

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

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Menarini International Operations Luxembourg S.A., Luxembourg

olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow-organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states 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 MEB.

To the best of the MEB'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: NL/H/1859/001-005/DC

Registration number in the Netherlands: RVG 106675-106676, 106678-106680

11 May 2011

Pharmacotherapeutic group:	angiotensin II antagonists, calcium channel blockers and diuretics
ATC code:	C09DX03
Route of administration:	oral
Therapeutic indication:	essential hypertension (substitution therapy, see next page)
Prescription status:	prescription only
Date of authorisation in NL:	21 December 2010
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SI, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10b

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Belfor HCT 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg and 40 mg/10 mg/25 mg, film-coated tablets, from Menarini International Operations Luxembourg S.A. The date of authorisation was on 21 December 2010 in the Netherlands.

The product is indicated for treatment of essential hypertension.

Belfor HCT is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component (olmesartan medoxomil and amlodipine or olmesartan medoxomil and hydrochlorothiazide) and a single-component formulation (hydrochlorothiazide or amlodipine).

A comprehensive description of the indications and posology is given in the SmPC.

The product is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, a calcium channel blocker, amlodipine besilate and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than each component alone.

Olmesartan medoxomil (OM) is an orally active, selective angiotensin II receptor (type AT₁) antagonist. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT₁ receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT₁) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

The amlodipine (AML) is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L-type channels into the heart and smooth muscle.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

This decentralised procedure concerns a so-called fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EU. For this kind of application the results of additional new pre-clinical tests or additional new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.

All three actives substances are well-established and have a favorable risk-benefit profile for the treatment of essential hypertension, both as monotherapies and as combined therapies in cases where the patient's hypertension requires multiple therapies with differing mechanisms of action to enable them to achieve goal blood pressure levels. The EMA guideline on fixed combinations is relevant for this application.

The combination of these 3 agents is expected to provide at least an additive blood pressure lowering effect, with the triple combination of OM/AML/HCTZ being more effective than the dual combinations of OM/AML, OM/HCTZ, or AML/HCTZ. The convenience of a fixed-dose combination of these 3 agents simplifies therapy and may increase compliance, further facilitating the achievement of blood pressure goals.

No new pharmacological studies were performed by the MAH to support the current application. As the three substances present in the combination are all well known and as there is sufficient clinical experience with the combination, this is acceptable. An adequate non-clinical overview containing up to date literature of all active substances was provided. Besides, a 3-month repeated dose toxicity study was performed in rats to evaluate the toxicity of the triple combination of OM, AML and HCTZ.

Various clinical studies have been conducted, including comparative bioavailability studies versus Benicar HCT® (olmesartan and hydrochlorothiazide) plus Norvasc® (amlodipine) or Antacal® (amlodipine). One pivotal study provides information on the efficacy of OM, AML, and HCTZ in combination. These studies are discussed in section II.3 'Clinical aspects'.

On 22 May 2007 the MAH requested scientific advice from the CHMP with regard to the preclinical and clinical development plans. In the meeting held on 16-19 June 2007 the CHMP adopted its advice. On 17 September 2007 the MAH again requested scientific advice from the CHMP. The questions concerned quality development. In the meeting held on 12-15 November 2007 the CHMP adopted its advice, which was presented to the MAH.

In 2008, the MAH sought scientific advice from the MEB. On 16 April 2008 and 27 August 2008 the MEB presented its advice with regard to the MAH's clinical development program.

No paediatric development programme has been submitted. On 4 November 2009 the EMA adopted a product-specific waiver for all subsets of the paediatric population from birth to less than 18 years of age (EMA-000667-PIP01-09).

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance olmesartan medoxomil

The active substance olmesartan medoxomil is an established substance, however not described in the European, British or US Pharmacopoeia (Ph.Eur., BP, USP*). It is a white to pale yellowish white powder, which is practically insoluble in water, slightly soluble in ethanol and acetonitrile and sparingly soluble in methanol and acetone. The drug substance does not exhibit polymorphism and has no chiral centers. It is not hygroscopic.

