LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
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Scientific discussion

Atacand Plus
Candesartan cilexetil/hydrochlorothiazide

SE/H/162/03-04/DC

This module reflects the scientific discussion for the approval of Atacand Plus. The procedure was finalised at 06th of February 2009. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AstraZeneca, Sweden has applied for a marketing authorisation for the product Atacand Plus 32mg/12.5mg and Atacand Plus 32mg/25mg tablets. The active substances candesartan cilexetil and hydrochlorothiazide, are the same as in Atacand Plus Mite 8 mg/12.5 mg tablets and Atacand Plus 16 mg/12.5 mg tablets, which were approved 1998 and 1999. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Atacand Plus 32mg/12.5mg is presented in the form of tablets containing 32mg candesartan cilexetil which corresponds to 23.1mg candesartan and 12.5mg hydrochlorothiazide.
Atacand Plus 32mg/25mg tablets contain 32mg candesartan cilexetil which corresponds to 23.1mg candesartan and 25mg hydrochlorothiazide. The excipients are lactose monohydrate, hydroxypropylcellulose, maize starch, carmellose calcium, magnesium stearate, macrogol and iron oxides. The tablets are packed in blister packs made of polyvinyl chloride/polyvinylidene chloride (PVC/PVDC) and a push-through aluminium foil.

II.2 Drug Substance

Candesartan cilexetil does not have a monograph in the Ph Eur. Full details synthesis and controls are integrated into the dossier, as there is no European Drug Master File (*whichever is relevant).*
Candesartan cilexetil is a white to off-white, crystalline powder with is practically insoluble in water. The structure of candesartan cilexetil has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. It is a chiral pro drug presented as a racemate, converting to the achiral active metabolite *in vivo.* The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

The Chemistry, Manufacturing and Control information on hydrochlorothiazide is provided in the dossier in the form of a Certificate of Suitability to the European Pharmacopoeia (CEP). A copy of the CEP is provided.

II.3 Medicinal Product

Atacand Plus 32mg/12.5mg and Atacand Plus 32mg/25mg tablets are formulated using excipients described in the current Ph Eur, except the **iron oxides,** which comply with **EC**

directive 95/45/EC (*whichever is relevant)*. All raw materials used in the product except lactose monohydrate are produced from non-animal sources. Lactose monohydrate is derived from milk fit for human consumption. Lactose monohydrate meets the requirements of the CPMP Guideline 'Note for Guidance on Minimising Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products' (EMEA/410/01). Regarding excipients of human or animal origin, there is no risk to patients.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility and polymorphism.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

Nonclinical summary and overview have been submitted. Reference is made to own and previously submitted non-clinical data supporting the authorisations for candesartan cilexetil monotherapy (up to 32 mg) and combination therapy (up to 16 mg/12.5 mg). Reference is also made to the open literature regarding toxicology, genotoxicity and carcinogenicity of hydrochlorothiazide monotherapy (up to 50 mg for hypertension). Studies conducted with the combination administered by the oral route, previously assessed by the authorities, include acute toxicity in rats, repeated dose toxicity up to 13 weeks in rat and dog, embryotoxicity in mice, rats, and rabbits, and in vitro and in vivo genotoxicity studies.

Here, in the applicant's overview it is reported that hydrochlorothiazide potentiated the toxicity of candersatan cilexetil with the major effects on the renal system. It is believed to be pharmacologically mediated via effects on the renin-angiotensin system of both compounds. The risk for primary and/or secondary renal-related adverse events are thus expected to increase with the combination 32 mg/25 mg as compared with the already approved combination of 16 mg/12.5 mg. In reproductive studies, the addition of hydrochlorothiazide to candersatan cilexetil was reported to show no qualitative differences in toxicity profile. Candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney and hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow and may cause neonatal thrombocytopenia. PhVWP has recently settled the SPC text for pregnancy and lactation (sections 4.3, 4.4 and 4.6) for angiotensin-II receptor antagonists (EMEA/CHMP/PhVWP/474692/2007). Candesartan cilexetil and hydrochlorothiazide alone were tested negative and positive for gene mutation in the mouse lymphoma assay, respectively. In combination, no evidence of a synergistic effect was reported. Both candesartan cilexetil and hydrochlorothiazide were tested positive for chromosome aberration in Chinese Hamster lung cells in vitro. In combination, evidence of an enhancing effect was reported only at the highest concentration tested of hydrochlorothiazide (200 µg/ml candesartan+3000 µg/ml hydrochlorothiazide). No genotoxicity was observed in bacterial cells (Ames test), in vitro/in vivo (DNA repair test in rat hepatocytes), or in vivo (mouse

