CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-093

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FKCMM

JUN 2 1 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-093

(BZ)
(BB)

SUBMISSION DATES: September 28, 1999
January 27, 2000
May 19, 2000
May 24, 2000
April 16, 1999

DRUG: candesartan cilexetil and hydrochlorothiazide tablets
Atacand HCT ™

DOSE: 16/12.5 mg and 32/12.5 mg tablets
CATEGORY: 4S
SPONSOR: AstraZeneca PLC

REVIEWER: B. Nhi Nguyen, Pharm.D.

TYPE OF SUBMISSION: NDA
INDICATION SEEKING: Treatment of hypertension

SYNOPSIS

AstraZeneca is seeking the approval of candesartan cilexetil (CC) /HCTZ 32/12.5 mg and 16/12.5 mg tablets for the second line treatment of hypertension. Since the single entities of the combination product are approved for the treatment of hypertension, the section 6 submission consists primarily of bioequivalence studies to show that the to-be-marketed formulation gives similar exposure as the formulations used in clinical trials.

There were five clinical studies that provide data that the fixed combination is superior to each component, and that each component is superior to placebo. These pivotal clinical studies were SH-AHK-004, AM124, EC408, AM153 and EC403. All studies except two (study EC403 and EC408) used formulations manufactured by Astra. Study EC 403 used tablets made by Takeda, the original manufacturer of CC. This study included doses that are lower (2, 4, 8 mg) than the ones to-be-marketed. In study EC408 the tablets (made in Japan) were encapsulated in for blinding purposes.

The 32/12.5 mg tablet was bioequivalent to both CC (16 mg x 2) and HCTZ (12.5 mg). The 16/12.5 mg tablet did not pass the bioequivalence criteria, because the upper limit of the 90% confidence interval for the ratio of Cmax of the fixed combination (16/12.5 mg) over the free combination (CC 16 mg and HCTZ 12.5 mg) was 126% for candesartan cilexetil.

The interaction studies had conflicting results. One study that used encapsulated tablets found no statistically significant interaction with AUC or Cmax when CC 16 mg and HCTZ 12.5 mg were used in combination or as monotherapy. Another study reported CC AUC was 24% higher and Cmax was 16% higher, while HCTZ AUC was 17% lower and Cmax was 11% lower when used in combination (8/12.5 mg tablet) versus the monotherapy. The latter results are in accord with previous data.

The sponsor did not conduct studies in special populations, nor did they examine any food effects. The sponsor has adequately validated the assay used in the bioequivalence and clinical studies. The dissolution method proposed was not adequate.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics finds the sponsor's submission for NDA 21-093 acceptable. However, the sponsor did not establish bioequivalence between the to-be- marketed 16/12.5 mg tablet and the formulation used in clinical studies because the ratio of the upper limit of Cmax was 1.26. It is our opinion that this upper limit of the 90% confidence interval is acceptable since CC has a wide therapeutic index and the slope of the dose-response curve is relatively shallow. Thus, relatively large changes in plasma concentration are needed to translate into clinically significant differences in effects.

The following dissolution method and specifications are recommended:

CC/HCTZ 16/12.5 mg tablet
Medium:
Apparatus:
Speed:
Specifications:

CC/HCTZ 32/12.5 mg tablet
Medium:
Apparatus:
Speed:
Specifications:

TABLE OF CONTENTS

BACKGROUND

Atacand HCT is a combination antihypertensive product that consists of candesartan cilexetil (CC) and hydrochlorothiazide (HCTZ). Candesartan cilexetil is a pro-drug to candesartan, an angiotensin II receptor antagonist with selectivity for the AT_1 receptor. The recommended starting dose for candesartan cilexetil in stable hypertensive patients is 16 mg once daily titrated to 32 mg if needed when used as monotherapy. HCTZ is a diuretic that further attenuates blood pressure when added to antihypertensive monotherapies. Both drugs are approved as individual entities for the treatment of hypertension in the United States. Because of the additive antihypertensive effect of combining HCTZ with other antihypertensive drugs, Astra Zeneca is seeking the approval of Atacand HCT as second line therapy for the treatment of hypertension.

Dosage Strength

The sponsor is proposing to market candesartan cilexetil/HCTZ tablets in strengths of 16/12.5 mg and 32/12.5 mg.

Pharmacokinetics of Candesartan

Candesartan cilexetil, also referred to as TCV-116 by Takeda exhibits linear pharmacokinetics for oral doses up to 32 mg. It is hydrolyzed during absorption to the active metabolite, candesartan (CV-11974 or H 212/9), which is partly metabolized to the inactive metabolite, CV-15959. The absolute bioavailability of candesartan is estimated to be 15%. Food with a high fat content does not affect the bioavailability.