** Ph.Eur., BP and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, UK or USA, respectively.*

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Olmesartan medoxomil is manufactured by an eight stage route of synthesis. Sufficient information has been presented on solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analysis data for various production batches. All batches comply with the specification.

Stability of drug substance

Stability studies have been provided on eight batches of drug substance. Five batches manufactured by a former production method have been stored for 36 months at 25°C/60% RH and 6 months at 40°C/75% RH. In addition 36 months data following storage at 25°C/60% RH, together with 6 months at 40°C/75% RH have been reported on three more production batches, manufactured at full-scale by the current production method.

Based on the results provided, the proposed retest period of 36 months at 25°C could be granted.

Active substance amlodipine besilate

The active substance amlodipine besilate is an established active substance described in the Ph.Eur. It is a white or almost white powder, which is slightly soluble in water and freely soluble in methanol. Amlodipine has one chiral centre. The polymorphic form applied is the anhydrous form.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the additional CEP specifications. Batch analytical data have been provided for two batches per manufacturer. Results for all tests were well within specifications limits.

Stability of drug substance

For one supplier, stability data have been provided on six batches of amlodipine besilate stored in accordance with ICH requirements at 25°C/60% RH for up to 60 months and at 40°C/75% RH for six months. For the other manufacturer stability data were presented on six batches of amlodipine besilate stored in accordance with ICH requirements at 25°C/60% RH for up to 3 years and at 40°C/75% RH for six months.

No changes were observed in the batches stored at long-term and accelerated conditions for either manufacturer. Based on the results, the claimed retest periods could be granted: 2 years for one supplier and 3 years for the other.

Active substance hydrochlorothiazide

The active substance hydrochlorothiazide is an established active substance described in the Ph.Eur. It is a white or almost white crystalline powder, which is very slightly soluble in water, sparingly soluble in alcohol and soluble in acetone. Hydrochlorothiazide has a monocrystalline structure.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for

pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Only the limit for any other impurity is stricter on both CEPs than the limit mentioned in the Ph.Eur. Batch analytical data on three manufacturing-scale batches per manufacturer have been provided demonstrating compliance with the Ph.Eur.

Stability of drug substance

The active substance from one supplier is stable for 3 years when stored under the stated conditions. For the other manufacturer a retest period of 5 years has been approved. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition

Belfor HCT 20 mg/5 mg/12.5 mg contains 20 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide. The product is a light orange, round, film-coated tablet of 8 mm debossed C51 on one side.

Belfor HCT 40 mg/5 mg/12.5 mg contains 40 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide. The product is a light yellow, round, film-coated tablet of 9.5 mm debossed C53 on one side.

Belfor HCT 40 mg/10 mg/12.5 mg contains 40 mg olmesartan medoxomil, 10 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide. The product is a greyish red, round, film-coated tablet of 9.5 mm debossed C55 on one side.

Belfor HCT 40 mg/5 mg/25 mg contains 40 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 25 mg hydrochlorothiazide. The product is a light yellow, oval, film-coated tablet of 15 x 7 mm debossed C54 on one side.

Belfor HCT 40 mg/10 mg/25 mg contains 40 mg olmesartan medoxomil, 10 mg amlodipine (as amlodipine besilate) and 25 mg hydrochlorothiazide. The product is a greyish red, oval, film-coated tablet of 15x7 mm debossed C57 on one side.

The film-coated tablets are packed in packs with laminated polyamide/aluminium/polyvinyl chloride/aluminium blisters and 30 cc or 60 cc HDPE-bottles with a polypropylene child-resistant closure lined with innerseal and a silica gel dessicant.

The excipients are:

Tablet core – pregelatinised maize starch, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Film coat – polyvinyl alcohol, macrogol 3350, talc, titanium dioxide (E171), Iron (III) oxide yellow (E172), Iron (III) oxide red (E172) (20/5/12.5, 40/10/12.5, 40/10/25 mg only), Iron (II, III) oxide black (E172) (20/5/12.5 mg only).

