day) ROX-2150	Dose (mg/kg/day) CS-866	Concentration (mg/mL) ROX-2150	Concentration (mg/mL) CS-866	Dose volume (mL/kg)	Sex	Main group No. of animals	Main group Animal No.	Satellite group No. of animals	Satellite group Animal No.
Control[a)]	0	0	0	0	5	M	15	1001-1015	3	1201-1203
						F	15	1101-1115	3	1301-1303
CS-8663 110 mg/kg	10	100	2	20	5	M	15	2001-2015	5	2201-2205
						F	15	2101-2115	5	2301-2305
CS-8663 330 mg/kg	30	300	6	60	5	M	15	3001-3015	5	3201-3205
						F	15	3101-3115	5	3301-3305
ROX-2150 30 mg/kg	30	0	6	0	5	M	15	4001-4015	5	4201-4205
						F	15	4101-4115	5	4301-4305
CS-866 300 mg/kg	0	300	0	60	5	M	15	5001-5015	5	5201-5205
						F	15	5101-5115	5	5301-5305

a): 0.5 w/v% MC solution
M: Male, F: Female

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Dosing

Doses: Amlodipine besylate and olmesartan medoxomil were administered (at an amlodipine:olmesartan medoxomil dose ratio of 1:10) at two dose levels: 10:100 or 30:300 mg/kg/day. Two additional groups of rats received either amlodipine besylate alone or olmesartan medoxomil alone at 30 or 300 mg/kg/day, respectively (Table 3.1.1.1). Control animals received the vehicle. Doses were selected on the basis of a 28 day oral toxicity study in male rats (same strain) in which 30 mg amlodipine/kg/day resulted in a statistically significant decrease in mean body weight gain, elevated heart weight relative to vehicle control and distention of the intestinal tract. Administration of olmesartan medoxomil at a dose of 300 mg/kg/day resulted in statistically significant increases relative to vehicle control in blood urea nitrogen, creatinine and potassium. Mean absolute heart weight was significantly decreased relative to control. Though no histopathological changes in the kidney were noted for olmesartan medoxomil in this study, studies reviewed previously under NDA 21,286 demonstrated progressive nephropathy at doses as low as 300 mg/kg/day (seen as early as 3 months). There is no preliminary data with the combination of amlodipine besylate and olmesartan medoxomil.

Route, Mode and Duration of Administration: Orally by stomach tube (5 ml/kg), once daily, for 13 weeks.

Observations and Measurements

Clinical Signs: All animals were observed thrice daily (twice during weekends) for clinical signs and mortality.

Body Weight and Food Consumption: Recorded for all animals, prior to dosing, twice in week 1, and thereafter once a week and on the day of necropsy.
Ophthalmology: Conducted on all main study animals once pretest and in week 12.
Urinalysis: 24 hr urine samples were collected from individual toxicology group animals (10/sex/group in order from the lowest number) during study week 13 under free access to food and water. The following parameters were assessed: urine volume, water intake, osmotic pressure, total protein, creatinine, sodium, potassium and chloride.
Hematology[1] and Clinical Biochemistry[2]: Blood samples were collected prior to terminal necropsy from all surviving main study animals from the abdominal aorta under ether anesthesia. The animals were faster overnight.
Pathology: Animals were fasted overnight prior to terminal necropsy. External appearance and all organs/tissues in the cranial, thoracic and abdominal cavities were examined. Representative samples of the protocol tissues (Table 3.1.1.2) were collected from all main study animals and processed for microscopic examination which was performed on the tissues from all main study animals in the control and high dose combination groups and for all unscheduled deaths/sacrifices. All gross lesions, organs that were subjected to weighing and organs/tissues in which treatment-related changes were noted in the high dose combination group were also subjected to microscopic evaluation for all animals in the remaining groups.

TABLE 3.1.1.2
TISSUES SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

adrenals* π	liver π	sternum (including bone marrow)
brain (cerebrum, cerebellum) π	lungs (including bronchus) π	stomach
cecum	mammary glands* (inguinal region, both sides)	sublingual glands*
colon	optic nerves*,	submandibular glands*
duodenum	ovaries* π	submandibular lymph node
epididymides* π	pancreas,	mesenteric lymph node
esophagus	parathyroids*	testes* π
eyeballs*	Pituitary π	thoracic aorta
femoral skeletal muscles*	prostate	thymus π
femurs* (including bone marrow)	rectum	thyroids* π
gross lesions	sciatic nerves*	tongue
Harderian glands*	seminal vesicles*,	trachea,
heart π	skin* (inguinal, both sides)	urinary bladder
ileum,	spinal cord (lumbar)	uterus (both horns)* π
jejunum	spleen π	vagina
kidneys* π		

*: Paired organs were examined unilaterally; π: Organ weighed

[1] erythrocytes, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes ratio, white blood cell count, white blood cell differential, platelets, prothrombin time, activated partial thromboplastin time and fibrinogen. blood chemistry (ALT, AST, AP, total bilirubin, total protein, albumin, globulins, glucose, urea, creatinine, creatine kinase, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol, A/G ratio

[2] ALT, AST, AP, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, total cholesterol, phospholipids

Toxicokinetics: Blood samples for determination of levels of amlodipine and olmesartan were collected from toxicokinetics animals on study day 1 (1st dose) and in weeks 4 (27th dose) and 13 (90th dose) at 0 (prior to dosing, except for day 1), 2, 4, 7 and 24 hr after dosing (5 rats/sex/treatment group/time point). Blood was also collected from control animals (3 males and 3 females/time point) at one time point (2 hr after dosing) on study 1 and in weeks 4 and 13. The animals were killed after week 13 blood sampling and abdominal organs were macroscopically examined. No organs/tissues were preserved.

Results

Analysis of Formulations: The formulation was stable for at least 12 days at 6°C and for at least 4 hr at room temperature. Mean concentrations of all samples analyzed were in the range of 92.5% to 100% of target concentrations.

Mortality: Five animals (one male and 4 females) died during the study. Of these, a male (#3005) and a female (#3112) receiving 30:300 mg (amlodipine:olmesartan medoxomil)/kg/day died on days 23 and 52, respectively, and were considered to have succumbed to an effect of the test substance. The male had no apparent clinical signs but the female had exhibited unkempt fur from week 7. Body weight and food consumption for these two animals were remarkably lower than for the vehicle control group. Necropsy revealed distention of the small and large intestines. Histopathology revealed luminal dilatation of the intestine in the male. The findings were comparable to those for animals that died in the amlodipine besylate treated group (females #4112, 4101 and 4106 died on study days 8, 15 and 25, respectively). The amlodipine besylate-treated female that died on day 15 had exhibited decreased spontaneous movement, abdominal distention and hypothermia a day before death. Necropsy revealed distention of the intestine in all 3 decedent animals in the amlodipine group. Microscopic examination showed luminal distention of the small and/or large intestine. The sponsor concludes that all deaths were due to an excessive pharmacological effect of amlodipine, resulting in peristaltic motion disorder of the intestinal tract. In addition to the deaths in the main study groups, a female in the toxicokinetics group receiving the high dose combination died after the week 4 blood sampling. Further details are not given in the submission.

Clinical Signs: Test substance-related clinical signs (unkempt fur) were restricted to animals receiving amlodipine besylate alone (30 mg/kg/day) or in combination with olmesartan medoxomil (30:300 mg/kg/day).

Body Weights: A statistically significant reduction (dose-dependent for the combination dose groups) in mean body weight gain was noted for males (Table 3.1.1.3, Fig. 3.1.1.1) and females (Table 3.1.1.4, Fig. 3.1.1.2) for all treated groups relative to concurrent control from study day 7 to the end of the dosing period (Table 3.1.1.5).

Food Consumption: A statistically significant decrease in mean food consumption relative to control was noted for both sexes at 30:300 (amlodipine:olmesartan medoxomil) mg/kg/day for the entire duration of the study. At 10:100 (amlodipine:olmesartan medoxomil) mg/kg/day, significantly ($p < 0.05$) lower values were observed for males for the first 5 weeks and for females for the first 3 weeks of administration. Reduced food consumption ($p < 0.05$) was also noted for both sexes receiving amlodipine besylate at all time points for the first 8 weeks of dosing. Olmesartan medoxomil-treated animals demonstrated decreases in food consumption ($p < 0.05$) for the first 5 (males) or 6 (females) weeks. Thereafter, the values were comparable to that of the control group.

