Bundesinstitut für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Candesartan Amlodipin Zentiva
DE/H/3677/001 + 003/DC

Candesartan Amlodipin Zentiva
DE/H/3677/02/DC - withdrawn

Marketing authorisation holder in the Reference Member State, Germany :

Zentiva Pharma GmbH

Date: 09.04.2015

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Candersartan Amlodipin Zentiva 8 mg / 5 mg Candersartan Amlodipin Zentiva 16 mg / 10 mg *(withdrawn: Candersartan Amlodipin Zentiva 16 mg / 5 mg)*
INN (or common name) of the active substance(s):	Candesartan-cilexetil & amlodipine besilate
Pharmaco-therapeutic group (ATC Code):	C09DB
Pharmaceutical form(s) and strength(s):	Tablet, 8mg/5mg; 16mg/10mg *(withdrawn:Tablet, 16 mg / 5 mg)*
Reference Number for the Decentralised Procedure	DE/H/3677/001/DC, DE/H/3677/003/DC *withdrawn : DE/H/3677/002/DC*
Reference Member State:	DE
Member States concerned:	BG; CY; CZ; EE; EL; HU; LT; LV; PL; PT; RO ; SK
Applicant (name and address)	Zentiva k.s. U. Kabelovny 130 Dolni Mecholupy, 102 37 Prague 10, Czech Republic
Names and addresses of manufacturers responsible for batch release in the EEA	Zentiva k.s. U. Kabelovny 130 Dolni Mecholupy, 102 37 Prague 10, Czech Republic

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Scientific discussion during the initial procedure

This assessment report is published by BfArM following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to BfArM as Reference Member State (RMS) and the national competent authorities in the Concerned Member States (CMS).

It reflects the scientific conclusion reached at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the BfArM (www.bfarm.de).

To the best of the BfArM`s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: DE/H/3677/001 + 003/DC (withdrawn: DE/H/3677/002/DC)
Registration number in Germany: 88639.00.00, 88641.00.00
Pharmacotherapeutic group: Angiotensin II antagonists and calcium channel blockers
ATC code: C09DB
Route of administration: Oral use
Therapeutic indication: "Candersartan Amlodipin Zentiva is indicated as substitution therapy in adult patients with essential hypertension whose blood pressure is adequately controlled with amlodipine and candesartan given concurrently at the same dose level"
Prescription status: subject to medical prescription

For product information for healthcare professionals and users, including information on pack sizes and presentations, see SPC, PL and labelling.

1. INTRODUCTION

These applications concern a fixed dose combination (FDC) which is not yet authorised in the EU. A substitution indication in the treatment of essential hypertension is applied for.

Candesartan is an angiotensin II (Ang-II) receptor antagonist acting on the AT1 receptor subtype thus blocking the effect of Ang-II in the renin angiotensin system (RAS) cascade. It is administered orally as the inactive prodrug candesartan cilexetil which is rapidly and completely converted to candesartan during gastrointestinal absorption.
Amlodipine is a L-type Ca2+ channel blocker of the dihydropyridine group with a long-lasting effect on the L-type Ca2+ channel. By inhibiting the transmembrane influx of calcium ions into vascular smooth muscle, the intracellular Ca2+ concentration is decreased, leading to vasodilatation.

Candesartan Amlodipin Zentiva tablets were developed as immediate release formulations containing the drug substances candesartan cilexetil and amlodipine as besilate in the following strengths: 16mg / 10 mg and 8mg / 5 mg. It should be noted that the applicant has withdrawn the Marketing

Authorisation Application for the 16mg / 5mg dose strength after conducting a new bioequivalence study (code 12/13/CAA/BSD) in response to the major objection raised by the RMS in the Day70 Assessment Report. In this study no bioequivalence between the test product (Candesartan Amlodipin Zentiva 16mg/5mg) and the reference products Atacand 16mg / Norvasc 5 mg tablets could be achieved and subsequently the application for the 16mg/5mg dosage was withdrawn.