The qualitative composition of the different strengths is the same, and the composition is partly quantitatively proportional.

Pharmaceutical development

The development of the drug product has been adequately described, the choice of excipients is justified and their functions explained.

Products containing OM, AML and HCTZ are currently registered and marketed as separate drug products. Fixed dose combinations containing OM and HCTZ (Olmotec plus) and OM/AML (Belfor) are also marketed. The objective was to develop an immediate-release fixed combination containing the active substances mentioned above.

Similarity factors of all dissolution profiles at three different pH values demonstrated that the dissolution profile of the intermediate strengths were similar to the high and low dose strengths. Two batches (40/10/25 mg and 20/5/12.5 mg) were used in a pivotal bioequivalence study and serve as reference batches for the intermediate strengths. This is considered to be acceptable.

Since no drug product contains the three active substances, the reference formulation used consists of a combination of tablets. One combination is 40mg OM/25 mg HCTZ + 10 mg AML or 20/12.2+5 mg. The other combinations is 40 mg OM/10 mg AML + 25 mg HCTZ or 20/5+12.5 mg. Dissolution profiles of the reference batches have been provided demonstrating similarity. From a chemical pharmaceutical point of view it has been demonstrated that the drug product is comparable with the reference products.

Manufacturing process

The manufacturing process is considered to be a conventional process consisting of direct compression followed by film-coating. Blending times have been adequately validated. The process validation has been performed on full-scale batches. It has been demonstrated that full production-scale batches of each strength can be manufactured in line with the specifications. Sufficient process validation results have been included in the dossier.

Control of excipients

All excipients with the exception of silicified microcrystalline cellulose comply with the Ph.Eur. For silicified microcrystalline cellulose an adequate specification has been provided. The Opadry film-coating systems consist of excipients which are in line with the Ph.Eur. The iron oxides in the Opadry systems are in line with European directives. The excipients have been adequately specified.

Quality control of drug product

The product specification includes tests for appearance, diameter, colour, debossed code, identification of the active substances by retention time and UV-spectrum, uniformity of dosage units, dissolution microbial contamination, colour identity test, water content, degradation products and assay of the active substances. The release and shelf-life specifications are identical with the exception of water content and degradation products. The release and shelf-life specification is acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from a total of 47 batches have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data from 127 batches, three batches per strength and per packaging, have been included in the dossier. The batch sizes are three pilot-scale batches and 1 full-scale batch for the extreme batches 20/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg. For all other strengths at least two pilot-scale batches per strength and packaging have been included. The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in a 7-tablet count HDPE bottle of 30 ml, Al-Al blisters or a 90-tablet count HDPE bottle of 60 ml. Up to 24 months of long term and 6 months of accelerated stability data are available.

The studied parameters remain within the specified limits and there appeared to be no significant changes with time. A trend that was observed in both accelerated and long-term studies in all strengths and packagings, was an increase in degradation products and a slight decrease in assay.

The proposed shelf-life that can be granted is 36 months without special storage conditions for the product packed in 7-tablet count HDPE bottle of 30 ml, Al-Al blisters or 90-tablet count HDPE bottle of 60 ml.

Several commitments have been made with regard to the drug product; these can be found on page 21-22 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. magnesium stearate is derived from a vegetable source.

II.2 Non-clinical aspects

Good Laboratory Practice

The MEB has been assured that the non-clinical study has been conducted in accordance with acceptable standards of Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Pharmacology

The pharmacological action of all three substances has been well documented in literature. No new pharmacological studies were performed to support the current application. As the three substances present in the combination are all well known, and there is sufficient clinical experience with the combination, this is acceptable. An adequate non-clinical overview containing up to date literature of all active substances was provided.

Pharmacokinetics

No new pharmacokinetic studies have been performed. This is acceptable; the pharmacokinetic profile of the three substances is well known and documented.