TABLE 3.1.1.3
GROUP MEAN BODY WEIGHTS (GM) FOR MALES

Test Article Dose		Day 1	7	14	21	28	35	42	49	56	63	70	77	84	91
Vehicle 0 mg/kg	Mean	126	151	183	209	229	243	255	264	272	279	284	288	292	294
	S.D.	5	6	6	6	7	8	8	9	9	10	11	11	12	12
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CS-8663 110 mg/kg	Mean	125	140D2**	157D2**	175D2**	192D2**	206D2**	215D2**	223D2**	229D2**	236D2**	242D2**	248D2**	252D2**	257D2**
	S.D.	6	6	9	10	13	14	15	14	14	14	16	14	15	16
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CS-8663 330 mg/kg	Mean	125	129D2**	146D2**	154D2**	169D2**	180D2**	185D2**	195D2**	197D2**	200D2**	200D2**	214D2**	219D2**	225D2**
	S.D.	5	8	8	13	13	14	16	16	17	16	14	12	14	14
	n	15	15	15	15	14	14	14	14	14	14	14	14	14	14
ROX-2150 30 mg/kg	Mean	126	145T2*	164A2**	179A2**	180A2**	182A2**	185A2**	197A2**	203A2**	214T2**	222A2**	227T2**	237T2**	241T2**
	S.D.	6	8	12	14	21	15	17	21	14	11	18	16	18	17
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CS-866 300 mg/kg	Mean	124	144T2*	165T2**	186A2**	204A2**	216A2**	227A2**	236T2**	245A2**	254T2**	260T2**	265T2**	271T2**	275T2**
	S.D.	5	8	8	11	12	13	14	14	15	15	17	17	18	17
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15

Significantly different from control : * P≤0.05, ** P≤0.01
A2:Aspin-Welch Test Two-Side , D2:Dunnett Test Two-Side , T2:t Test Two-Side

TABLE 3.1.1.4
GROUP MEAN BODY WEIGHTS (GM) FOR FEMALES

Test Article Dose		Day 1	7	14	21	28	35	42	49	56	63	70	77	84	91
Vehicle 0 mg/kg	Mean	106	119	129	139	145	152	155	160	163	166	168	171	170	171
	S.D.	4	4	5	6	6	6	6	7	7	7	7	7	8	8
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CS-8663 110 mg/kg	Mean	106	112D2**	121D2**	129D2**	137D2**	143D2**	147D2**	150D2*	155D2*	156D2*	159D2*	162D2*	164	163D2*
	S.D.	4	4	5	6	7	7	8	9	9	10	10	10	9	10
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CS-8663 330 mg/kg	Mean	107	109D2**	115D2**	117D2**	120D2**	124D2**	124D2**	125D2**	129D2**	133D2**	135D2**	138D2**	141D2**	141D2**
	S.D.	3	5	5	7	6	7	8	11	11	10	8	10	7	8
	n	15	15	15	15	15	15	15	15	14	14	14	14	14	14
ROX-2150 30 mg/kg	Mean	107	113T2**	120A2**	123T2**	130T2**	132A2**	135A2**	141A2**	142T2**	147A2**	153T2**	155T2**	157T2**	160T2**
	S.D.	4	6	9	8	9	10	11	12	10	12	10	11	11	10
	n	15	15	14	13	12	12	12	12	12	12	12	12	12	12
CS-866 300 mg/kg	Mean	106	115T2*	125T2*	132T2**	138T2**	145T2**	147T2**	152T2**	156T2*	158T2**	161T2*	162T2**	164T2*	164T2*
	S.D.	4	4	5	5	5	6	6	6	7	7	7	8	7	6
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15

Significantly different from control : * P≤0.05, ** P≤0.01
A2:Aspin-Welch Test Two-Side , D2:Dunnett Test Two-Side , T2:t Test Two-Side

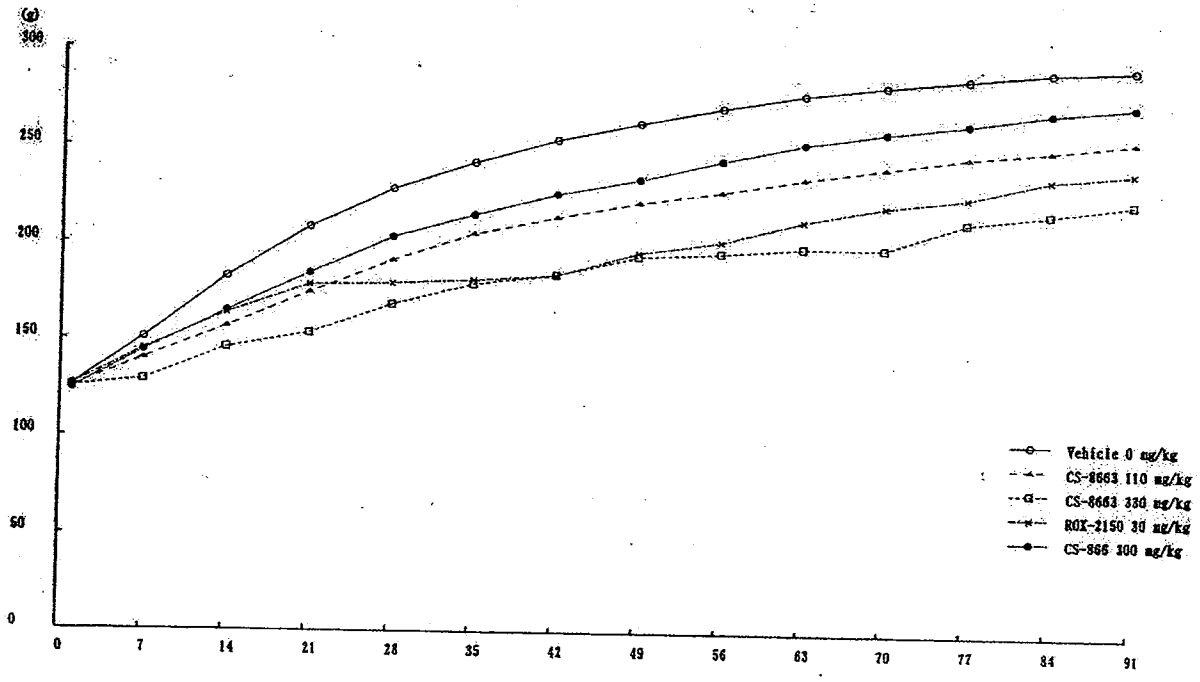

Fig. 3.1.1.1.: Group mean body weights, males (treated up to 91 days)

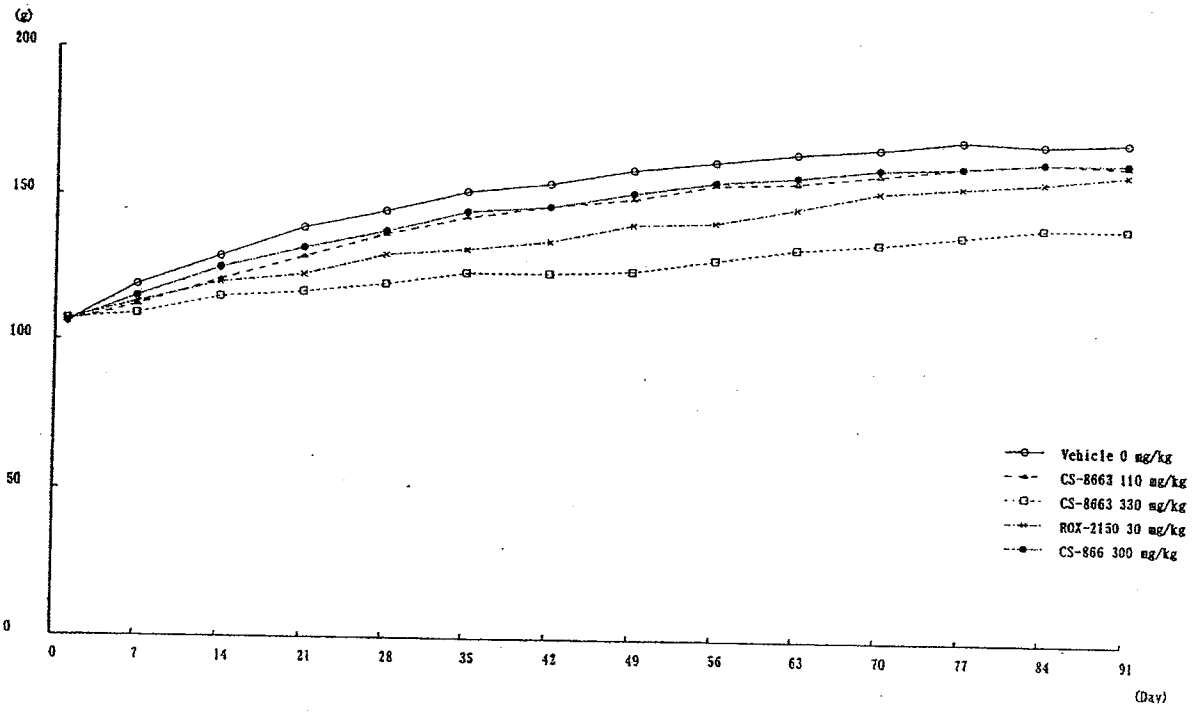

Fig. 3.1.1.2.: Group mean body weights, females (treated up to 91 days)
ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil.

TABLE 3.1.1.5
MEAN BODY WEIGHT CHANGE RELATIVE TO CONTROL AT THE END OF DOSING PERIOD

Sex	Test group	No. of animals	Mean body weight in week 13
Male	CS-8663 110 mg/kg	15	-13%**
	CS-8663 330 mg/kg	14	-23%**
	ROX-2150 30 mg/kg	15	-18%**
	CS-866 300 mg/kg	15	-6%**
Female	CS-8663 110 mg/kg	15	-5%*
	CS-8663 330 mg/kg	14	-18%**
	ROX-2150 30 mg/kg	12	-6%**
	CS-866 300 mg/kg	15	-4%*

Values in the table indicate percentage of change against the control mean (-: decrease).
*** (**): p≤0.05 (0.01) (significantly different from the control group)**

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil.

Ophthalmoscopy: No remarkable ocular changes
Urinalysis: A statistically significant, non-dose-dependent mean increase in urine volume and water intake, and a decrease in osmotic pressure relative to control was noted for both sexes at all doses. A significant increase in daily output of potassium and chloride was noted for both sexes with olmesartan medoxomil alone and for males with olmesartan medoxomil in combination with amlodipine besylate (dose-dependent). In addition, a significant decrease from concurrent control in total protein concentration was noted for males in all drug treated groups (Table 3.1.1.6).

