AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Candesartan cilexetil	REFERRING TO PART	
DOCUMENT NO.	SH-AHM-0013	OF THE DOSSIER	
VERSION NO.	1		
STUDY CODE	SH-AHM-0013		
DATE	27 December, 1999		

Comparison between candesartan cilexetil 16 mg and lisinopril 20 mg and their combination in patients with type II diabetes mellitus and microalbuminuria. - CALM Study -

STUDY CO-ORDINATING INVESTIGATORS SIGNATORY

STUDY CENTRE(S)

This was a multicentre study including 14 centres in Australia, 11 centres in Denmark, 6 centres in Finland and 13 centres in Israel.

PUBLICATION (REFERENCE)

Not applicable

STUDY PERIOD

- DATE OF FIRST PATIENT ENROLLED: June 1997
- DATE OF LAST PATIENT COMPLETED: July 1999

PHASE OF DEVELOPMENT

IIb

OBJECTIVES

The primary objective of the study was to estimate the effects of candesartan cilexetil 16 mg once daily (o.d.) and lisinopril 20 mg o.d. on urinary albumin excretion (UAE) after 12 weeks of treatment in hypertensive patients with type II diabetes mellitus and microalbuminuria.

The secondary objectives were to estimate the effects of candesartan cilexetil monotherapy (16 mg o.d.), lisinopril monotherapy (20 mg o.d.) and their combination on UAE after 24 weeks of treatment; on blood

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pressure (BP) 22-24 h post dose after 12 and 24 weeks of treatment, respectively, and on glomerular filtration rate (GFR) after 12 and 24 weeks of treatment, respectively, and on tolerability.

STUDY DESIGN

Double-blind, active control, randomised, parallel group design

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Type II diabetes mellitus (according to the WHO definition), hypertension (sitting diastolic blood pressure 90-110 mmHg at randomisation), urinary albumin/creatinine ratio (UACR) 2.5-25 mg/mmol after 2 weeks of placebo run-in, glycosylated haemoglobin (HbA1c) 5.5-10.0% at the start of the run-in period, female or male 30-75 years of age, signed informed consent. Excluded were fertile women or patients with impaired renal function, severe cardiovascular diseases or with standard contraindications to the study drugs.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Candesartan cilexetil 16 mg tablets o.d., batch numbers H 1191-01-01-02 and H 1191-01-01-05, oral administration.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Comparator drug, dosage and formulation	Batch no.
Lisinopril 20 mg o.d., encapsulated tablet	H 1290-01-01-01, H 1290-01-01-04
Placebo (candesartan cilexetil 16 mg) o.d., tablet	H 1203-03-01-01, H 1203-03-01-02
Placebo (lisinopril 20 mg) o.d., capsule	H 1292-01-01-01, H 1292-01-01-02, H 1292-01-01-03

DURATION OF TREATMENT

Four weeks of single-blind placebo run-in treatment followed by a period with 24 weeks of double-blind treatment (12 weeks on candesartan cilexetil 16 mg o.d. or lisinopril 20 mg o.d., followed by 12 weeks on candesartan cilexetil 16 mg monotherapy, lisinopril 20 mg monotherapy or the combination of the two products).

MAIN VARIABLE(S):

- EFFICACY

  Primary: the change in UACR from baseline (week 0) to week 12.
  Secondary: the change from baseline in:

  a) UACR to week 24
  b) BP to week 12
  c) BP to week 24
  d) GFR to week 12
  e) GFR to week 24

- SAFETY

Adverse events, laboratory assessments.

STATISTICAL METHODS

Assessment of treatment effects on UACR, all time spans, both in the analysis of the intention to treat and the per protocol data sets, was performed by adjusting for design factors as treatment, centre and treatment-by-centre interaction, and for the effect of baseline levels, body weight and the change in blood pressure. Assessments of blood pressure and heart rate included adjustment for baseline levels, besides the design factors named above.

PATIENTS

12-week analysis

	Candesartan cilexetil	Lisinopril	Total
No. planned	110	110	220
No. randomised and treated	99	99	198
Males/Females	66/33	62/36	128/69
Mean age (range)	59.7 (30-86)	60.0 (39-76)	59.8 (30-86)
No. analysed for efficacy	99	98	197
No. analysed for safety	99	98	197
No. completed	85	90	175

24-week analysis

	Candesartan cilexetil	Lisinopril	Combination (C+L)	Total
No. randomised and treated	66	64	68	198
Males/Females	48/18	43/21	37/30	128/69
Mean age (range)	59.7 (30-86)	59.9 (39-75)	59.8 (35-76)	59.8 (30-86)
No. analysed for efficacy	66	64	67	197
No. analysed for safety	66	64	67	197
No. completed	40	41	44	125

SUMMARY - CONCLUSION(S)

- EFFICACY RESULTS

Both candesartan cilexetil 16 mg o.d. and lisinopril 20 mg o.d. reduced UACR significantly after 12 weeks therapy. In the candesartan group, the adjusted mean reduction was 30% (95% CI 15;42, $p<0.001$) compared to 46% in the lisinopril group (95% CI 35;56, $p<0.001$). There was no significant difference in reduction of UACR between the two treatments. After 24 weeks of treatment, the reduction in UACR in the group treated with the combination of candesartan and lisinopril (50%) was significantly ($p=0.036$) greater than that in the candesartan group (24%) and numerically greater than that in the lisinopril group (39%). Both the sitting

trough diastolic blood pressure (DBP) and systolic blood pressure (SBP) were significantly reduced after 12 weeks of treatment with candesartan (adjusted mean reduction 12.4/9.5 mmHg) or lisinopril (adjusted mean reduction 15.7/9.7 mmHg), with no significant differences between the treatments. In addition, 12 weeks of treatment with the combination of candesartan and lisinopril further reduced the DBP by 6.0 mmHg and SBP by 10.6 mmHg, corresponding to a total reduction of DBP by 16.3 mmHg and SBP by 25.3 mmHg from baseline to after 24 weeks of treatment. The differences between monotherapy with either candesartan or lisinopril and the combination of the two therapies with respect to the effects on blood pressure were highly significant. GFR was slightly reduced by lisinopril and the combination of candesartan and lisinopril, but not by candesartan. There was no consistent change in HbA1c throughout the study.

- SAFETY RESULTS

Candesartan cilexetil 16 mg o.d. was well tolerated. The proportion of patients experiencing at least one adverse event (AE) during each 12-week double-blind period was similar in all treatment groups (40-55%). Overall, the most commonly reported AEs during the double-blind periods were respiratory infections, cough and headache. The number of patients experiencing serious adverse events (SAE) was low, and varied between 2-3 patients in each treatment group per 12-weeks period (except during the first 12-week period with candesartan monotherapy when no patient experienced any SAE). Furthermore, the number of patients discontinuing due to an AE was low across all treatment groups/periods. During the first 12 weeks of treatment, four patients in the candesartan treatment group and five patients in the lisinopril treatment group withdrew due to an AE. During the second phase of the study (weeks 12-24), two additional patients in the lisinopril monotherapy group, and three patients on combination therapy, withdrew due to an AE. Elevated values of urea and/or creatinine and/or potassium were noted in single patients during the study. The means of B-urea, S-creatinine, S-potassium and S-uric acid increased slightly in the combination treatment group.

DATE OF THE REPORT

27 December, 1999