The proposed indication is: "Candesartan Amlodipin Zentiva is indicated as substitution therapy in adult patients with essential hypertension whose blood pressure is adequately controlled with amlodipine and candesartan given concurrently at the same dose level".

Currently, no fixed combination of amlodipine and candesartan has been approved in the EU. However, in Japan, 2 fixed combinations containing candesartan and amlodipine (8mg/5mg and 8mg/2.5mg) were approved in 2010.

This decentralised application concerns an abridged application, according to article 10b of Directive 2001/83/EC, so called fixed combination application, as amended. The dossier submitted provides the scientific basis for this application of fixed combinations of candesartan cilexetil + amlodipine as besilate (i.e. 16mg / 10mg and 8mg / 5 mg) tablets under Candesartan Amlodipin Zentiva trade names.
Marketing authorisation is applied for with DE as the Reference Member State and with BG, CY, CZ, EE, EL, HU, LT, LV, PL, PT, RO and SK as the Concerned Member States. Overall, the submitted dossier is considered adequate.

Since the indication applied for is substitution of a free combination by the respective fixed combination, it is necessary - in terms of pharmaceutical / clinical equivalence - to show that the components of the FDC products applied for are bioquivalent to the respective approved monocomponent innovator products (Guideline on the investigation of bioequivalence: CPMP/QWP/EWP/1401/98 Rev.1). Therefore, one bioequivalence study (Code: 45/11/CAA/BSD) has been submitted. This study is presented as "final integrated and statistical report" (dated 2012-07-03), as well as in the clinical overview and summary and as tabulated study report. The test product was the highest strength of the fixed combination Candesartan Amlodipin Zentiva (16mg / 10 mg). The reference products used in this bioequivalence study was the free combination of Atacand® (16mg) by Astra Zeneca GmbH (registered since 03.12.1997 / 26.04.2007 in Germany) and Norvasc® (10mg) by Pfizer (registered since 11.05.1993 / 03.03.2004 in Germany).
For the other Candesartan Amlodipin Zentiva dose-strenght 8mg / 5mg a biowaiver has been applied for. The applicant has withdrawn the Marketing Authorisation Application for the originally submitted application for the 16mg/5mg dose strength as in the subsequently conducted BE study no bioequivalence with the originators Atacand 16mg and Norvasc 5mg could be shown.

The applicant has also conducted a PK interaction study (code 11/13/CAA/TP1) in response to the major objection raised by the RMS in the Day70 Assessment Report.

The clinical overview (dated May 2012) is clearly written and is based on comprehensive literature (approx. 100 publications). It provides a review of the findings on the pharmacodynamic and pharmacokinetic properties, as well as of the efficacy and safety of candesartan and amlodipine as individual therapeutics. In addition numerous publications on combined therapies of amlodipine and other angiotensin II (Ang-II) receptor antagonist acting on the AT1 receptor subtype are adequately reviewed.Overall, the bibliographical data submitted are eligible to support the efficacy and safety of the combined use of Candesartan and Amlodipin in the treatment of essential hypertension.
The applicant has submitted a risk management plan.
The active substances are not considered new active substances.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current

manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

According to the applicant, the bioequivalence study (Code: 45/11/CAA/BSD) and the interaction study (code 11/13/CAA/TP1) were conducted in compliance with Good Clinical Practice (GCP). During review, there was no indication for GCP non-compliance.

2. QUALITY ASPECTS

2.1 Drug substances

2.1.1 Candesartan cilexetil

Candesartan cilexetil is an ester prodrug that is hydrolysed to the active form candesartan during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist with actions similar to those of losartan. It is used in the management of hypertension and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors.
It is a white or almost white powder, practically insoluble in water; slightly soluble in dehydrated alcohol and freely soluble in dichloromethane. It exhibits polymorphism. Candesartan cilexetil is marketed as a mono-substance product with the trade names Atacand.

Two ASMF's have been provided, two manufacturers . On Day 120 a certificate of suitability has been submitted for Candesartan Cilexetil manufactured by one manufacturre. Thus, the ASMF from this manufacturer is no longer valid for this application.
The chemical-pharmaceutical documentations and Expert Reports are of sufficient quality in view of the present European regulatory requirements.
The control tests and specifications for drug substance product are adequately drawn up.
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The retest periods of 5 years is stated in the CEP and the proposed retest period of 2 years is justified in ASMF.