TABLE 3.1.1.6
STATISTICALLY SIGNIFICANT CHANGES IN URINE CHEMISTRY VALUES IN RATS TREATED ORALLY WITH AMLODIPINE (ROX-2150), OLMESARTAN MEDOXOMIL (CS-866) OR COMBINATION (CS-8663)

Sex	Male				Female			
Test article	CS-8663		ROX-2150	CS-866	CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)	110	330	30	300	110	330	30	300
No. of animals	10	10	10	10	10	10	10	10
Urine volume	+253%**	+400%**	+191%**	+138%**	+171%**	+119%**	+158%**	+165%**
Water intake	+153%**	+121%**	+47%**	+32%**	+63%**	+44%**	+50%**	+38%**
Osmotic pressure	-58%**	-61%**	-60%**	-45%**	-56%**	-65%**	-63%**	-56%**
Na	N	+133%**	N	+33%*	N	N	N	+60%*
K	+69%**	+92%**	N	+38*	+36%*	N	N	+36%**
Cl	+56%*	+111%**	N	+33%*	N	N	N	+43%*
Creatinine	N	N	N	N	N	-36%*	N	N
Total protein	-72%**	-87%**	-58%**	-61%**	N	N	N	-75%*

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).
N: No remarkable changes
* (**): p≤0.05 (0.01) (significantly different from the control group)

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil.

Hematology: Dose-dependent decreases ($p < 0.05$) in RBC, hemoglobin and hematocrit relative to control were noted for both sexes at all combination doses and in animals receiving olmesartan medoxomil alone. Significant ($p < 0.05$) increases in MCV, MCH and MCHC were noted in animals receiving the high dose combination or receiving olmesartan medoxomil alone. These changes were attributed to olmesartan medoxomil. A shortening of prothrombin time in both sexes receiving the combination or just olmesartan medoxomil, and shortening of activated partial thromboplastin time in males receiving the combination were also noted (Table 3.1.1.7).

Clinical Chemistry: Mild to moderate, dose-dependent increases ($p < 0.05$) in blood urea nitrogen (up to 3.5-fold) were noted in animals of both sexes treated with the combination, olmesartan medoxomil or amlodipine besylate alone. Increased ($p < 0.05$) creatinine was noted in animals receiving olmesartan medoxomil alone and in males receiving the high dose combination. A significant increase in alkaline phosphatase relative to control was noted for both sexes in all dose groups. Decreases in protein in males in all dose groups were judged to be related to the malnutrition that was associated with suppression of body weight gain (Table 3.1.1.8).

TABLE 3.1.1.7
NOTEWORTHY FINDINGS FOR HEMATOLOGY PARAMETERS

Sex	Male				Female			
Test article	CS-8663		ROX-2150	CS-866	CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)	110	330	30	300	110	330	30	300
No. of animals	15	14	15	15	15	14	12	15
RBC	-10%**	-18%**	N	-10%**	-11%**	-16%**	+5%**	-13%**
Hb	-8%**	-13%**	N	-7%**	-10%**	-12%**	+2%**	-11%**
Ht	-8%**	-15%**	N	-8%**	-10%**	-13%**	N	-13%**
MCV	N	+5%**	N	+2%**	N	+3%**	-4%**	+1%**
MCH	N	+6%**	N	+2%**	+2%**	+6%**	-2%**	+3%**
MCHC	N	+2%**	N	N	+1%*	+2%**	+1%**	+1%**
Reticulocyte ratio	N	+33%**	N	N	N	N	N	N
Platelet	N	-5%*	+8%**	-7%**	N	N	+18%**	N
PT	-4%**	-5%**	N	-3%**	-3%*	-3%**	-7%**	-3%**
APTT	-14%**	-19%**	N	-12%**	N	N	+20%*	N
Fibrinogen	N	N	N	N	+16%**	+24%**	N	+12%**
WBC	N	N	-20%**	N	N	N	N	+10%*
Lymphocyte ratio	N	N	N	N	+9%*	+14%**	N	N
Segmented neutrophil ratio	N	N	N	N	-23%*	-33%**	N	N
Erythroblast	N	N	N	↑*	N	N	N	↑**

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).
↑: Increase (not calculated since mean value in the control group was zero)
N: No remarkable changes
* (**): $p \leq 0.05$ (0.01) (significantly different from the control group)

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

TABLE 3.1.1.8
NOTEWORTHY FINDINGS FOR CLINICAL CHEMISTRY PARAMETERS

Sex	Male				Female			
Test article	CS-8663		ROX-2150	CS-866	CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)	110	330	30	300	110	330	30	300
No. of animals	15	14	15	15	15	14	12	15
AST	-31%**	-39%**	-28%**	-25%**	N	N	+14%**	-6%*
ALT	-32%**	-18%*	-33%**	-19%**	+8%*	+64%**	N	N
ALP	+22%**	+31%**	+10%*	+14%**	+32%**	+91%**	+29%**	+25%**
Total cholesterol	+16%**	+27%**	N	+8%**	+14%**	+28%**	N	+10%**
Triglyceride	-35%**	-50%**	-52%**	N	+55%*	+227%**	+73%**	N
Phospholipid	+9%**	+19%**	N	+7%**	+9%**	+24%**	N	+6%*
Total bilirubin	N	N	N	N	↓**	↓**	N	↓**
Indirect bilirubin	N	N	N	N	↓**	↓**	N	↓**
Glucose	N	N	N	N	N	N	N	+8%**
BUN	+171%**	+353%**	+24%**	+124%**	+185%**	+170%**	+20%**	+180%**
Creatinine	N	+48%**	N	+23%**	+21%**	N	N	+26%**
Na	-2%**	-3%**	-3%**	-1%**	-3%**	N	-4%**	-3%**
K	+9%**	+30%**	N	+9%**	+13%**	+11%**	-9%*	+15%**
Cl	N	+3%**	-6%**	N	-2%**	+2%**	-9%**	-1%**
Ca	-3%**	-5%**	-2%**	-2%**	N	-5%**	N	-2%*
Inorganic phosphorus	N	N	-13%**	+17%**	N	N	N	+35%**
Total protein	-3%*	-8%**	-3%**	-5%**	N	-9%**	N	-3%*
Albumin	0%**	-7%**	N	-4%**	N	-4%**	N	N
A/G	N	N	0%**	N	N	+13%*	+13%**	N

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).
↓: Decrease (not calculated since mean value in the control or dose group was zero)
N: No remarkable changes
* (**): $p \leq 0.05$ (0.01) (significantly different from the control group)

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Organ Weights: Statistically significant and dose-dependent decreases in mean absolute and relative (to body) pituitary weights were noted for females (only absolute decrease in case of males) with all dose combinations and with amlodipine besylate alone relative to control. A dose-dependent and significant ($p < 0.05$) decrease in absolute thymus weight was observed for both sexes with olmesartan medoxomil alone or in combination with amlodipine besylate. Significant ($p < 0.05$) decreases in absolute and relative spleen weights were noted for both sexes dosed at 30:300 (amlodipine:olmesartan medoxomil) mg/kg/day. Relative weight of kidney increased for both sexes at all doses. Statistically significant increases in relative liver weights were noted at all doses except for males receiving olmesartan medoxomil. Absolute heart weight was significantly decreased for animals in the combination and olmesartan medoxomil groups. In the females of all dose groups, significant and dose-dependent decreases in absolute and relative uterus weights were noted. Relative ovary weight was significantly ($p < 0.05$) increased for females receiving olmesartan medoxomil with or without amlodipine besylate (Table 3.1.1.9).

TABLE 3.1.1.9
NOTEWORTHY FINDINGS FOR ORGAN WEIGHTS

Sex	Male				Female			
Test article	CS-8663		ROX-2150	CS-866	CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)	110	330	30	300	110	330	30	300
No. of animals	15	14	15	15	15	14	12	15
Body weight at necropsy	-14%**	-25%**	-22%**	-7%**	-6%*	-23%**	-11%**	-6%**
Brain								
absolute	-3%**	-6%**	-5%**	-2%*	-2%*	-7%**	-4%**	N
relative	+14%**	+25%**	+24%**	+7%**	N	+20%**	+7%**	+4%**
Pituitary								
absolute	-18%**	-28%**	-18%**	-11%**	-17%*	-43%**	-30%**	N
relative	N	N	+7%*	N	-13%*	-27%**	-22%**	N
Thyroid								
absolute	N	-25%**	-20%**	N	N	-20%**	-19%**	N
relative	N	N	N	N	N	N	N	N
Thymus								
absolute	-15%**	-30%**	-15%**	-10%*	-11%*	-36%**	N	-10%**
relative	N	N	+10%*	N	N	-18%**	N	N
Heart								
absolute	-15%**	-23%**	N	-17%**	-9%**	-19%**	+11%**	-15%**
relative	N	N	+23%**	-10%**	N	+6%*	+26%**	-9%**
Lung								
absolute	-6%**	-20%**	-14%**	-8%**	N	-17%**	-4%*	N
relative	+8%**	+6%**	+8%**	N	+5%**	+7%**	+7%**	+2%*
Liver								
absolute	-9%**	-18%**	-5%*	-9%**	N	N	+10%**	N
relative	+6%**	+9%**	+22%**	N	+10%**	+33%**	+23%**	+4%**
Spleen								
absolute	-7%*	-32%**	-20%**	N	N	-31%**	-8%*	N
relative	+10%**	-5%**	+5%*	N	N	-9%**	N	N
Kidney								
absolute	+6%**	-13%**	-10%**	N	+15%**	N	N	+11%**
relative	+23%**	+15%**	+15%**	+9%**	+22%**	+25%**	+13%**	+18%**
Adrenal								
absolute	N	-9%**	-12%**	N	N	-28%**	-16%**	N
relative	+6%**	+19%**	+13%**	+13%**	N	N	N	N
Testis								
absolute	-5%**	-15%**	-4%**	-5%**	/	/	/	/
relative	+11%**	+14%**	+24%**	N	/	/	/	/
Epididymis								
absolute	-6%*	-22%**	-10%**	-3%*	/	/	/	/
relative	+9%**	N	+16%**	+4%*	/	/	/	/
Ovary								
absolute	/	/	/	/	+22%**	N	N	+20%**
relative	/	/	/	/	+27%**	+18%*	N	+26%**
Uterus								
absolute	/	/	/	/	-32%**	-78%**	-58%**	-28%**
relative	/	/	/	/	-29%*	-72%**	-53%**	-24%**

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).
N: No remarkable changes
/: Not applicable
* (**): $p \leq 0.05$ (0.01) (significantly different from the control group)

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Gross Pathology: Distention of the small and large intestines was noted in one high dose combination male (#3005) found dead on day 38 and in all 3 deceased animals receiving amlodipine besylate. A dark red focus in the glandular stomach was noted in two high dose combination animals that died early in the study. The major gross findings in animals that survived to term were distention of the small and large intestines, dark red focus in the glandular stomach and unkempt fur and were confined to animals in amlodipine besylate and amlodipine besylate/olmesartan medoxomil groups. Smallness of the uterus was noted in females dosed at 30:300 (amlodipine:olmesartan medoxomil) mg or 30 mg amlodipine besylate/kg/day (Table 3.1.1.10).