micronucleus test and rat bone marrow chromosomal aberration test) following treatment with the combination.

An ERA for candesartan has been submitted. The PEC/NEC ratios for microorganisms, surface water, ground water and sediment are all below 0.1. The ERA did not identify a potential risk to the environment.

In addition, in the non-clinical documentation a new study for the authorities was submitted (Study no 01-033 dated 22 May 2002; Single ascending oral dosing of candesaratn cilexetil in juvenile beagle dogs). It was concluded by the applicant that no findings attributable to treatment were noted on any of the parameters investigated in male and female juvenile dogs receiving single ascending doses of 20, 100 and 300 mg/kg candesartan cilexetil.

IV. CLINICAL ASPECTS

IV.1 Introduction

Despite the availability of a range of effective antihypertensive medications, the majority of hypertensive patients do not reach treatment goals recommended by professional guidelines with a single antihypertensive drug.

Patients who do not reach treatment goals with a single antihypertensive drug can achieve further blood pressure reduction with a combination of two or more drugs with different modes of action. In the large scale ASCOT trial on high risk hypertensives about 9 out of 10 patients were given two or more antihypertensive drugs in order to reduce blood pressure to <140/90 mmHg.

Candesartan cilexitil (hereafter called candesartan) and HCT have complimentary modes of actions and additive antihypertensive effects so that combinations of candesartan/HCT are more efficacious than each of their monocomponents. The objective of the development of candesartan/HCT fixed dose tablets of higher strengths, i.e. 32/12.5 mg and 32/25 mg, is to provide additional dosing options to patients whose blood pressure is not optimally controlled with candesartan 32 mg or HCT 12.5 to 25 mg monotherapy, and to simplify treatment by reducing, if possible, the number of daily medicaments. The use of a fixed dose combination tablet, as opposed to free combinations, is attractive to patients and prescribers and may increase compliance.

Fixed combination tablets containing candesartan and HCT were first approved in 1998 and are approved for second line treatment of essential hypertension in more than 80 countries, including European countries, USA, Canada and Australia. The approved once daily dosages are 8/12.5 mg, 16/12.5 mg, and in the US also 32/12.5 mg and 32/25 mg (the 32/25 mg tablet is not yet launched).

IV.2 Pharmacokinetics

Bioequivalence

In support of the application, two bioequivalence studies have been submitted:

- Study SH-AHK-0013 determined that 1 tablet of candesartan/HCT 32/12.5 mg and the combination of 2 tablets of candesartan 16 mg and 1 tablet of HCT 12.5 mg are bioequivalent with regard to AUC and C_{max}.

- Study D2456C00004 determined, as its primary objective, that 1 tablet of candesartan/HCT 32/25 mg and 2 tablets of the candesartan/HCT 16/12.5 mg are bioequivalent with regard to AUC and C_{max}. Study D2456C00004 demonstrates, as its secondary objective, that there is no pharmacokinetic drug-drug interaction between candesartan 32 mg and HCT 25 mg at concomitant administration.

Bioequivalence was demonstrated between the fixed combination tablets candesartan cilexetil/HCT 32/12.5 mg and 32/25 mg, respectively, with respect to both AUC and Cmax.

Interactions
In order to evaluate drug-drug interactions between candesartan and HCT, study D2456C00004 (secondary aim) and three *in vitro* studies together with three previously submitted clinical studies were presented.

There was no indication of in vitro metabolic interaction to a clinically relevant extent between candesartan or HCT with any of the CYP-enzymes examined at concentrations up to 100 µmol/L. The results of the clinical study D2456C00004 did not indicate any interaction between the two drugs at the applied dose level.