2.1.2 Amlodipine besilate

Amlodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine. It is used in the management of hypertension and angina pectoris.
It is a white or almost white powder, slightly soluble in water and isopropyl alcohol; sparingly soluble in alcohol and freely soluble in methyl alcohol. Amlodipine besilate is marketed as a mono-substance product with the trade name Norvasc.
Two certificates of suitability have been provided. The control tests and specifications for drug substance product are adequately drawn up by the applicant.
Stability studies have been performed with the drug substance. The retest period of 5 years is stated on both CEP's.

2.2 Drug Product

The strength Candesartan 16mg/ Amlodipin 5mg has been withdrawn.

Candesartan/Amlodipine drug product is a white to off-white, round biconvex tablets, embossed with the relevant strength (8/5 and 16/10) on each side. 16/10 tablets are engraved with a halving score.

The manufacturers responsible for batch release in the EEA are:
1. Zentiva, k.s., U kabelovny 130, 102 37, Prague 10 - Dolní Měcholupy, Czech Republic
The active ingredients and excipients used are well known and of pharmacopoeial quality. Batch analysis data for nine batches are provided. All results meet the specified requirements. Batch release of the drug products will be done by Zentiva.

The manufacturing process is a standard process consisting of wet granulation. Candesartan cilexetil and a part of excipients are blended in a granulation vessel. Tablets are produced on rotary tableting machine. The tablets are packed into blisters. The proposed batch sizes are 100,000, 1,000,000 and 2,000,000 tablets.

The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on six batches (three batches of each strength). The batch analysis results show that the finished products meet the specifications proposed.

The container is transparent PVC/PE/PVDC//Al blisters. The package sizes are 14, 28, 30, 56, 84, 90 or 98 tablets for each strength.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 24 months for the drug product is considered acceptable and the storage conditions are "store at temperature below 30°C in original package in order to protect from light".

3. NON-CLINICAL ASPECTS

3.1 Pharmacology

Candesartan cilexetil

Candesartan cilexetil, a prodrug that is hydrolyzed to candesartan during absorption from the gastrointestinal tract, is a nonpeptide, orally effective, potent and selective AT1 subtype angiotensin II receptor antagonist.
The main finding concerning the pharmacology of Candesartan cilexetil published within the last 10 years seems to be that candesartan is an inverse agonist at the AT1 receptor (Yasuda et al. 2008).

Amlodipine

Amlodipine is a L-type Ca2+ channel blocker of the dihydropyridine group (with a Kd value of about 1 nM). Its effect on the L-type Ca2+ channel are long-lasting. By inhibiting the transmembrane influx of calcium ions into vascular smooth muscle, the intracellular Ca2+ concentration is decreased, leading to vasodilatation. Amlodipine also has a relaxing effect on vascular smooth muscle by stimulating the release of the vasodilating NO from the vascular endothelium.
Amlodipine has been shown to exhibit antioxidant activity (Mason 2011), and by an inhibition of inflammation reduced atherosclerotic lesions in mice (Yoshii et al. 2006).

3.2 Pharmacokinetics

Candesartan cilexetil

The pharmacokinetics of candesartan cilexetil in rats and dogs is described by Kondo et al. (1996). Candesartan cilexetil is a prodrug that is metabolized to candesartan by ester hydrolysis during gastrointestinal absorption, and to a minor extent by hepatic first-pass metabolism. Following oral administration of candesartan cilexetil to rats, unchanged drug was not detected in the systemic circulation, indicating complete hydrolysis to candesartan during absorption from the small intestine. The bioavailability of candesartan was 19 – 28 % in fed rats, 5 % in fed dogs, and 18 % in fasted dogs. In rats and in dogs linear pharmacokinetics was observed over the dose range 1 – 100 mg/kg. In rats, oral candesartan cilexetil is widely distributed throughout the body. Candesartan has been shown to cross the blood-brain barrier poorly, if at all. In rats candesartan crosses the placental barrier and is distributed to the breast milk of lactating rats. Candesartan and its metabolites are extensively bound to plasma proteins (> 99 %) in rats, dogs and humans. Hydrolysis of candesartan cilexetil occurs at the ester moiety, resulting in the formation of candesartan; this is followed by glucuronidation at the carboxylic acid and tetrazole ring. In rats given candesartan cilexetil,

