AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Atacand® 4/8/16 Tablets, Atacand® Protect 32mg Tablets and Atacand® PLUS 8/12.5 mg / 16/12.5 mg Tablets
ACTIVE INGREDIENT: Candesartan cilexetil and Candesartan cilexetil /Hydrochlorothiazide

Study No: NIS-CDE-ATA-2008/1 (NCT00608153)
Compliance of patients with essential hypertension treated with **Ca**ndesartan or Candesartan/Hydrochlorothiazide - CoCa

Developmental phase: IV
Study Completion Date: November 01, 2008 (data base lock)
Date of Report: September 24, 2009

OBJECTIVES:

This in practice evaluation program (IPEP) with at maximum daily dose of 32 mg candesartan or 16/12.5 mg candesartan/hydrochlorothiazide (candesartan/HCT) had the objective to evaluate, under routine daily medical care conditions, the subject compliance as well as the efficacy and tolerability of candesartan or candesartan/HCT in patients suffering from essential hypertension. In detail, this study had the following objectives:

Primary objective:

- to estimate under daily routine conditions the compliance rate, defined as the number of subjects with regular intake [7 days/week or 5-6 days/week] of the prescribed dose of candesartan or candesartan/HCT as judged by the physician at the end of the observational period after approximately 3 months;

Secondary objectives:

- to assess under naturalistic conditions the subjects' reason(s) for being compliant or non-compliant with the intake of the prescribed dose of candesartan or candesartan/HCT;
- to assess under daily routine conditions the subjects' reason(s) for withdrawal of the prescribed dose of candesartan or candesartan/HCT;
- to assess under daily routine conditions whether physicians are using procedures to improve the subjects' compliance regarding the intake of candesartan or candesartan/HCT and to get insight into the type and effects of these procedures;
- to evaluate under daily routine conditions the effect of candesartan or

candesartan/HCT on blood pressure values, by estimating the change of systolic and diastolic blood pressure, separately by the (maximum) prescribed daily dose of candesartan or candesartan/HCT;

- to assess the correlation between the compliance as judged by the physician, the medication adherence as stated by subject and actual systolic and diastolic blood pressure of subjects treated with candesartan or candesartan/HCT;
- to gain further insight into the occurrence of unknown, unexpected and/or rarely occurring adverse events (AE) by estimating the incidence under daily routine conditions.

METHODS:

This study was a so-called 'Anwendungsbeobachtung (AWB)' according to the German Drug Law (AMG, §67(6)), i.e. a specific type of post marketing surveillance study, and was performed in Germany by AstraZeneca GmbH.

Under daily routine conditions and without any intervention by the sponsor regarding the selection of patients, diagnostic procedures, therapeutic decisions (medicinal and non-medicinal therapy, treatment duration, etc.) or routine assessments, the participating physicians were asked to document compliance relevant data from candesartan or candesartan/HCT treated outpatients suffering from essential hypertension.

Paper CRFs were completed by the participating physicians and sent to a contract research organisation, Anfomed GmbH, for further processing. All data from the CRFs was entered into a SAS 9.2 data base. All tasks of data management and statistical analysis were done using this analysis system. To improve the data quality, multiple plausibility and consistency checks were performed based upon a Data Cleaning Plan. Invalid, inconsistent and/or implausible data were re-checked and corrected, where possible. However, no query process or on site monitoring was used to obtain corrective statements from the physicians.

Due to the non-interventional character of this PMS project, only an exploratory analysis with descriptive statistics has been performed.

RESULTS:

This IPEP was performed in Germany between 02-January-2007 (first subject in) and 18-DEC-2007 (last subject out).

Patient population

Overall, 1880 patients were documented in the IPEP by 483 participating office based physicians. Out of these 1880 patients, 96 (5.1%) patients had to be excluded from the efficacy analyses because these patients fulfilled at least one of the criteria for non-evaluability (such as missing date of first visit, date of first visit before study start, no data after first visit, follow-up visit date earlier than first visit, no information that the

patients was treated). 1784 of 1880 patients were considered as evaluable for statistical analysis.