The active metabolite, candesartan, is highly bound (>99%) to plasma proteins. Maximum serum concentrations are reached 3-4 hours after intake.

The terminal half-life is ~9 hours. Total plasma clearance of candesartan is 0.37 mL/min/kg (renal clearance 0.19 mL/min/kg). After oral administration, 26% of the dose is excreted unchanged in the urine.

Pharmacokinetics of HCTZ

The bioavailability of HCTZ is ~70%. The decline in drug plasma concentration is biphasic with a terminal phase half-life of about 10 hours. Half-life has been observed to vary between 5.6 to 14.8 hours. It is excreted mainly unchanged in the urine.

Pharmacokinetics of the Coadministration of Candesartan Cilexetil and HCTZ

A pharmacokinetic interaction study found that repeated once daily administration of HCTZ 25 mg with candesartan cilexetil 12 mg increased the Cmax and AUC of candesartan by ~20%. The same parameters were decreased ~ 10-15% for HCTZ when coadministered with CC. This modest interaction is not expected to have any clinical relevance since the dose-response relationship for the two compounds is relatively shallow, i.e. modest changes in plasma concentration will result in small changes in effect.

CC Formulation and Manufacturing

Candesartan cilexetil 4 and 8 mg tablets were formulated and manufactured by Takeda Chemical Industries, Ltd., Japan. These were subsequently transferred to Astra. Astra then developed the

16 and 32 mg tablets. All four strengths are approved for monotherapy in the treatment of hypertension in the U.S. For detailed information on the formulation of CC 16 and 32 mg tablets see Appendix II.

SUMMARY OF SUBMISSION

The sponsor submitted eight studies that contain pharmacokinetics; six bioequivalence studies and two descriptive studies. The following studies were not reviewed because they did not contain the dosage strength to be marketed.

SH-AHK-0002 – single dose bioequivalence study that includes CC/HCTZ 8/12.5 mg tablets
SH-AHK-0010 – single dose bioequivalence study that includes CC/HCTZ 8/12.5 mg tablets
TCV-116/EC028 – multiple dose PK descriptive/interaction study with CC 12 mg capsule and HCTZ 25 mg capsule

Bioequivalence

The sponsor has shown that the single dose fixed combination of CC/HCTZ 32/12.5 mg tablet manufactured by Astra is bioequivalent to the free combination of CC 16 mg x 2 tablets and HCTZ 12.5 mg tablets manufactured by Astra. The formulation of the free combination of CC 16 mg tablet and the HCTZ 12.5 mg tablet is the same as the formulation used in the pivotal clinical trial AM153.

The ninety percent confidence intervals for the ratio of the fixed combination over the free for AUC_{0-t}, $AUC_{t-\infty}$,, and Cmax were within 80 – 125% (see table below).

Fixed/Free	Estimate	90 % CI
Candesartan cilexetil		
AUC_{0-t}	1.02	(0.96, 1.08)
$AUC_{0-\infty}$	1.04	(0.98, 1.10)
Cmax	1.03	(0.93, 1.14)
HCTZ		
AUC_{0-t}	0.99	(0.95, 1.05)
$AUC_{0-\infty}$	1.00	(0.95, 1.05)
Cmax	1.03	(0.96, 1.10)

The sponsor has not shown bioequivalence between the fixed combination of CC/HCTZ 16/12.5 mg tablet manufactured by Astra and the fixed combination tablet manufactured by Takeda or the free combination of CC 16 mg and HCTZ 12.5 mg manufactured by Astra. The formulation of the CC 16 mg tablet and HCTZ 12.5 mg tablet is the same as that used in the pivotal clinical trial AM153.

As shown in the table below, the 90% confidence interval of Cmax for single dose CC was over 125% for both the ratio of the fixed Astra combination to the free combination and of the fixed Astra combination to the Takeda combination.

	Estimate	90 % CI
Candesartan cilexetil		
Astra/Free		
AUC_{0-t}	1.10	(1.04, 1.16)
$AUC_{0-\infty}$	1.08	(1.02, 1.13)
Cmax	*1.15*	*(1.05, 1.26)*
Astra/Takeda		
AUC_{0-t}	1.11	(1.05, 1.18)
$AUC_{0-\infty}$	1.09	(1.03, 1.15)
Cmax	*1.19*	*(1.09, 1.31)*
HCTZ		
Astra/Free		
AUC_{0-t}	0.98	(0.94, 1.02)
$AUC_{0-\infty}$	0.98	(0.94, 1.02)
Cmax	0.96	(0.90, 1.08)
Astra/Takeda		
AUC_{0-t}	1.04	(1.00, 1.09)
$AUC_{0-\infty}$	1.03	(0.99, 1.08)
Cmax	1.04	(0.97, 1.12)

Additionally, CC/HCTZ 8/12.5 mg was not bioequivalent to the free tablets. See table below.