In conclusion, bioequivalence was demonstrated and there was no indication of a clinically relevant interaction between candesartan and HCT at the presently investigated dose levels.

IV.3 Pharmacodynamics

The pharmacodynamics of candesartan and hydrochlorothiazide has been studied extensively and reported in previous applications. No new pharmacodynamic studies were included in the present application.

Candesartan is an antagonist of the angiotensin II type 1 (AT1) receptor, hereby inhibiting endogenous angiotensin II activity. It shows a slow dissociation from the AT1 receptor, which results in a long duration of action (>24 hours) when administered once daily. It reduces systemic vascular resistance and blood pressure in hypertensive patients without a reflex increase in heart rate. It also reduces renal vascular resistance without compromising the glomerular filtration rate.

HCT is a diuretic that acts by inhibiting the reabsorption of sodium from the cortical dilution segment. It increases the urinary excretion of sodium and chloride. However, HCT has a long-term antihypertensive effect by reduced peripheral resistance that occurs already at doses that cause negligible diuresis. The exact mechanism of action is unknown.

IV.4 Clinical efficacy

The clinical programme includes four randomised controlled studies that are summarised in the table. In all studies, the treatment period was eight weeks. The Applicant refers to study EC-016 to as supportive because it was not performed with a 32/12.5 mg or a 32/25 mg dose strength.

In addition, a meta-analysis providing information on the overall dose relation of efficacy for different strengths of candesartan and HCT combinations has been performed. The latter study was based on all sponsor conducted candesartan/HCT combination studies of parallel-group design that were placebo-controlled.

Study code	Treatment groups	Design	Number of randomised patients
AM 153	Candesartan/HCT 32/12.5 mg Candesartan 32 mg HCT 12.5 mg Placebo	Placebo run-in, placebo-controlled, parallel-group	275
D2456C00002	Candesartan/HCT 32/25 mg Candesartan 32 mg HCT 25 mg Placebo	Placebo run-in, placebo-controlled, parallel-group	1524
D2456C00001	Candesartan/HCT 32/12.5 mg Candesartan/HCT 32/25 mg Candesartan 32 mg	Candesartan monotherapy run-in (add-on), parallel-group	1975
EC-016	Candesartan/HCT 4/12.5 mg Candesartan/HCT 8/12.5 mg HCT 12.5 mg	HCT monotherapy run-in (add-on), parallel-group	234

The study participants consisted of men and women (about 1:1 ratio) with essential/primary hypertension. In AM-153 there were about 76% Caucasians and 21% Blacks and in D2456C00002 the corresponding proportions were about 87% and 10%; in the other studies, the patient population was almost exclusively Caucasian. Mean age was 52-56 years and the proportion of patients that were 65 years or older ranged between 12% and 25.6%. The mean sitting blood pressure at randomisation was close to 150/100 mmHg and the mean duration of hypertension ranged between 6 and 10 years. Overall, the patient population appears to be fairly representative.

Primary variables

The changes from baseline to the end of the 8-week randomised study period in sitting diastolic blood pressure (DBP) and sitting systolic blood pressure (SBP) were used as primary efficacy variables. The mean values are presented in the table.

Study code	Treatment groups	Change in sitting SBP/DBP from baseline (mm Hg) [a]
AM 153	Candesartan/HCT 32/12.5 mg	-22.1 / -14.5
	Candesartan 32 mg	-8.6 / -10.6
	HCT 12.5 mg	-5.9 / -6.3
	Placebo	-3.2 / -3.7
D2456C00002	Candesartan/HCT 32/25 mg	-21.4 / -13.9
	Candesartan 32 mg	13.1 / -9.3
	HCT 25 mg	-11.6 / -7.7
	Placebo	-3.7 / -3.3
D2456C00001	Candesartan/HCT 32/12.5 mg	-13.0 / -8.8
	Candesartan/HCT 32/25 mg	-15.5 / -10.0
	Candesartan 32 mg	-6.1 / -5.6
EC-016	Candesartan/HCT 4/12.5 mg	-11.0 / -7.0
	Candesartan/HCT 8/12.5 mg	-13.4 / -7.9
	HCT 12.5 mg	-5.4 / -3.3