The mean age of these patients was 63.2 years, The youngest patient was 25 and the oldest one was 96 years old. Of all patients 868 (48.7%) were male and 914 (51.3%) were female. The mean body mass index (BMI) was 28.67 kg/m², indicating that the patients were on average overweight.

The majority of patients (61,6%) were diagnosed with hypertension for more than 5 years (new diagnosis 5.1%; 1-2 years duration 17.9%; 2-5 years duration 15.5%; 5-10 years duration 29.1%; > 10 years duration 32.5%).

Baseline blood pressure averaged 147/86 mmHg with a standard deviation of 18.7/11.3 mmHg. The distribution of blood pressure according to the ESH-ESC 2007 classification of hypertension was optimal (BPs < 120 mmHg, BPd < 80 mmHg) in 2.5%, normal (BPs 120-129 mmHg, BPd 80-84 mmHg) in 9.1% , high normal (BPs 130-139 mmHg, BPd 85-89 mmHg) in 17.8%, grade 1 hypertension (BPs 140-159 mmHg, BPd 90-99 mmHg) in 38.7%, grade 2 hypertension (BPs 160-179 mmHg, BPd 100-109 mmHg) in 23.7%, and grade 3 hypertension (BPs≥180 mmHg, BPd ≥ 110 mmHg) in 8.2% of patients.

Relevant medical history was documented in 1402 patients (78.6%). The most common reported diseases were hypercholesterolemia (38.7%), obesity (35.9%), diabetes mellitus (23.4%), coronary artery disease (21.6%), cardiac failure (11.4%) and myocardial infarction (6.4%).

During the observational time 1163 patients (65.2%) had received treatment concomitant to candesartan or candesartan/HCT. For these patients relevant cardiovascular medication was reported as follows: beta blockers in 48.2% of patients; calcium canal antagonists in 22.9%, diuretics in 19.2%. In total 8.1% of patients received ACE-inhibitors, 34.1% lipid lowering medication, 9.9% antiplatelet drugs and 19.8% anti-diabetics.

63.2% of patients were prescribed candesartan as monotherapy and 36.8% candesartan in combination with hydrochlorothiazide. The prescribed candesartan dose ranged from 2 mg/d up to 64 mg/d. The most often prescribed dose was 16 mg/d (monotherapy 54.7%, combination therapy 80.2%), followed by 8 mg/d (monotherapy 28.7%, combination therapy 17.3%) and 32 mg/d (monotherapy 11.3%, combination therapy 1.7%). The only available fixed dose combination of candesartan plus hydrochlorothiazide on the market at the time of this IPEP contained 12.5 mg HCT. The average dose of candesartan increased from 14.62 mg/d at visit 1 to 15.33 mg/d at visit 2 for the monotherapy group during the study and for the combination therapy group from 15.42 mg/d at visit 1 to 16.50 mg/d at visit 2. The mean observational time per patient within this IPEP was 4.26 months with a median of 4.0 months.

Premature study termination was documented in 36 patients (2.0%). The most frequent reasons were adverse events (0.8%), patient's wish to discontinue (0.5%), lack of efficacy (0.3%).

The majority of patients (85.8%) took candesartan or candesartan/HCT regularly (7 days a week) and 13.3% took the prescribed medication mostly (5-6 days a week) according to the physicians' judgment at visit 2. Only 0.7% of patients took the medication rarely (1-4 days a week), and 0.1% of patient took it never (0 days a week) as judged by the physicians. Similar to the judgement by the physicians, a regular intake was reported by the majority of patients.

Various reasons for being non-compliant with the intake of the study drug were reported by the patients. The most frequent reasons were: I forgot to take the tablets, I did not have the tablets with me when I should take them, I was otherwise occupied. I take my blood pressure myself and if it is well, (sometimes) I do not take the tablet(s).

In 901 patients (50.5%) the physicians documented procedures to improve the patient's compliance (regularly 26.6%, sometimes 23.9%, never 11.3%, no answer 38.2%). The most used procedures were talking to patients (24.4%), blood pressure measurements (23.5%), explaining the risk of non-compliance (16.5%).