TABLE 3.1.1.10
SUMMARY OF MAJOR NECROPSY FINDINGS IN ANIMALS THAT SURVIVED TO TERM

Sex	Male					Female				
Test article		CS-8663		ROX-2150	CS-866		CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)	0	110	330	30	300	0	110	330	30	300
No. of animals	15	15	14	15	15	15	15	14	12	15
General descriptions										
Unkempt fur	0	0	2	1	0	0	0	7	1	0
Undernourishment	0	0	9	6	0	0	1	10	3	0
Intestine										
Distention, ileum	0	0	4	4	0	0	0	0	2	0
Distention, colon and rectum	0	0	0	0	0	0	0	1	0	0
Stomach										
Dark red focus, glandular stomach	0	3	3	1	0	0	3	4	0	1
Uterus										
Small	/	/	/	/	/	0	0	14	3	0

Values in the table indicate the number of animals.
/: Not applicable.

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Histopathology: Main histopathological findings considered directly related to treatment were noted in the intestine, stomach, kidney and adrenal. Mild luminal dilatation of the ileum and/or colon was observed in both sexes treated with the amlodipine and olmesartan medoxomil combination at 30:300 mg/kg/day (includes a male that died prematurely) or amlodipine besylate alone (includes 3 deceased females). In addition, diffuse mucosal thickening of the above tissues was noted in these animals. Minimal erosion in the fundic region of the stomach was noted in both sexes dosed with the combination, a male dosed with amlodipine besylate and a female dosed with olmesartan medoxomil.

In kidneys, non dose-dependent increased incidence (relative to control) and minimal or mild thickening of the arterial wall of the afferent arterioles/interlobular arteries and increased incidence of regeneration of renal tubules were noted in both sexes given amlodipine:olmesartan medoxomil combinations or olmesartan medoxomil alone. Additionally, increased incidence (relative to control) of mineralization in the papilla was noted in both sexes with the low dose combination. None of these findings were noted in deceased animals. Minimal hypertrophy of adrenal glomerular cortical cells was noted in females dosed at 30:300 (amlodipine:olmesartan medoxomil) mg/kg/day, and in both sexes dosed at 30 mg amlodipine/kg/day. Minimal vacuolation of the fascicular cortical cells of the adrenal was observed in males given amlodipine and olmesartan medoxomil

combinations of 10:100 or more mg/kg/day or amlodipine besylate alone and in females receiving the high dose combination. In females, minimal or mild hypertrophy of the mammary gland ducts and atrophy of the uterus and vagina were noted at 30:300 (amlodipine:olmesartan medoxomil) mg/kg/day or amlodipine besylate alone, and vacuolation of the lutein cells in the ovary was noted in animals receiving the high or low dose combination or olmesartan medoxomil alone (Table 3.1.1.11).

TABLE 3.1.1.11
TREATMENT-RELATED MICROSCOPIC FINDINGS FOR SCHEDULED SACRIFICES

Sex		Male					Female				
Test article			CS-8663		ROX-2150	CS-866		CS-8663		ROX-2150	CS-866
Dose (mg/kg/day)		0	110	330	30	300	0	110	330	30	300
No. of animals		15	15	14	15	15	15	15	14	12	15
Adrenal											
Vacuolation, cortical cell, fascicular	(±)	0	5	13	10	0	0	0	2	0	0
Hypertrophy, cortical cell, glomerular	(±)	0	0	0	11	0	0	0	6	12	0
Intestine, ileum											
Dilatation, lumina	(+)	0	0	5	3	0	0	0	0	2	0
Thickening, mucosal, diffuse	(±)	0	0	0	2	0	0	0	1	0	0
Intestine, cecum											
Cell infiltration, mucosal	(±)	1	0	5	4	0	1	NE	2	NE	NE
Intestine, colon											
Dilatation, lumina	(+)	0	0	6	0	0	0	0	3	0	0
Thickening, mucosal, diffuse	(±)	0	0	1	1	0	0	0	2	3	0
Kidney											
Regeneration, tubular	(±/+)	2	15	14	1	14	0	12	7	0	5
Mineralization, papillary	(±/+)	3	12	3	4	3	2	12	2	0	3
Thickening, arterial wall, afferent arteriole/interlobular artery	(±/+)	0	14	14	0	15	0	13	13	0	15
Lymph node, mesenteric											
Microgranuloma	(±)	11	7	0	7	9	13	9	3	9	15
Mammary gland, inguinal											
Hypertrophy, ductal	(±/+)	0	0	0	0	0	0	0	9	2	0
Ovary											
Vacuolation, lutein cell	(±/+)	/	/	/	/	/	0	10	14	0	11
Spleen											
Hematopoiesis, extramedullary	(±/+)	9	6	2	5	9	0	1	3	2	1
Stomach											
Erosion, fundic	(±)	0	3	3	1	0	0	3	1	0	1
Thymus											
Atrophy	(±)	0	0	0	0	0	0	0	3	0	0
Uterus											
Atrophy	(±/+)	/	/	/	/	/	0	1	14	3	0
Vagina											
Atrophy	(±/+)	/	/	/	/	/	0	1	14	2	0

Values in the table indicate the number of animals.
NE: Not examined
/: Not applicable
±: Minimal, +: Mild

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Toxicokinetics: Based on dose normalized AUC values, in the combination groups, exposures to the individual drug components increased with increase in dose but were not dose proportional. Systemic exposure to amlodipine and olmesartan (the active metabolite of olmesartan medoxomil) increased with repetitive dosing of amlodipine besylate and olmesartan medoxomil, suggesting a tendency for accumulation. Levels for either sex were highest at the week 13 measurement (Tables 3.1.1.12 and 3.1.1.13). The mean week 13/day 1 ratios of the Cmax values for amlodipine and olmesartan were 2.9- and 1.6-fold for the low dose combination and 3.6- and 7.4-fold for the high dose combination, respectively. Similar ratios were noted for $AUC_{0\text{-}24h}$ values (3.4 and 2.0-fold for the low dose combination and 4.6- and 7.9-fold for the high dose combination, respectively). A similar pattern of accumulation (week 13/day 1 ratio) was noted with the repetitive administration of amlodipine besylate alone (Cmax 3.1, $AUC_{0\text{-}24h}$ 3.3) but not with the repetitive administration of olmesartan medoxomil alone. There is a subtle difference in the accumulation of olmesartan as compared to amlodipine with repetitive dosing in the combination groups. The levels of olmesartan but not amlodipine were significantly increased in the combination groups in weeks 4 and 13 relative to groups that received either drug alone. The differences in exposure to olmesartan between the high dose combination and olmesartan medoxomil alone groups (both groups were administered 300 mg olmesartan medoxomil/kg/day), were 6.9-fold and 8.5-fold for Cmax and $AUC_{0\text{-}24h}$ values, respectively, for the week 13 measurement. This suggests that amlodipine augments the plasma concentration of olmesartan. By contrast, olmesartan medoxomil had no effect on the amlodipine toxicokinetic parameters, although a significant accumulation was noted for amlodipine over the course of the study. There were no gender differences in any groups.

TABLE 3.1.1.12
13 WEEK TOXICITY STUDY IN RATS
MEAN TOXICOKINETIC PARAMETERS FOR OLMESARTAN (RNH-6270) IN RAT PLASMA

Sex	Male			Female		
Test article	CS-8663		CS-866	CS-8663		CS-866
Dose (mg/kg/day)	110	330	300	110	330	300
No. of animals	5	5	5	5	5	5
C_{max} (ng/mL)						
Day 1	3380	6310	8730	2360	3690	4580
Week 4	4370	30700	6240	3380	14400	4640
Week 13	5000	43100	5040	4180	28900[a)]	5640
T_{max} (h)						
Day 1	2.0	2.0	2.0	2.0	2.0	2.0
Week 4	2.0	2.0	2.0	2.0	2.0	2.0
Week 13	2.0	2.0	2.0	6.4	2.0[a)]	2.0
$AUC_{0\text{-}24h}$ (ng·h/mL)						
Day 1	14000	37100	32800	9630	17400	18400
Week 4	18800	187000	25400	16800	75400	26300
Week 13	20100	231000	22200	23800	166000[a)]	25500

Value in the table indicates the mean value.
Determination was also conducted on the control group (2 hours after dosing on day 1 and in weeks 4 and 13), and the concentrations of RNH-6270 were less than the quantification limit (1.00 ng/mL).
a): N=4 (1 animal died).