Toxicology

A 3-month repeated dose toxicity study was performed in rats to evaluate the toxicity of the triple combination of OM, AML and HCTZ (CS-8635). In order to evaluate if this triple combination induced any new toxicities or augmented existing toxicities, two groups were dosed with the combination OM/HCTZ and AML alone. Due to an excessive relaxation effect by AML on the intestinal smooth muscle in the rat, the absorption of both OM and HCTZ increased resulting in higher systemic exposures. This is a rat specific effect. Some effects that were seen in the OM/HCTZ group but were augmented in the CS-8635 group, are the result of this increased exposure. The larger volume of dosing due to the combination of three components might result in the increased contents of the stomach, as a secondary effect on the slower muscle movement of the intestinal tract. This could in turn lead to other effects on the stomach; ulcers are suggested by the applicant, and fibrosis could be the subsequent result. As the effect on the intestinal muscle is rat specific, the resulting effect on the stomach can be assumed to be rat specific as well. Moreover, no effects on the stomach were seen in humans, therefore this effect is not likely to be of relevance to humans.

There were no other findings that could be related to the combination of OM, HCTZ and AML, that were not seen for the individual components.

Both OM and its active metabolite RNH-6270 were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung, CHL), and tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. AML and HCTZ do not have any genotoxic potential. OM and AML showed no carcinogenic potential when administered to rats and mice for up to 2 years, removing any concerns based on the in vitro clastogenicity activity of OM. Equivocal evidence for hepatocarcinogenicity in male mice was seen for HCTZ in a 2 year study. Relevance for humans is unlikely. No carcinogenicity study was conducted for the triple combination.

OM, AML and HCTZ were not teratogenic in rats, rabbits and/or mice. OM showed some developmental toxicity in rats. These findings at the low dose were similar to that observed for other ARBs. Litter size was decreased and the number of intrauterine deaths was increased after treatment with AML. AML has also been shown to prolong both the gestation period and the duration of labor in rats. Reproductive toxicity with the triple combination is expected to confirm previous findings for OM, AML, or HCTZ. Therefore, additional reproductive toxicity study was not considered necessary and none has been conducted for the combination therapy of OM, AML and HCTZ.

Environmental risk assessment

No environmental risk assessment has been performed. As this product is expected to replace the three separate components, no increase in use is anticipated which would result in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Introduction

The clinical pharmacology programme for CS-8635 (triple fixed-dose combination of OM/AML/HCTZ) consisted of 14 Phase 1 studies and one pivotal Phase 3 study.

The programme of Phase 1 studies included six studies, which were conducted specifically for the registration of CS-8635 in addition to eight supporting studies which were conducted for registration of the OM/AML dual fixed-dose combination and for registration of the OM/HCTZ dual fixed-dose combination. In this assessment report only the phase 1 studies concerning the triple combination which are pivotal for this application will be assessed and the study with the different amlodipine reference products (study CS8663-A-E102). For the additional studies with the dual combinations and the two studies with pilot triple combination (CS8635-A-U103 and -104) and the dual combination studies, reference is made to the corresponding applications of the dual products.

Quality of clinical studies, compliance with GCP

The pivotal 3-month study was performed in accordance with GLP regulations.

The clinical studies were conducted in compliance with ethical principles that have their origin in the Declarations of Helsinki and in accordance with the following:

- International Conference on Harmonisation E6 Guideline for Good Clinical Practice (GCP);
- United States Food and Drug Administration (FDA) GCP guidelines;
- US Code of Federal Regulations Title 21, Parts 50, 54, 56, and 312.

Pharmacokinetics

The pharmacokinetics of olmesartan, amlodipine and hydrochlorothiazide in combination therapy are in general well investigated. The triple combination product to be marketed is bioequivalent at the low dose (OM/AML/HCTZ 20/5/12.5 mg) and high dose (OM/AML/HCTZ 40/10/25 mg) level both with the combination of the dual fixed dose reference products Azor (OM/AML) and hydrochlorothiazide and the combination of the dual fixed dose reference product Benicar HCT (OM/HCTZ) and amlodipine in the corresponding doses.