Overall blood pressure values were documented for 1751 patients for both visit 1 and visit 2. In these patients the mean blood pressure was 147/86 mmHg at visit 1 and 134/80 mmHg at visit 2. The mean decrease of systolic blood pressure was -13 mmHg between visit 1 and visit 2, while diastolic blood pressure decreased by -6 mmHg. The heart rate decreased slightly from 75 bpm at visit 1 to 73 bpm at visit 2. The number of patients with blood pressure values <140/80 mmHg was 513 (29.3%) at visit 1 and 1106 (63.2%) at visit 2.

Separated by monotherapy and by combination with HCT the mean systolic blood pressure decreased with candesartan by –14 mmHg and with candesartan/HCT by –13 mmHg, while the mean diastolic blood pressure decreased with candesartan by –7 mmHg and with candesartan/HCT by –6 mmHg from visit 1 to visit 2.

Values for blood pressure separated by the most common prescribed daily doses 8, 16 or 32 mg were recorded for visit 1 and visit 2. For patients receiving candesartan as monotherapy the mean systolic blood pressure decreased with 8 mg by -14 mmHg, with 16 mg by -15 mmHg, with 32 mg by -14 mmHg, while the mean diastolic blood pressure decreased with 8 mg by –8 mmHg, with 16 mg by –7 mmHg, and with 32 mg by –6 mmHg. For patients receiving candesartan in combination with HCT the mean systolic blood pressure decreased with 8 mg by -12 mmHg, with 16 mg by -12 mmHg, with 32 mg by -18 mmHg, while the mean diastolic blood pressure decreased with 8 mg by –6 mmHg, with 16 by –7 mmHg, and with 32 mg by –9 mmHg.

In 1726 patients with good compliance as judged by the physicians and in 14 patients with poor compliance as judged by the physicians blood pressure values were documented. For the patients with good compliance the mean systolic and diastolic blood pressure values decreased by –13/-6 mmHg, from 146/86 to 133/80 mmHg, whereas the mean values decreased by –10/-6 mmHg, from 168/97 to 158/91 mmHg in patients with poor compliance as judged by the physicians.

Similar to the judgment of patient's compliance by the physicians the systolic and diastolic blood pressure were separated by good and poor compliance as reported by the

patient. For patient's self-reported good compliance at visit 2 the mean decrease was by –13/-6 mmHg, from 146/86 to 133/80 mmHg (1652 patients) and for patient's self-reported poor compliance by –14/-6 mmHg, from 150/89 to 136/83 mmHg (29 patients).

At visit 2 the efficacy of candesartan or candesartan/HCT was rated as good or very good in most cases by patients and physicians (about 95%). Similarly, tolerability was assessed as good or very good in 98% of cases by the patients and physicians at visit 2. No distinct difference between patients and physicians assessment of efficacy and tolerability could be detected for patients prescribed candesartan as monotherapy or in combination with HCT.

Of the 1784 evaluable patients, 39 patients (2.2%) experienced in total 46 adverse events after the start of the observational time. The most common documented adverse events were general disorders and administration site conditions (8 patients, 0.45%) and infections and infestations (5 patients, 0.28%), cardiac disorders (5 patients, 0.28%), investigations (5 patients, 0.27%), gastrointestinal disorder (4 patients, 0.21%), vascular disorders (3 patients, 0.16%) and disorders of the nervous system (3 patients, 0.16%). In 16 patients (0.9%) adverse events led to treatment discontinuation. In one patient (0.06%) the treatment was temporarily stopped.

4 of these events were judged to be caused by candesartan or candesartan/HCT treatment (orthostatic blood pressure, allergic dermatitis, diarrhea, skin rash).

10 of the above mentioned adverse events (urinary tract infection with fever, suspicion of coronary heart disease, left ventricular insufficient, tachyarrhythmia, hospitalization without any reported reason, angina pectoris, skin rash, malignant hypertension, death due to plasmacytoma, unspecified death) that occurred in 9 patients were classified as serious (SAE), including 1 adverse event with assessment of causal relationship to the study drug (skin rash). 2 patients died. One patient died on an unspecified date and the cause of death was unexplained while for the other patient the cause of death was reported as plasmacytoma. Both cases were not judged to be caused by candesartan or candesartan/HCT treatment.