	Estimate	CI
Candesartan cilexetil		
Fixed/Free		
AUC_{0-24}	1.10	90% (1.02, 1.19)
Cmax	*1.15*	*90% (1.04, 1.28)*
HCTZ		
Fixed/Free		
AUC_{0-24}	0.97	90% (0.94, 1.01)
Cmax	1.00	90 % (0.93, 1.08)

The three bioequivalent studies described above also reported descriptive PK parameters. These are included below. Pharmacokinetic parameters (mean ± SD) for CC and for HCTZ are similar between fixed and free combinations for single dose 32/12.5 mg.

	Fixed	Free
Candesartan cilexetil 32 mg		
AUC_{0-t} (ng*h/mL)	2262.2 ± 585.9	2278.6 ± 460.3
$AUC_{0-\infty}$ (ng*h/mL)	2478.6 ± 612.7	2550.6 ± 508.4
Cmax (ng/mL)	211.7 ± 73,6	214.0 ± 65.3
T ½ (hrs)	10.5 ± 2.2	11.4 ± 3.5
HCTZ 12.5 mg		
AUC_{0-t} (ng*h/mL)	437.5 ± 114.8	436.7 ± 105.3

AUC $_{0-\infty}$ (ng*h/mL)	474.2 ± 122.3	473.7 ± 110.9
Cmax (ng/mL)	76.0 ± 26.6	77.8 ± 24.8
T ½ (hrs)	6.8 ± 1.4	7.1 ± 1.8

Single dose PK parameters (mean ± SD) were similar for the fixed combination (Astra and Takeda) and the free combination of CC 16 mg and HCTZ 12.5 mg. See table below.

	Astra	Takeda	Free
Candesartan cilexetil 16 mg			
AUC $_{0-t}$ (ng*h/mL)	1113.6 ± 321.9	1005.2 ± 345.1	1012.7 ± 283.8
AUC $_{0-\infty}$ (ng*h/mL)	1187.8 ± 351.5	1093.6 ± 365.5	1094.1 ± 292.9
Cmax (ng/mL)	111.3 ± 38.7	95.7 ± 45.3	97.9 ± 37.7
T ½ (hrs)	8.9 ± 2.0	10.0 ± 2.8	9.7 ± 2.3
HCTZ 12.5 mg			
AUC $_{0-t}$ (ng*h/mL)	414.4 ± 96.8	399.7 ± 104.3	422.0 ± 101.2
AUC $_{0-\infty}$ (ng*h/mL)	446.3 ± 100.4	434.2 ± 110.1	453.9 ± 107.2
Cmax (ng/mL)	69.8 ± 21.2	67.0 ± 19.2	72.0 ± 19.6
T ½ (hrs)	6.5 ± 1.2	6.6 ± 1.3	6.2 ± 1.2

Steady state pharmacokinetics (mean ± SD) for candesartan cilexetil 8 mg and HCTZ 12.5 mg are summarized in the table below. The fixed combination has a slightly greater AUC and Cmax for candesartan cilexetil when used in combination compared to candesartan cilexetil alone.

Parameter	Candesartan Cilexetil	Free combination	Fixed combination
AUC $_{0-24}$ (ng*h/mL)	677 ± 228	695 ± 155	773 ± 193
Cmax (ng/mL)	67.9 ± 34.7	71.2 ± 24.5	82.7 ± 28.1
T ½ (hr)	9.07 ± 2.06	8.51 ± 1.98	9.77 ± 8.71

Steady state HCTZ pharmacokinetics (mean ± SD) are shown in the tablet below. HCTZ AUC and Cmax of the fixed combination are slightly smaller compared to that for HCTZ alone.

Parameter	HCTZ	Free combination	Fixed combination
AUC $_{0-24}$ (ng*h/mL)	520 ± 99.9	442 ± 84.1	433 ± 78.9
Cmax (ng/mL)	68.3 ± 14.6	60.0 ± 12.1	61.4 ± 19.2
T ½ (hr)	8.83 ± 0.993	9.17 ± 1.32	9.03 ± 1.01

PK in moderate essential hypertension

The first dose pharmacokinetics of candesartan cilexetil 16 mg and HCTZ 12.5 mg were described in a subgroup of mild to moderate essential hypertensives in the pivotal clinical study EC408. There were no statistically significant differences in Cmax or AUC when the drugs were used in combination or individually.

Mean candesartan plasma concentration-time curves were similar in patients treated with candesartan cilexetil alone and candesartan cilexetil with HCTZ. There were no significant

differences in AUC_{0-t} between candesartan cilexetil alone and candesartan cilexetil with HCTZ (AUC_{0-t} 2067.3 ± 963.9 and 1851.0 ± 678.9ng*h/mL, respectively).