TABLE 3.1.1.13
13 WEEK TOXICITY STUDY IN RATS
MEAN TOXICOKINETIC PARAMETERS FOR AMLODIPINE IN RAT PLASMA

Sex	Male			Female		
Test article	CS-8663		ROX-2150	CS-8663		ROX-2150
Dose (mg/kg/day)	110	330	30	110	330	30
No. of animals	5	5	5	5	5	5
C_{max} (ng/mL)						
Day 1	42.1	199	169	49.9	177	174
Week 4	89.9	329	407	76.7	301	383
Week 13	151	660	540	111	675[a)]	511
T_{max} (h)						
Day 1	2.4	2.4	3.6	2.4	2.4	2.0
Week 4	3.6	4.8	3.2	2.4	5.2	3.4
Week 13	3.6	4.4	4.0	6.8	4.3[a)]	2.4
$AUC_{0\text{-}24h}$ (ng·h/mL)						
Day 1	434	2410	2450	544	1980	2390
Week 4	1120	4940	5580	957	4330	5940
Week 13	1910	9110	8090	1280	10400[a)]	7930

Value in the table indicates the mean value.
Determination was also conducted on the control group (2 hours after dosing on day 1 and in weeks 4 and 13), and the concentrations of Amlodipin were less than the quantification limit (1.00 ng/mL).
a): N=4 (1 animal died).

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate were expressed in terms of the base.

3.1.2. Evaluation of the Effects of Amlodipine on Olmesartan Exposure in Male F344 Rats Co-administered Amlodipine Besylate and Olmesartan Medoxomil

Key Study Findings: The $AUC_{0\text{-}24h}$ for olmesartan increased (>2-fold on day 28) only in the group which was administered a high combination dose of 100 mg olmesartan medoxomil/kg and 10 mg amlodipine/kg. There was no increase in olmesartan exposure when 10 mg amlodipine/kg was administered with 10 mg olmesartan medoxomil/kg.

Study No.: C-B287, Report #APS-153-010 and APS-153-018 b(4)
Location of Report: EDR
Conducting Laboratory and Location:

Dates of Study: The animals were dosed on May 31 and euthanized on June 28, 2006.
GLP Compliance: No
Drug, Lot #: Amlodipine besylate, lot #F40456, 101.2% pure; Olmesartan medoxomil, lot #0001, 99.2% pure
Formulation: The drugs were suspended in 0.5% (w/v) methylcellulose aqueous solution, once every 7 days, and used within 8 days of preparation (stored at 2 to 10°C). All of the investigational drugs were stable for 1 day at 23°C and for 16 days at 4°C.
Animals

Species/Strain: Rats, F344/DuCrlCrlj SPF (from Charles River)
#/Sex/Group: 5 males/group (see Table 3.1.2.1).
Age: 5 weeks old at initiation of dosing
Weight: 122-137 gm, at initiation of dosing
Husbandry: Animals were housed individually in cages. Food and water were available *ad libitum*.

Dosing

Doses: Amlodipine and olmesartan medoxomil were administered together at 8 different dose ratios (9 dose levels). Three additional groups of rats received olmesartan medoxomil at 1, 10 or 100 mg/kg/day. There were no control or amlodipine besylate only groups for this study (Table 3.1.2.1). Doses were selected on the basis of a 3 month oral toxicity study in the same rat strain in which deaths occurred in the high dose combination (30:300 amlodipine: olmesartan medoxomil mg/kg/day) and 30 mg amlodipine/kg/day groups. In addition, statistically significant decreases in mean body weight gain and food consumption were noted in animals receiving 10:100 or more mg amlodipine:olmesartan medoxomil/kg/day (see review section #3.1.1).
Route, Mode and Duration of Administration: Orally by stomach tube (5 ml/kg), once daily, for 28 days.

Observations and Measurements

Clinical Signs: All animals were observed thrice daily (twice during weekends) for clinical signs and mortality.
Body Weight and Food Consumption: Recorded for calculating dose volume. Data was neither tabulated nor evaluated.

TABLE 3.1.2.1
STUDY DESIGN

Group No.	Test group	Dose (mg/kg/day)		Final concentration (mg/mL)		Dose volume	Sex	No. of animals	Animal No.
		CS-866	ROX-2150	CS-866	ROX-2150	(mL/kg/day)			
1	CS-866: 1mg/kg	1	0	0.2	0	5	M	5	1001-1005
2	CS-866: 10 mg/kg	10	0	2	0	5	M	5	2001-2005
3	CS-866: 100 mg/kg	100	0	20	0	5	M	5	3001-3005
4	CS-866: 1 mg/kg + ROX-2150: 1 mg/kg	1	1	0.2	0.2	5	M	5	4001-4005
5	CS-866: 10 mg/kg + ROX-2150: 1 mg/kg	10	1	2	0.2	5	M	5	5001-5005
6	CS-866: 100 mg/kg + ROX-2150: 1 mg/kg	100	1	20	0.2	5	M	5	6001-6005
7	CS-866: 1 mg/kg + ROX-2150: 3 mg/kg	1	3	0.2	0.6	5	M	5	7001-7005
8	CS-866: 10 mg/kg + ROX-2150: 3 mg/kg	10	3	2	0.6	5	M	5	8001-8005
9	CS-866: 100 mg/kg + ROX-2150: 3 mg/kg	100	3	20	0.6	5	M	5	9001-9005
10	CS-866: 1 mg/kg + ROX-2150: 10 mg/kg	1	10	0.2	2	5	M	5	10001-10005
11	CS-866: 10 mg/kg + ROX-2150: 10 mg/kg	10	10	2	2	5	M	5	11001-11005
12	CS-866: 100 mg/kg + ROX-2150: 10 mg/kg	100	10	20	2	5	M	5	12001-12005

M: Male

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.

Toxicokinetics: Blood samples for test substance determination were collected from the jugular vein on study day 1 (1st dose) and in week 4 (28th dose) at 0 (prior to dosing, except for day 1), 2, 4, 7 and 24 hr after dosing (5 rats/treatment group/time point). The animals were killed after final blood sampling in week 4 and discarded without further examination.

Results

Analysis of Formulations: No information provided.

Mortality: No deaths occurred in any group.

Clinical Signs: Not given

Toxicokinetics: Maximum plasma concentration (Cmax) for olmesartan (the active metabolite of olmesartan medoxomil) was reached at 2hr, and for amlodipine was reached between 2.4 and 4 hr. Cmax and AUC_{0-24h} values for olmesartan increased with increase in dose but were not dose proportional to the dose of olmesartan medoxomil administered either alone or in combination with amlodipine besylate on day 1 or day 28. The levels of olmesartan were approximately 2-fold higher on day 1 than on day 28 for all dose ratio combinations with amlodipine besylate except for 3:100 and 10:100 (amlodipine:olmesartan medoxomil) mg/kg/day. The exposure values for olmesartan were nearly similar on day 1 and on day 28 for the 3:100 (amlodipine:olmesartan medoxomil) mg/kg/day group, and >2- fold higher on day 28 than on day 1 for the 10:100 (amlodipine:olmesartan medoxomil) mg/kg/day group. This suggests that the

highest dose of amlodipine (10 mg/kg/day) when given in combination with the highest dose of olmesartan medoxomil (100 mg/kg/day) increased systemic exposure to olmesartan by more than 2-fold relative to plasma levels of olmesartan noted for the group receiving 100 mg olmesartan medoxomil/kg/day alone. The mean amlodipine Cmax or AUC values increased more than dose proportionally on both days of measurement. However, the values were much higher (approx 2- and >3-fold higher, respectively, at 3 and 10 mg amlodipine/kg) on day 28 than on day 1 of dosing indicating some accumulation at high doses of amlodipine. The exposure values for amlodipine were similar among the groups receiving the same amlodipine dose, irrespective of the olmesartan medoxomil dose. This suggests olmesartan medoxomil had no effect on amlodipine exposure.

TABLE 3.1.2.2
MEAN TOXICOKINETIC PARAMETERS FOR OLMESARTAN IN RAT PLASMA

Group No.	Dose (mg/kg/day)		Day 1			Day 28		
	AML	OM	Tmax(h)	Cmax(ng/ml)	AUC_{0-24h} (ng·h/ml)	Tmax(h)	Cmax(ng/ml)	AUC_{0-24h} (ng·h/ml)
1	0	1	2.0	83.2	264	2.0	36.4	116
2	0	10	2.0	644	2000	2.0	347	1260
3	0	100	2.0	4230	14700	2.0	1720	7640
4	1	1	2.0	99.1	301	2.0	47.3	132
5	1	10	2.0	957	2880	2.0	362	1180
6	1	100	2.0	5600	18900	2.0	1830	8440
7	3	1	2.0	88.5	260	2.0	43.7	129
8	3	10	2.0	757	2410	2.0	340	1160
9	3	100	2.0	2850	10400	2.0	2370	9470
10	10	1	2.0	93.7	310	2.0	43.5	173
11	10	10	2.0	1350	4000	2.0	727	2430
12	10	100	2.0	3480	15100	2.0	8440	31100

Value in the table indicates the mean value (n=5).