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

[a] Least squares mean or arithmetic mean (EC-016)

In the placebo controled studies, the applied for candesartan/HCT combinations caused a greater reduction in sitting SBP/DBP than the components. They also appear to be more efficacious than than candersartan alone when used as an add-on therapy after a candersartan run-in period (study D2456C00001). In absolute terms, the reductions are smaller in this study, which reflects the fact that a more 'treatment resistent' patient population was selected. Study EC-016 shows that an additional effect is also likely when candesartan/HCT is used after a HCT run-in period. However, the lower strengths of candesartan used in EC-016 makes an estimation of the magnitude of this effect uncertain.

In the studies AM-153 and D2456C00001, reduction of sitting DBP was statistically significantly greater with the combination treatment candesartan/HCT 32/12.5 mg as compared to the 32 mg candesartan or the 12.5 mg HCT monotherapy. In study AM-153, reduction in sitting SBP was not included in the confirmatory analysis. However, applying a post-hoc step-wise closed test procedure, combination treatment was confirmatorily statistically significantly more effective than the monocomponents also for reduction in sitting SBP. In the studies D2456C00001 and D2456C00002, for combination treatment with candesartan/HCT 32/25 mg, reduction of both sitting DBP and sitting SBP was statistically significantly greater as compared to the 32 mg candesartan or the 25 mg HCT monotherapy. Therefore, it was concluded that candesartan/HCT 32/12.5 mg and 32/25 mg have superior efficacy over the respective monotherapies.

In the add-on study D2456C00001, with candesartan 32 mg treatment run-in, reductions of both sitting DBP and sitting SBP were significantly greater with either of the combination treatments candesartan/HCT 32/12.5 mg and 32/25 mg as compared to the 32 mg candesartan monotherapy. This demonstrates that in patients whose blood pressure is not optimally controlled with candesartan 32 mg monotherapy, both candesartan/HCT 32/12.5 mg and 32/25 mg offer an additional blood pressure lowering effect.

In the add-on study EC-016, with HCT 12.5 mg treatment run-in, lower strengths of the candesartan/HCT combination (candesartan/HCT 4/12.5 mg and 8/12.5 mg) were significantly more efficacious in reducing sitting DBP and sitting SBP compared to HCT 12.5 mg monotherapy. This demonstrates that in patients whose blood pressure is not optimally

controlled with HCT 12.5 mg monotherapy, an additional blood pressure lowering effect with a combination with candesartan can be achieved.

In study D2456C00001 (after a run-in period with candesartan 32 mg), candesartan/HCT 32/25 mg produced a greater reduction than candesartan/HCT 32/12.5 mg in DBP as well as in SBP. These reductions were statistically significant. However, the magnitude of this differnce (-2.5/1.2 mm Hg) is rather modest.

Secondary variables
Controlled blood pressure was defined as a sitting blood pressure < 140/90 mm Hg at the end of the study, except for study AM-153 in which only DBP was used. A responder was defined as a patient with DSP < 90 or with a reduction from baseline ≥ 10 mm Hg.

Analysis of these variables, in general, gave the same results as the primary efficacy variables.

Dose-response meta-analysis
The Applicant made a meta-analysis of the dose-response over a wider range of candesartan/HCT dose combinations, using all sponsor conducted combination studies, including AM-153 and D2456C00001, with a suitable design (i.e. placebo controlled, randomised, parallel group).. The candesartan doses ranged between 0 and 32 mg and HCT doses between 0 and 25 mg. SBP and DBP response surfaces were then fitted to the data with multiple regression, using two different models (quadratic and E_{max}).

The predictions were similar for the two models and were, in general, close to the results of the submitted studies. Thus, the predictions suggested that addition of HCT to candesartan, even at 32 mg, could result in a substantially increase in efficacy. Another conclusion that can be drawn from the predictions is that while there may be an additional gain in efficacy from an increase in the candesartan dose from 16 to 32 mg, this gain is likely to be small.