Candesartan Cmax was 239.7 ng/mL and 219.6 ng/mL when dosed alone and when dosed with HCTZ, respectively. Tmax was 3 hours for both treatments, and there were no significant differences in $T_{½}$ between the two treatments.

HCTZ Cmax was 85.95 ng/mL and 81.20 ng/mL in patients treated with HCTZ alone and HCTZ with candesartan cilexetil, respectively. Tmax was 2 hours for HCTZ alone, and 3 hours for the combination. AUC_{0-t} and $T_{½}$ of HCTZ after dosing with candesartan cilexetil were on average 20% and 10% lower in comparison to AUC_{0-t} and $T_{½}$ with HCTZ alone (see table).

Descriptive Statistics for HCTZ PK parameters (mean ± SD)

Parameter	HCTZ Alone	HCTZ Fixed Combination
AUC_{0-t} (ng*h/mL)	667.7 ± 363.5	520.8 ± 272.1
Cmax (ng/mL)	85.95 ± 26.33	81.20 ± 22.49
Tmax (hr)*	2.0 (2.0, 6.0)	3.0 (2.0, 5.0)
T ½ (hr)	8.14 ± 4.11	6.15 ± 2.72

* median (min, max)

The pharmacokinetics in these patients is similar to that in healthy volunteers.

Drug interaction

At steady state CC 8 mg AUC is 16% higher and Cmax is 24% higher when given with HCTZ 12.5 mg then when administered as monotherapy (CC 8 mg). HCTZ 12.5 mg AUC is 17% lower and Cmax is 11% lower when administered as the fixed combination compared to monotherapy (HCTZ 12.5 mg). See also table below. These differences are unlikely to translate into clinically significant effects.

	Estimate	CI
Candesartan cilexetil 8 mg Fixed/Candesartan monotherapy		
AUC_{0-24}	1.16	95% (1.06, 1.27)
Cmax	1.24	95% (1.10, 1.41)
HCTZ 12.5 mg Fixed/HCTZ monotherapy		
AUC_{0-24}	0.83	95% (0.79, 0.87)
Cmax	0.89	95% (0.81, 0.97)

Formulation

The formulations proposed for commercial use are included in the table below:

Ingredient	Function	Formula, 16/12.5 mg (mg/tablet)	Formula, 32/12.5 mg (mg/tablet)
Candesartan cilexetil	active	16	32
HCTZ USP	active	12.5	12.5
Lactose Monohydrate NF	filler		

Cornstarch NF	disintegrant				
Polyethylene glycol 8000 NF	lubricant				
Hydroxypropyl Cellulose NF	binder				
Carboxymethylcellulose calcium NF	disintegrant				
Magnesium Stearate NF	lubricant				
Ferric Oxide NF, yellow	colorant				
Ferric Oxide NF, reddish-brown	colorant				
Total					

The formulation of the single entities is listed in Appendix II.

Assay

The sponsor determined candesartan cilexetil concentration by
HCTZ concentration was determined by
Both assays were validated and had acceptable precision, accuracy and sensitivity.

Dissolution studies

Based on the series of dissolution studies conducted by the sponsor on the two strengths of the to be marketed formulation using both the sponsor proposes the following dissolution method and specification for the 16/12.5 mg tablet:

Medium:
Apparatus:
Speed:
Specifications:

For the 32/12.5 mg tablet, the medium is the same except that will be used instead of The sponsor argues that should be chosen over because causes a pyramid formation which hinders the dissolution of HCTZ, and was too discriminating for HCTZ.

COMMENTS TO BE SENT TO THE SPONSOR

1. Dissolution is occurring very rapidly with a Almost complete dissolution is attained in minutes. Therefore, these conditions in our opinion would not be sensitive enough to pick up the differences between lots with different release characteristics. The rotation speed of is not too sensitive and would provide adequate discrimination. Based on this, the following dissolution method and specifications are recommended for CC/HCTZ.

CC/HCTZ 16/12.5 mg tablet
Medium:
Apparatus:
Speed:
Specifications:

CC/HCTZ 32/12.5 mg tablet
Medium:
Apparatus:

Speed:
Specifications:

/S/ 6/21/00

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I

Optional Intra-division OCPB Briefing date: June 21, 2000

Briefing attendees:
Paul Hepp
Mehul Mehta
Chandra Sahajwalla
Patrick Marroum
Gabriel Robbie

/S/ 6/21/2000

FT Initialed by Patrick Marroum, Ph.D

CC list: HFD-110: NDA 21-093; HFD-860: (Nguyen, Mehta); CDER Central Document Room