TABLE 3.1.2.3
MEAN TOXICOKINETIC PARAMETERS FOR AMLODIPINE IN RAT PLASMA

Group No.	Dose (mg/kg/day)		Day 1			Day 28		
	AML	OM	Tmax(h)	Cmax(ng/ml)	AUC_{0-24h} (ng·h/ml)	Tmax(h)	Cmax(ng/ml)	AUC_{0-24h} (ng·h/ml)
4	1	1	3.2	2.25	24.6	4.0	3.76	39.1
5	1	10	2.8	2.31	25.4	3.2	3.15	32.4
6	1	100	2.8	2.40	26.7	2.8	3.61	34.8
7	3	1	2.8	8.34	91.4	2.4	18.3	204
8	3	10	2.8	9.15	83.9	3.6	17.7	190
9	3	100	2.4	8.46	83.6	2.8	17.5	187
10	10	1	2.8	39.4	380	2.4	114	1460
11	10	10	3.0	30.3	316	3.2	145	1770
12	10	100	4.0	33.7	350	2.4	120	1480

Value in the table indicates the mean value (n=5)

3.1.3. Mechanistic Study of the Increase in Olmesartan Exposure in Male F344 Rats Co-administered Amlodipine Besylate and Olmesartan Medoxomil

Key Study Findings: The motile activity of the digestive tract, as indicated by the migration of carbon powder, was significantly decreased in rats treated with amlodipine besylate alone or in combination with olmesartan medoxomil but not with olmesartan medoxomil alone. This conclusion was supported by a significant increase in the weight of the GI tract with its contents in rats treated with amlodipine besylate alone or in combination with olmesartan medoxomil relative to control or olmesartan medoxomil alone. These effects of amlodipine were probably responsible for increasing the absorption of olmesartan medoxomil as indicated by an increase in olmesartan exposure when olmesartan medoxomil was co-administered with amlodipine besylate. Amlodipine showed no effects on the elimination profile of olmesartan.

Introduction: In the 3 month toxicity study, combined administration of amlodipine besylate and olmesartan medoxomil to rats resulted in increased systemic exposure to olmesartan as compared to exposure in the group given olmesartan medoxomil alone. It was suggested that amlodipine at high doses might influence absorption of olmesartan medoxomil because of its relaxant effect on the intestinal smooth muscle. Thus, in the present study, the motile activity of the digestive tract was evaluated in rats treated with amlodipine besylate and olmesartan medoxomil for 4 weeks (experiment I). In additional animals, the effect of amlodipine on the elimination of intravenously administered olmesartan was evaluated (experiment II).

Study No.: C-B288, Report #APS-153-011 and APS-153-017 b(4)
Location of Report: EDR
Conducting Laboratory and Location:

Dates of Study: The animals were first dosed on June 6 and the study was completed on July 7, 2006.

GLP Compliance: No

Drug, Lot #: Amlodipine besylate, lot #F40456, 101.2% pure; Olmesartan medoxomil, lot #0001, 99.2% pure

Formulation: Amlodipine besylate and olmesartan medoxomil were suspended in 0.5% (w/v) methylcellulose aqueous solution, once every 7 days, and used within 8 days of preparation (stored at 2 to 10°C). Both of these formulations were stable for 1 day at 23°C and for 16 days at 4°C. Olmesartan (the metabolite) was prepared in water for injection and diluted with physiological saline to a final concentration of 10 mg/ml on the day of administration. The olmesartan formulation was stable for 8 days (stored at 2 to 10°C) at 100 mg/ml.

Animals

Species/Strain: Rats, F344/DuCrlCrlj SPF (from Charles River)
#/Sex/Group: 5 males/group (see Table 3.1.2.1).
Age: 5 weeks old at initiation of dosing
Weight: 108-124 gm, at initiation of dosing
Husbandry: Animals were housed individually in cages. Food and water were available *ad libitum*.

Dosing

Doses: In experiment I (absorption), amlodipine besylate (doses are expressed in terms of the base) and olmesartan medoxomil were administered at oral doses of 0:0, 30:300, 0:300 or 30:0 (Table 3.1.3.1). Doses for this study were selected on the basis of a 3 month oral toxicity study in the same rat strain in which deaths occurred in the high dose combination (30:300 amlodipine:olmesartan medoxomil mg/kg/day) and 30 mg amlodipine/kg/day groups. In addition, statistically significant decreases in mean body weight gain and food consumption were noted in animals receiving 10:100 or more mg amlodipine:olmesartan medoxomil/kg/day (see section 3.1.1 for details). In experiment II (metabolism), a single intravenous dose of olmesartan (10 mg/kg) was administered to groups of rats that were treated for 4 weeks with amlodipine besylate, olmesartan medoxomil or the combination (Table 3.1.3.1). The intravenous dose level of olmesartan was set at 10 mg/kg to mimic the olmesartan exposure level after oral administration of 300 mg olmesartan medoxomil/kg/day.

Route, Mode and Duration of Administration: Animals in experiment I were treated orally by stomach tube (5 ml/kg), once daily (see footnote to the table for duration). Animals in experiment II received a single dose of olmesartan intravenously (1 ml/kg, at the rate of 1.2 ml/min), *via* tail vein, after 4 weeks of oral administration of test drugs (see footnote to the table for details). Animals in the control group received the vehicle (0.5% methylcellulose solution).

TABLE 3.1.3.1
STUDY DESIGN

Test group	Dose (mg/kg/day)		Final concentration (mg/mL)		Dose volume (mL/kg/day)	Sex	Experiment I		Experiment II	
	CS-866	ROX-2150	CS-866	ROX-2150			No. of animals	Animal No.	No. of animals	Animal No.
Control[a)]	0	0	0	0	5	M	8	1001-1008	8	1009-1016
CS-8663 330mg/kg	300	30	60	6	5	M	8	2001-2008	8	2009-2016
CS-866 300 mg/kg	300	0	60	0	5	M	8	3001-3008	8	3009-3016
ROX-2150 30 mg/kg	0	30	0	6	5	M	8	4001-4008	8	4009-4016

a): 0.5 w/v% MC solution
M: Male

ROX-2150: Amlodipine besylate; CS-866: Olmesartan medoxomil; CS-8663: Amlodipine besylate and olmesartan medoxomil. The doses of amlodipine besylate are expressed in terms of the base.
Test substance administered for 31 (animal #xxx1 – xxx4), 32 (animal #xxx5 – xxx8), 29 (animal #xxx9 – xxx12) or 30 (animal #xxx13 – xxx16) days.

Observations and Measurements

Clinical Signs: All animals were observed thrice daily (twice during weekends) for clinical signs and mortality. However, results were not included in the submission.

Body Weight and Food Consumption: Recorded for the purpose of calculating dose volume. Data was neither tabulated nor evaluated.

Motile Activity of Digestive Tract (Experiment I): Two hours after the 31st (n=4/group) or 32nd (n=4/group) administration of amlodipine besylate, olmesartan medoxomil or their combination, carbon powder suspended in 5% (w/v) gum arabic solution was administered orally by a stomach tube (5 ml/kg). The animals were killed 30 min later and their digestive tracts dissected. The entire length of the small intestine (from the pyloric region to ileocecal junction) and the migration distance of the carbon powder in the intestine were measured. The migration ratio of the carbon powder (%) was calculated as:

[migration distance of carbon powder (cm) / length of small intestine] X 100

Additionally, the stomach, small intestine and cecum were weighed with their contents. All samples were discarded without further examination.

Toxicokinetics (Experiment II): Blood samples for determination of amlodipine and olmesartan were collected from the jugular vein (non-anesthetized animals) 2 hr after dosing on study days 1 (n=8) and 28 (n=8). 24 hrs after the final oral dose of amlodipine besylate, olmesartan medoxomil or the combination (i.e., on day 29 or day 30), all animals received an intravenous dose of olmesartan. Blood samples were collected from the jugular vein (non-anesthetized animals) on day 29 (half the animals in each group) or day 30 (the remaining half in each group) at 0 (prior to dosing), 0.25, 1, 3 and 6 hr after olmesartan dosing. The animals were killed after final blood sampling and discarded without further examination.

Results

Analysis of Formulations: No information provided.

Mortality: Two animals receiving 30:300 (amlodipine:olmesartan medoxomil) mg/kg/day were found dead, one (#2011) prior to dosing on day 28 and the other (#2014) after dosing on day 29. Necropsy of the dead animals revealed dark foci in the cecum (#2011) and dilatation of the ileum (#2014). The cause of death was attributed to treatment.

Clinical Signs: Not given

Motility Activity of Digestive Tract: The migration ratio of carbon powder in the small intestine was significantly decreased for groups treated with amlodipine besylate alone or in combination with olmesartan medoxomil relative to the control group. In contrast, the migration ratio did not differ significantly ($p > 0.05$) for the group that received olmesartan medoxomil alone relative to the control group (Table 3.1.3.2). This suggests that amlodipine suppressed the motility and caused relaxation of the intestinal smooth muscle, leading to trapping of the contents and increasing the weight of the GI tract segments. Thus, the GIT segments of rats treated with amlodipine besylate alone or in combination with olmesartan medoxomil weighed more ($p<0.05$) relative to control group segments (Table 3.1.3.3).

TABLE 3.1.3.2

THE MIGRATION RATIO OF CARBON POWDER IN RATS TREATED WITH AMLODIPINE BESYLATE, OLMESARTAN MEDOXOMIL OR THEIR COMBINATION FOR 4 WEEKS

Test group	Dose (mg/kg/day)		No. of animals	Migration ratio (%)
	AML	OM		
Control	0	0	8	61.7 ± 8.3[§]
Amlodipine besylate and OM	30	300	8	53.0 ± 7.8*
Olmesartan medoxomil	0	300	8	62.0 ± 6.6
Amlodipine besylate	30	0	8	34.2 ± 8.3**

[§]: Mean ± S.D.