IV.5 Clinical safety

According to the Applicant, the clinical experience with candesartan/HCT, in currently approved dosages, demonstrates that the combination is a well-tolerated antihypertensive therapy. The current safety profile of candesartan/HCT is based on data from patients who have received candesartan, HCT or candesartan/HCT combinations in clinical trials and/or in clinical practice. The estimated cumulative exposure to candesartan/HCT tablets during marketed use is approximately 9.3 million patient-years including doses up to candesartan/HCT 32/12.5 mg (April 2007).

The clinical safety evaluation is primarily based on each of the available controlled clinical studies with candesartan/HCT 32/12.5 mg and 32/25 mg dose groups in patients with hypertension, ie, studies AM-153, D2456C00001 and D2456C00002. Two of these studies included a candesartan/HCT 32/12.5 mg dose group (D2456C00001 and AM-153) and 2 studies included a candesartan/HCT 32/25 mg dose group (D2456C00001 and D2456C00002). Studies D2456C00001 and D2456C00002 are large studies with safety populations of 1971 and 1519 patients, respectively. In total, the 3 studies number 3765 patients in their safety populations. Of these, 718 patients were treated with candesartan/HCT 32/12.5 mg and 1155 with candesartan/HCT 32/25 mg.

Data from patients who received either candesartan/HCT 32/12.5 mg or 32/25 mg were pooled together for demographic subgroup analyses with regard to frequencies of adverse events (AEs).

A grouping of clinical studies with pooled AE data from patients randomised to either candesartan/HCT 16/12.5 mg, candesartan/HCT 16/25 mg, candesartan/HCT 32/12.5 mg, candesartan/HCT 32/25 mg, candesartan 16 mg, candesartan 32 mg, HCT 12.5 mg, HCT 25 mg or placebo is used to provide an additional context to the safety profile of the candesartan/HCT 32/12.5 mg and 32/25 mg dose strengths. The total number of patients in the analysis is 5586.

Dizziness was amongst the most common AEs in the combination treatment groups (2.3% - 4.7%); albeit, with differences between and within studies. According to the Applicant, no causal relationship was evident from the data and dizziness is therefore not considered to be an adverse drug reaction.

Dyslipidaemia was reported in study D2456C00001, but data supplied by the Applicant showed that this AE was unlikely to be treatment related.

There were no AEs at any frequency interpreted as causally related to treatment with candesartan/HCT beyond those in the approved Prescribing Information as attributed to either of the monocomponents.

The frequencies of patients with discontinuations due to AEs in studies D2456C00001 and D2456C00002 were similar across treatment groups. In study AM-153, the frequencies of discontinuations due to AEs varied somewhat between treatment groups but the frequency in the candesartan/HCT 32/12.5 mg group was similar to that of placebo. The mean frequencies of discontinuations in patients in the placebo controlled studies were 2.3% for patients in the candesartan/HCT 32/12.5 mg and 32/25 mg groups combined and 4.3% in the placebo groups.

Overall, serious adverse events were uncommon and there was no findings suggesting any new safety issues with the applied for fixed combinations.

IV.6 Discussion on the clinical aspects

Candesartan/HCT fixed dose tablets of higher strengths (32/12.5 mg and 32/25 mg) could provide additional dosing options to patients whose blood pressure is not optimally controlled with candesartan 32 mg or HCT 12.5 to 25 mg monotherapy. The use of a fixed dose combination tablet, as opposed to free combinations, is attractive to patients and prescribers and may increase compliance. The additional gains in efficacy compared with 16/12.5 mg may be small but could, nevertheless, be of benefit for selected patients.

The additional risk connected with the new fixed combination tablets is deemed to be very low. Candesartan/HCT has a favourable safety profile and no new safety issues have been identified with the higher strengths. Hypotonia due to an exaggerated pharmacodynamic effect is a possibility but that risk could be minimised by a careful dose titration.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product has been made.

The risk/benefit ratio is considered positive and *Atacand Plus* is recommended for approval.

VI. APPROVAL

Products approved in the MR/DCP procedure:
The Decentralised procedure for *Atacand plus 32 mg/12,5 and 32 mg/25 mg tablets* was successfully finalised on 2009-02-06.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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