conjugated metabolites of candesartan were detected in the plasma and faeces and accounted for 63 and 24 % of the total radioactivity in rat plasma and bile, respectively. Candesartan is glucuronidated at the carboxylic acid and tetrazole ring. Similar qualitative metabolites were observed in dogs. Following oral administration of candesartan cilexetil to rats and dogs, candesartan and other metabolites were predominantly excreted in the faeces, and the terminal half-lives were 3.8 h (rats) and 4.3 h (dogs). There has been no evidence for the inhibition or induction of CYP3A4, CYP2C9 or P-glycoprotein by candesartan cilexetil, and hence pharmacokinetic drug interactions are unlikely.

Amlodipine

Amlodipine is well absorbed after oral administration, and the bioavailability in humans is between 64 and 80%. The volume of distribution is approximately 21 l/kg, indicating a high tissue affinity of amlodipine. Amlodipine is strongly bound to plasma protein (humans 98 %, dogs 97 %, rats 94 %; Stopher et al. 1988).

In all species, amlodipine is extensively metabolized by the liver to inactive metabolites. The main metabolic pathway is oxidation of the dihydropyridine ring to the pyridine analogue.

In humans, 10% of the parent compound and 60% of metabolites excreted in the urine, and the terminal plasma elimination half life is about 35 50 hours.

3.3 Toxicology

3.3.1 Candesartan cilexetil

Detrimental effects of both ACE inhibitors and AT1 receptor antagonists administered during the second and third trimesters of pregnancy are well known. Several case reports describe oligohydramnios, fetal growth retardation, pulmonary hypoplasia, limb contractures, calvarial hypoplasia and neonatal death in association with maternal ACE inhibitor or AT1 receptor antagonist treatment during the second and third trimesters of pregnancy. Surviving infants may exhibit renal damage. The fetal abnormalities are probably related to extreme sensitivity of the fetus to the hypotensive effect of these drugs, and both ACE inhibition and AT1 receptor blockade seem to disrupt fetal vascular perfusion and renal function. Oligohydramnios seems to result from decreased foetal renal function (reviews in Alwan et al. 2005, Bois et al. 2005).

There is an ongoing discussion about the contraindication for the use of ACE inhibitors and AT1 receptor antagonists during the first trimester of pregnancy. The renin-angiotensin system (RAS) plays an important role in growth and development. Schütz et al. (Am. J. Pathol. 1996, 149: 2067-2079) demonstrated the presence of all components of the RAS in very early human development (30 – 35 days of gestation), and that both AT1 and AT2 receptors are expressed very early in development (24 days of gestation); the authors concluded that angiotensin II plays a role in the growth and differentiation of the kidney, adrenal gland, heart and liver. In early embryos, AT2 receptors are involved in multiple aspects of the morphogenesis of the kidney and urinary tract (Miyazaki and Ichikawa 2001, Comparative Biochemistry and Physiology 128: 89-97). Chung et al. (The Lancet 2001, 357: 1620) believe that AT1 receptor antagonists should never be used during pregnancy or in women who are likely to become pregnant, particularly since AT1 receptor antagonists may lead to activation of the angiotensin II AT2 receptor, which is thought to be involved in vascular development and growth. Cooper et al. (N Engl J Med 2006, 354: 2443-2451) studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and found that infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations of the cardiovascular system and of the central nervous system, and the authors concluded that exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided (Editorial by Friedman, N Engl J Med 2006, 354: 2498-2500). However, the PhVWP report on ACE inhibitors and angiotensin II receptor antagonists (AIIRAs) and Recommendations on the use during the first trimester of pregnancy (EMEA/CHMP/PhVWP/474692/2007) concludes that a contraindication during the first trimester of pregnancy is not justified.