* (**): $p<0.05$ (0.01) (Significant difference from the control group, Student's *t*-test)

TABLE 3.1.3.3
THE WEIGHTS OF GASTROINTESTINAL TRACTS OF RATS TREATED WITH AMLODIPINE BESYLATE, OLMESARTAN MEDOXOMIL OR THEIR COMBINATION FOR 4 WEEKS

Test group	Dose (mg/kg/day)		No. of animals	Wt of GIT[π] (gm)
	AML	OM		
Control	0	0	8	15.2 ± 1.44[§]
Amlodipine and OM	30	300	8	18.6 ± 1.61[**]
Olmesartan medoxomil	0	300	8	14.9 ± 1.34
Amlodipine	30	0	8	18.3 ± 2.89[*]

[π] : stomach, small intestine and cecum with contents
[§] : Mean ± S.D.
[*] ([**]) : $p<0.05$ (0.01) (Significant difference from the control group, Student's *t*-test)

Toxicokinetics: The levels of olmesartan determined (C_{2h}) on day 1 and day 28, prior to intravenous administration of olmesartan, were approximately the same for the olmesartan medoxomil alone group. However, the concentration of olmesartan, as noted in the previous study, was substantially higher (3.7-fold) on day 28 than day 1 for the combination dosing group. Also, the concentrations of amlodipine tended to be higher on day 28 than on day 1 for both the combination (1.4-fold) and the amlodipine alone (2.5-fold) dose groups (Table 3.1.3.4). These findings suggest the reproducibility of toxicokinetics noted in the previous toxicity studies.

TABLE 3.1.3.4
TK PARAMETERS FOR OLMESARTAN AND AMLODIPINE BEFORE SINGLE I.V. ADMINISTRATION OF OLMESARTAN TO RATS TREATED WITH AMLODIPINE BESYLATE, OLMESARTAN MEDOXOMIL OR THEIR COMBINATION

Test group	Dose (mg/kg/day) AML/ OM		No. of animals	Olmesartan		Amlodipine	
				Day 29 C_{2h} (ng/ml)	Day 29 C_{2h} (ng/ml)	Day 29 C_{2h} (ng/ml)	Day 29 C_{2h} (ng/ml)
Amlodipine besylate and OM	30	300	8	5220	19100[§]	175	248
Olmesartan medoxomil	0	300	8	4660	5320	0	0
Amlodipine besylate	30	0	8	0	0	156	388

[§] : n = 7, one male was found dead prior to dosing on day 28

The effect of olmesartan loading on the ability to excrete olmesartan (the active metabolite of olmesartan medoxomil) was measured in rats treated with olmesartan medoxomil with or without amlodipine besylate. The $t_{½}$ value for olmesartan was similar (0.77 to 1.19 hr, $p > 0.05$) in all groups including the control suggesting amlodipine had no effect on the elimination profile of olmesartan. As noted in previous studies, C_0, Cmax and AUC values for olmesartan were higher in the combination group relative to the group that received olmesartan medoxomil alone (Table 3.1.3.5).

TABLE 3.1.3.5
TK PARAMETERS FOR OLMESARTAN AFTER SINGLE I.V. ADMINISTRATION OF OLMESARTAN TO RATS TREATED ORALLY FOR 4 WEEKS WITH AMLODIPINE BESYLATE, OLMESARTAN MEDOXOMIL OR THEIR COMBINATION

Test group	Dose (mg/kg/day) AML/ OM		No. of animals	Olmesartan (Day 29 or 30) C_0 (ng/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-6h} (ng·h/ml)	$AUC_{0-\infty}$ (ng·h/ml)
Control*	0	0	8	44200	22500	0.25	0.77	21600	21600
Amlodipine besylate and OM	30	300	6	65200	38300	0.25	1.19	42700	43800
Olmesartan medoxomil	0	300	8	42100	22000	0.25	0.94	21700	21800
Amlodipine besylate	30	0	8	58100	30700	0.25	0.79	30200	30300

Value in the table indicates the mean value.
*: similar to other dose groups, control group received a single intravenous administration of olmesartan at the end of week 4.

4.0. OVERALL SUMMARY AND EVALUATION

CS-8663 (Azor®) is a fixed dose combination of amlodipine besylate and olmesartan medoxomil. Racemic amlodipine is a dihydropyridine calcium channel antagonist. It was developed by Pfizer and was approved in 1992 as the besylate salt for the treatment of hypertension, chronic stable angina and vasospastic angina (Norvasc®, NDA 19,787). Olmesartan medoxomil is a non-peptidic, orally effective, specific antagonist of angiotensin II, active at the AT-1 receptor. It was developed by Sankyo and was approved in April 2002 for the treatment of essential hypertension (Benicar®, NDA 21,286). A combination of these drugs is expected to result in an additive or synergistic antihypertensive effect when compared to single drug treatment. Nonclinical studies performed with amlodipine besylate and olmesartan medoxomil combinations include a 3 month toxicity study in rats and two follow-up studies that examined the issue of increased plasma levels of olmesartan, the active metabolite of olmesartan medoxomil, in the presence of amlodipine besylate. In the toxicity study, the drugs were administered in a ratio of 1:10 (amlodipine:olmesartan medoxomil) on a weight basis. However, clinically it will be administered in a ratio of 1:2 to 1:8.

Repeat Dose Toxicity

The oral gavage administration of amlodipine besylate (30 mg amlodipine/kg/day), alone or in combination with 300 mg/kg/day olmesartan medoxomil, to F344 rats for 13 weeks resulted in several deaths (as early as day 23 in the combination group and as early as day 8 in the amlodipine besylate group). Necropsy of these animals (as well as the animals that survived to term) revealed distention of the intestine and it was concluded that the major cause of death was an excessive pharmacological effect of amlodipine besylate, resulting in peristaltic motion disorder of the intestinal tract. The target organs of toxicity were stomach, intestine and adrenal for amlodipine besylate, and kidneys for olmesartan medoxomil. Mild luminal dilatation and diffuse mucosal thickening of the ileum and/or colon were observed in both sexes dosed at 30:300 mg or 30:0 mg (amlodipine:olmesartan medoxomil)/kg/day. Minimal erosion in the fundic region of the stomach was noted with the combination and with amlodipine besylate alone. Minimal hypertrophy of adrenal glomerular cortical cells was noted for females dosed at 30:300 mg (amlodipine:olmesartan medoxomil)/kg/day, and for both sexes dosed at 30 mg amlodipine/kg/day. Minimal vacuolation of the fascicular cortical cells of the adrenal was observed in males given amlodipine besylate:olmesartan medoxomil combinations of 10:100 or more mg/kg/day or amlodipine besylate alone and in females receiving the high dose combination. In females, minimal or mild hypertrophy of the mammary gland ducts and atrophy of the uterus and vagina were noted at 30:300 mg (amlodipine:olmesartan medoxomil)/kg/day and with amlodipine besylate alone. Statistically significant and dose-dependent decreases in absolute and relative uterus weights were noted for treated groups relative to control. In kidneys, thickening of the arterial wall of the afferent arterioles/interlobular arteries and increased thickness of the renal tubules were noted for males and females treated with olmesartan medoxomil alone or in combination with amlodipine besylate. Also noted were increased relative kidney weights for all treated groups. Additional findings included dose-dependent statistically significant decreases in mean body weight gain and food consumption relative to concurrent control for both sexes in all treatment groups for the duration of the study. Decreased RBC, hemoglobin and hematocrit ($p < 0.05$) and increased mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration ($p < 0.05$) relative to

control were noted for both males and females treated with olmesartan medoxomil alone or in combination with amlodipine besylate. Biochemically, mild to moderate and dose-dependent increases ($p < 0.05$) in blood urea nitrogen were noted in animals of both sexes in all drug-treated groups. Increased creatinine ($p < 0.05$) was noted in males and females receiving olmesartan medoxomil alone and in males receiving the high dose combination. A significant increase in alkaline phosphatase was noted for both sexes in all drug-treated groups. A NOAEL was not established in this study.

Toxicokinetics

Olmesartan medoxomil is rapidly and completely bio-activated by ester hydrolysis to olmesartan (RNH-6270) during absorption from the gastro-intestinal tract. In the 13 week toxicity study, systemic exposure to amlodipine and olmesartan increased with repetitive dosing of amlodipine besylate and olmesartan medoxomil, suggesting a tendency for accumulation for either sex. The mean week 13/day 1 ratios of the $AUC_{0\text{-}24h}$ values for amlodipine and olmesartan were 3.4 and 2.0-fold for the low dose and 4.6- and 7.9-fold for the high dose combination, respectively. A similar pattern of accumulation (week 13/day 1 $AUC_{0\text{-}24h}$ ratio, 3.3) was noted with the repetitive administration of amlodipine besylate alone but not with the repetitive administration of olmesartan medoxomil alone. There is a subtle difference in the accumulation of olmesartan as compared to amlodipine with repetitive dosing in the combination groups. The levels of olmesartan but not amlodipine were significantly increased in the combination groups in weeks 4 and 13 relative to groups that received either drug alone. The differences in exposure to olmesartan between the high dose combination and olmesartan medoxomil alone groups (animals in both groups had received 300 mg olmesartan medoxomil/kg/day) were, 6.9-fold and 8.5-fold for C_{max} and $AUC_{0\text{-}24h}$ values, respectively, at the week 13 measurement. This suggests amlodipine besylate augments the plasma concentration of olmesartan. By contrast, olmesartan medoxomil had no effect on the amlodipine toxicokinetic parameters.