However, the bioequivalence study conducted with the low dose (OM/AML/HCTZ 20/5/12.5 mg) and high dose (OM/AML/HCTZ 40/10/25 mg) fixed triple combination tablet can not be extrapolated to the intermediate triple combination products strengths intended for marketing (OM/AML/HCTZ 40/5/12.5, 40/5/25, and 40/10/12.5 mg fixed triple dose combinations) on the basis of the bracketing approach alone.

The MAH also uses previous experience with comparable products containing two of the three active compounds (OM/AML tablets and OM/HCT tablets). The MAH did perform various bioequivalence studies with these tablets and showed that the small differences in active compounds and excipients did not influence bioequivalence. These results are expected as AML and HCTZ are BCS class I/III, hence slight differences in quantitative composition are of no concern. Additionally it was sufficiently shown for OM that the deviations in composition of the three intermediate strengths are too slight to affect bioavailability. Therefore, it can be concluded that bioequivalence of the intermediate strengths of CS-8635 tablets is assured on the basis of the bracketing design in combination of additional information and bioequivalence studies including similar tablets with corresponding active ingredients and excipients.

The pharmacokinetics of olmesartan, amlodipine and hydrochlorothiazide after administration of the high dose triple combination product (OM/AML/HCTZ 40/10/25) are not affected by coadministration of a high-fat meal.

During the procedure it was noted that bioequivalence for olmesartan between the fixed triple combination and olmesartan given as a mono-component as a part of triple therapy has not been shown with the data package submitted in this procedure. With regard to the bioequivalence for OM between the OM mono-component formulation and the OM/AML/HCTZ fixed dose combination, formulation BE drift analysis showed the mean ratios of the bioequivalence for AUC_{0-t} , AUC_{0-max} and C_{max} were either within the 0.80-1.25 interval or slightly outside. The possibility of 'bioequivalence drift' was discussed. Although it was agreed with the MAH that these deviations may not be relevant and may not lead to a potential risk to public health when switching from three single component tablets to a fixed dose triple combination tablet,

the Board decided to limit the indication of the fixed dose triple combination to substitution therapy for patients that are adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component and a single-component formulation. This decision was made in order to reflect that a study demonstrating bioequivalence of the mono components was not performed.

The results of study CS8635-A-U101 indicate that there is no drug-drug interaction between the olmesartan or hydrochloride component of Benicar HCT (40 mg OM plus 25 mg HCTZ) and amlodipine 10 mg administered as Norvasc (AML).

The results of study CS8635-A-U102 indicate that there is no drug-drug interaction between the olmesartan or amlodipine component of fixed dose olmesartan/amlodipine 40/10 mg tablet and hydrochlorothiazide administered as a 25 mg tablet.

The results of study CS8635-A-E105 indicate that the pharmacokinetics of olmesartan, amlodipine, and hydrochlorothiazide are dose proportional after administration of the high dose triple combination product (OM/AML/HCTZ 40/10/25) and low dose triple combination product (OM/AML/HCTZ 20/5/12.5).

The population pharmacokinetic analysis did not reveal any unexpected interactions of changes in the pharmacokinetics of either compound administered alone or in combination.

Clinical efficacy

One pivotal study provides information on the efficacy of the triple combination of OM, AML, and HCTZ on blood pressure. Combination therapy with an angiotensin-II- antagonist, a calcium channel blocker and a diuretic is considered a rational approach to treat patients with hypertension requiring more than two antihypertensive agents. With these particular agents from the three drug classes adequate knowledge has been gained. These data support the bioequivalence pharmacokinetics studies for the sought substitution indication.

Study design

The study comprised a 3-week (maximum) washout period (Period I), a 12-week randomised, double-blind, parallel-group period (Period II), and a long-term (40 week) open-label extension period (Period III) (see table 1).