There is a discussion about the possible carcinogenic effects of AT1 receptor antagonists. AT1 receptor antagonists like Candesartan induce both an increase in plasma renin activity and in plasma Ang II concentrations. It has been suggested (Levens et al. 1992; Gasparo et al. 1995) that elevated plasma Ang II concentrations could stimulate Ang II receptors not belonging to the subtype 1 (e.g. AT2 or AT4 receptors) thereby possibly leading to undesirable (e.g. mitogenic) effects. Ang II is a mitogen, stimulating the growth of e.g. vascular smooth muscle cells and cardiomyocytes, the release

of growth factors and the expression of certain proto-onkogens (Timmermans et al. 1993; Edwards and Ruffolo 1994; Edwards et al. 1995). However, these effects are blocked by AT1 receptor antagonists and, therefore, seem to be mediated by stimulation of AT1 receptors. Recently, Sipahi et al. (The Lancet 2010) have shown in a meta-analysis that AT1 receptor antagonists seem to be associated with a modestly (1.2 %) increased risk of new cancer occurrence. Therefore, both from a pre-clinical and clinical point of view the carcinogenic potential of AT1 receptor antagonists is under discussion. The CHMP (EMEA/H/A-5(3)/1274) concluded that "the weak evidence of a small increase in the risk of new cancer occurrence associated with AT1 receptor antagonists is limited by several bias", that "the current evidence from clinical trials and epidemiological studies do not support a signal of increased cancer risk associated with AT1 receptor antagonists" and that "preclinical studies do not provide a clear biological mechanism to support the hypothesis of an increased risk of cancer with AT1 receptor antagonists"; the conclusion of the CHMP was that "the currently available evidence does not confirm a meaningful increased risk of cancer with the use of AT1 receptor antagonists".

3.3.2 Amlodipine

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.
In a rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility.
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity.

4. CLINICAL ASPECTS

4.1 Pharmacokinetics

One bioequivalence study (Code: 45/11/CAA/BSD) has been submitted. The submitted bioequivalence study is a pivotal, single-centre, randomized, open-label, single-dose, two-period, two-sequence, two-treatment crossover study designed to evaluate the comparative bioavailability of candesartan and amlodipine from Candesartan Amlodipin Zentiva 16mg / 10 mg tablets (Zentiva, k.s., Czech Republic) and Atacand® (16mg) tablets plus Norvasc® (10mg) tablets administered as free combination to 34 healthy subjects under fasting conditions (for more details see clinical assessment report).

The results of this bioequivalence study are summarized in the below depicted two tables:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) - Amlodipine

Treatment	AUC_{0-72} p x h/ml/	$AUC_{0-\infty}$ pg x h /ml	C_{max} pg/ml	t_{max} h
Test (N=33)	234849.88 ± 53795.97 (CV=22.91%)		6693.4 ±1433.11 (CV=21.41%)	6.00 (4.00-12.00)
Reference (N=33)	227435.55 ± 45482.86 (CV=20%)		6424.87 ± 1390.73 (CV=21.65%)	6.02 (3.00 - 14.2)
***Ratio (90% CI)**	102.67% (99.44 - 106.00%)		104.38% 100.09 - 108.08%)	
AUC_{0-t} Area under the plasma concentration curve from administration to last observed				

concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration
at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values; Profile of Subject 18 was excluded*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) - <u>Candesartan</u>

Treatment	AUC_{0-t} ng x h / ml/	$AUC_{0-\infty}$ ng x h / ml	C_{max} ng/ml	t_{max} h
Test (N=33)	1483.80 ± 503.5 (CV=33.93%)	1538.72 ± 536.34 (CV=34.86%)	145.91 ± 42.59 (CV=29.19%)	3.50 (1.50 – 6.50)
Reference (N=33)	1378.22 ± 386.97 (CV=28.08%)	1451 ± 431.39 (CV=29.73%)	132.02 ± 43.1 (CV=32.65%)	4.10 3.00 – 6.50)
***Ratio (90% CI) (Test / Ref.)**	105.79% (98.70 – 113.40%)	104.33% 97.58-111.56%)	110.97% (101.04 – 121.88%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration
at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values; Profile of Subject 18 was excluded*

The PK parameters measured in this bioequivalence study were adequate. The 90% confidence intervals for all relevant parameters are within the predefined acceptance range for candesartan and amlodipine. The results are consistent with the assumption of bioequivalence between test and reference.