Two follow-up studies were conducted to explain this phenomenon. The dosage titration study suggested that the impact of amlodipine on olmesartan exposure depended on the dosage of both amlodipine besylate and olmesartan medoxomil. The exposure values for olmesartan increased (>2-fold) only in the group which was administered a sufficiently high dose (10:100 (amlodipine:olmesartan medoxomil) mg/kg/day). The no effect dose of amlodipine on olmesartan exposure was 10 mg/kg when olmesartan medoxomil was administered at 10 mg/kg. Olmesartan medoxomil had no effect on amlodipine exposure, although a significant accumulation was noted for amlodipine on day 28 relative to the day 1 measurement. Since 30 mg/kg was the dose of amlodipine that produced enhanced pharmacological effects, its influence on the absorption of olmesartan medoxomil from the gut was studied. The motile activity of the digestive tract was significantly decreased in rats treated with amlodipine besylate alone or in combination with olmesartan medoxomil but not with olmesartan medoxomil alone. Increased smooth muscle relaxation by amlodipine had caused a longer retention of contents in the GI tract. This effect of amlodipine was probably responsible for increasing the absorption of olmesartan medoxomil. Amlodipine showed no effects on olmesartan elimination.

The highly pronounced systemic exposure to olmesartan when olmesartan medoxomil was co-administered with amlodipine besylate was not associated with excessive pharmacologic or toxicologic effects of olmesartan medoxomil at the dosage combinations studied in the 13 week study. A much higher dosage combination (>30:300 mg (amlodipine:olmesartan

medoxomil)/kg/day) would likely have revealed the more severe effects of olmesartan medoxomil that were noted in the original NDA review for olmesartan medoxomil (NDA 21,286).

Evaluation

The combined administration of amlodipine besylate and olmesartan medoxomil to rats did not augment any existing toxicities of the individual agents, nor induce any new toxicities and resulted in no toxicologically synergistic effects. However, a significant increase in systemic exposure to olmesartan (8.5-fold increase in AUC) was observed in the presence of amlodipine besylate. Mechanistic studies demonstrated that the observed increase in olmesartan exposure in the presence of amlodipine besylate is dependent on the dose of each drug in the combination and a change in the absorption of olmesartan medoxomil as a result of a marked relaxant effect of amlodipine on the intestinal smooth muscle. The highly pronounced systemic exposure to olmesartan, however, did not translate into unexpectedly toxic effects when compared to effects produced by olmesartan medoxomil alone. Furthermore, findings from human PK studies (report #CS8663-A-U101) demonstrated no interactions between the two drugs; mean olmesartan AUC values for groups receiving the combination (10:40 mg amlodipine:olmesartan medoxomil/day) or olmesartan medoxomil alone (40 mg/day) were, respectively, 6891 and 6794 ng.h/ml. Thus, it is concluded that the observed large increase in systemic exposure to olmesartan resulting from co-administration of amlodipine besylate in rats not a concern for humans when the combination is administered in accordance with the proposed labeling for this product.

Recommendations on Labeling: See page 6

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/s/

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REVIEW AND EVALUATION OF REPEATED DOSE TOXICITY STUDY PROTOCOL

IND Number: 70,410
Sequence Number/Date/Type of Submission: 022/September 20, 2005/Amendment
Center Receipt Date: September 23, 2005
Sponsor: Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
Reviewer: G. Jagadeesh, Ph.D.
Division: Cardiovascular and Renal Products (HFD-110)
Reviewer Receipt Date: September 29, 2005
Review Completion Date: October 11, 2005

DRUGS CS-8663 (Olmesartan medoxomil / Amlodipine besylate)

PHARMACOLOGICAL CLASS
Olmesartan: Angiotensin II receptor class 1 (AT_1 receptor) antagonist
Amlodipine: Dihydropyridine calcium channel blocker

INVESTIGATIONAL USE Treatment of hypertension at a dose of olmesartan medoxomil / amlodipine besylate at 40 mg : 10 mg.

CLINICAL FORMULATION Commercially available supplies of Benicar® (olmesartan medoxomil, Sankyo) and Norvasc® (amlodipine besylate, Pfizer) tablets.

Background: At a meeting held between the Division and Sankyo Pharma Development on December 20, 2004, it was agreed that a 3 month study using rats is sufficient to evaluate the safety of the subject combination of approved drugs. The agency guidance on "Nonclinical Safety Evaluation of Drug Combinations" recommends a toxicity study of 3 months duration for a chronic indication.

Protocol for 3-Month Toxicity Study in Rats

This GLP study (Study #B-5681) will be performed at a CRO. The toxic potential of olmesartan medoxomil/amlodipine besylate (CS-8663) will be assessed by its daily oral administration to male and female F344/DuCrlCrlj SPF rats for 13 weeks. The animals will be approximately 6 weeks of age and weigh approximately 90-150 g at the start of dosing, and be individually housed. Food and water will be available *ad libitum*. Rats will receive test substance, as a suspension in 0.5% w/v methylcellulose, orally by stomach tube at a dose volume of 5 ml/kg. Olmesartan/amlodipine will be administered at a dose ratio of 10:1 at 2 dose levels: 100/10 and 300/30 mg/kg/day. A third group will receive 300 mg/kg/day olmesartan alone and a fourth group will receive 30 mg/kg/day amlodipine alone. A fifth group will serve as a control and will receive methylcellulose, 5 ml/kg. Additional satellite animals in each group will be used for toxicokinetic study (see Table 1 for group composition).

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TABLE 1
GROUP COMPOSITION

Test group	Dose level (mg/kg/day)		Concentration (mg/mL)		Dose volume (mL/kg)	Sex	Main group		Satellite group for TK	
	ROX-2150	CS-866	ROX-2150	CS-866			No. of animals	Animal No.	No. of animals	Animal No.
Control	0	0	0	0	5	M	15	1001-1015	3	1201-1203
						F	15	1101-1115	3	1301-1303
CS-8663 110 mg/kg	10	100	2	20	5	M	15	2001-2015	5	2201-2205
						F	15	2101-2115	5	2301-2305
CS-8663 330 mg/kg	30	300	6	60	5	M	15	3001-3015	5	3201-3205
						F	15	3101-3115	5	3301-3305
ROX-2150 30 mg/kg	30	0	6	0	5	M	15	4001-4015	5	4201-4205
						F	15	4101-4115	5	4301-4305
CS-866 300 mg/kg	0	300	0	60	5	M	15	5001-5015	5	5201-5205
						F	15	5101-5115	5	5301-5305

M: Male, F: Female

Doses for this study were selected based on the results of a 28-day dose range-finding toxicity study in the same strain of rat. In that study, olmesartan medoxomil was administered at doses of 100 or 300 mg olmesartan/kg/day, and amlodipine besylate was administered to other groups at doses of 3, 10 or 30 mg amlodipine/kg/day. Though there were no deaths and no treatment-related clinical signs, statistically significant reductions in body weight gain and food consumption were noted for males receiving 30 mg amlodipine/kg/day. Among red blood cell indices, RBC, hematocrit and hemoglobin parameters in the female group receiving 10 or more mg amlodipine/kg/day were significantly ($p < 0.05$) higher than in the control group. A significant ($p < 0.05$) decrease in RBC counts, hemoglobin and hematocrit were noted in the male group receiving 300 mg olmesartan/kg/day, and in the female group receiving 100 or more mg/kg/day of olmesartan. Amlodipine-related biochemical changes included a significant ($p < 0.05$) decrease in total cholesterol, phospholipids, triglycerides, total protein, potassium and calcium in both sexes receiving 30 mg/kg/day. Males and females treated with olmesartan at 300 mg /kg/day showed a significant ($p < 0.05$) increase in urea nitrogen and creatinine relative to control. A statistically significant increase and a statistically significant decrease in heart weight (relative to control) were observed in the high dose groups of both sexes receiving amlodipine and olmesartan, respectively.

All animals in the 3 month study will be observed once daily prior to treatment initiation. During the study, all animals will be observed twice daily for mortality and for clinical signs. Body weight and food consumption will be recorded at weekly intervals. Ophthalmic examinations will be performed before dosing and in week 10-13 of study. Blood sampling for hematology and clinical chemistry will be done at the end of the dosing period. For toxicokinetics study, blood will be drawn from the cervical vein of satellite animals on day 1 and during study weeks 4 and 13 at 0, 2, 4, 7 and 24 hr after dosing. All surviving main study and moribund animals will be killed by exsanguination after collecting blood samples. Complete necropsies will be performed

on all animals (including moribunds) with a recording of macroscopic observations for all protocol tissues. Representative samples of the protocol tissues will be collected at necropsy from all animals and processed. Histopathological examination will be performed on all tissues from all animals in the control and 330 mg CS-8663/kg/day groups and all animals that die or are sacrificed as moribund during the study. The tissues/organs from animals in all other groups will be examined only if treatment-related changes are suspected from the results of 330 mg CS-8663/kg/day and control groups. Animals found dead will be necropsied soon after discovery.

EVALUATION

For the assessment of general toxicity, the draft guidance "Nonclinical Safety Evaluation of Drug Combinations" (Jan 2005) recommends a 3 month duration for a chronic indication. Doses proposed by Sankyo for their 3 month study are based on the results of a 28 day dose range-finding study in which the toxicological profiles of olmesartan and amlodipine were individually evaluated. Dose levels of 300 mg olmesartan and 30 mg amlodipine/kg/day were proposed as the highest doses to be tested since adverse effects were noted at these levels in the pilot study. Furthermore, based on a rat to human exposure comparison, even the proposed lower doses in rats, 100/10 mg olmesartan-amlodipine/kg/day, will result in comparable or higher exposures than in humans.

RECOMMENDATION: Protocol is acceptable.

Supervisor Concurrence signed

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/s/

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10/18/2005 09:03:03 AM
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