No separate bioequivalence study has been performed with the Candesartan Amlodipin Zentiva 8mg /5 mg dose strength applied for. Instead, justifications for a biowaiver for this dose strength have been submitted and accepted at day 120 of the procedure.

The applicant has also conducted a PK interaction study (code 11/13/CAA/TP1) in response to the major objection raised by the RMS in the Day70 Assessment Report. No interaction between candesartan and amlodipine.

4.2 Pharmacodynamics

The pharmacodynamic characteristics of candesartan and amlodipine as individual therapeutics are well known and well described in the clinical overview and summary. No new PD data for the fixed combinations were submitted and are not required for this application.

4.3 Clinical efficacy

The clinical overview (dated May, 2012) presents, among others, the aforementioned bioequivalence study (Code: 45/11/CAA/BSD) and provides reasons which justify the biowaiver for the lower dose strength.
Moreover, this document provides a critical review on the findings of the pharmacodynamic and pharmacokinetic properties, as well as on efficacy and safety of candesartan and amlodipine as individual therapeutics. In addition, available literature (4 publications) on the (free) combination of candesartan + amlodipine in hypertension are presented and discussed, coming to the conclusion that the combined application leads to a greater blood pressure lowering effect than the respective individual therapies (at similar dosage). Furthermore, as supportive data, positive results of publications on combined therapies of amlodipine + other angiotensin II (Ang-II) receptor antagonist acting on the AT1 receptor subtype are presented and discussed in these documents (details see PAR, section "Additional data").

4.4 Clinical safety

The safety of the two components of the fixed combination applied for (as individual therapeutics) is established. Available data on the combined administration of the two components of the proposed fixed combination as free combination do not indicate any safety problems.

4.5 Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System and asked the RMS to replace the previously submitted DDPS with the new Summary of Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS accepts this substitution

4.6 Risk Management Plan

The applicant stated that risk minimization measures for the identified safety concerns of hypotension and abnormal hepatic function will involve monitoring of these adverse events as part of routine pharmacovigilance activities. No additional risk minimization activities are required at present. This is endorsed.
Furthermore there is currently an outstanding safety referral on RAS-acting agents being investigated by the European Medicines Agency, candesartan as an Angiotensin-II-Receptor-Antagonist is involved in this referral.
Therefore the RMP and SPC/PIL of the combination of amlodipine and candesartan has to be updated following the outcome of the ongoing Art.31 Referral on RAS-acting agents.
An updated RMP should be submitted as track change version within 3 months after end of the Art.31 Referral an RAS-acting agents.

Periodic Safety Update Report (PSUR)

PSUR submission should follow the conventional submission scheme, half-yearly in the first two years, if not stated otherwise in the EMA EURD-List

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published non-clinical and clinical data. Pharmacodynamic and pharmacokinetic characteristics as well as efficacy and safety of candesartan and amlodipine are well known. The combined application of both substances is supported by 4 publications on the (free) combination of candesartan + amlodipine in hypertension and further supported by publications on combined therapies of amlodipine and angiotensin II (Ang-II) receptor antagonist acting on the AT_1 receptor subtype.

The indication applied for is substitution of the free combination by the respective fixed dose combination (FDC) product at equal dosages. In the conducted BE study bioequivalence could be

shown between the test tablets (fixed dose combination of Candesartan 16mg/Amlodipine 10mg) and the free combination of the originators Atacand 16mg and Norvasc 10 mg tablets. Relevant PK interactions were excluded in an interaction study.