The open-label studies from previous trials have been provided in the safety analyses (also discussed in Belfor procedure NL/H/1113-1115/001-003/DC). Information on the 40 week open-label extension have been submitted in answers to some of the questions of the first round (see also table 3).

Within each of the dual combination treatment categories, it was planned that 12 subjects would receive placebo (9 subjects would ultimately remain on the dual combination treatment and 3 subjects would ultimately switch to the triple combination treatment).

Table 1: Treatment sequence during the 12 weeks of placebo controlled study design.

		N	Day 1 to Week 2	Week 2 to Week 4	Week 4 to Week 12
800 subjects	naïve	591	OM/AML/HCTZ 40/10/0 mg		OM/AML/HCTZ 40/10/0 mg (600 subjects)
		9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/10/0 mg		
800 subjects	naïve	591	OM/AML/HCTZ 40/0/25 mg		OM/AML/HCTZ 40/0/25 mg (600 subjects)
		9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/0/25 mg		
800 subjects	naïve	591	OM/AML/HCTZ 0/10/25 mg		OM/AML/HCTZ 0/10/25 mg (600 subjects)
		9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 0/10/25 mg		

*In total, the OM 40 mg + AML 10 mg + HCTZ 25 mg treatment group was comprised of approximately 600 subjects, consisting of 200 subjects from each of the three dual combination assignments at Week 4. AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

General inclusion/exclusion criteria

Patients were **included** if mean sitting trough cuff blood pressure was $\geq 140/100$ mmHg (SeSBP ≥ 140 mmHg and SeDBP ≥ 100 mmHg) or mean sitting trough cuff blood pressure was $\geq 160/90$ mmHg (SeSBP ≥ 160 mmHg and SeDBP ≥ 90 mmHg). The difference in mean SeSBP/SeDBP between 2 consecutive visits prior to randomization must have been $\leq 20/10$ mmHg.

Most important **exclusion** criteria were: DBP < 90 mmHg or SBP < 140 mmHg (off antihypertensive medication); uncontrolled hypertension; signs or symptoms which could exacerbate the occurrence of hypotension such as volume and salt depletion; cardiovascular or renal comorbidities.

Outcomes/endpoints

The MAH defined change from baseline in **SeDBP** at week 12 as the primary efficacy endpoint. Secondary analyses included changes in SeSBP, 24-hour ambulatory BP measurements, and different responder definitions (e.g. % patients reaching treatment goal). Several subgroup analyses were performed to evaluate consistency of the observed effect.

Results

The **primary efficacy endpoint** of change from baseline in **SeDBP** at week 12 with the last observation carried forward (LOCF) demonstrated a LS mean reduction in SeDBP of 21.8 mmHg for the triple combination therapy group and a range of 15.1 mmHg to 18.0 mmHg for dual combination therapy, with significantly ($p < 0.0001$) greater reduction for the triple combination (see table 2). Difference in **SeDBP** was reached within 2 weeks of triple therapy.

Table 2: Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 12 with LOCF – CS8635-A-U301 – Full Analysis Set

Seated Diastolic Blood Pressure Statistics	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
n [1]	624	627	593	614
Baseline [2]				
Mean (SD)	101.0 (7.81)	100.6 (8.16)	101.2 (7.58)	100.9 (7.46)
Week 12 with LOCF [3]				
Mean (SD)	83.2 (9.86)	84.1 (11.70)	86.4 (9.45)	79.4 (10.57)
Change from Baseline				
Mean (SD)	-17.8 (9.47)	-16.5 (10.84)	-14.8 (8.78)	-21.5 (10.25)
LS Mean (SE)	-18.0 (0.45)	-16.9 (0.45)	-15.1 (0.46)	-21.8 (0.45)
P-value [4]	<0.0001	<0.0001	<0.0001	<0.0001
Comparisons	Between treatment comparisons [5]			
		LS Mean (SE)		P-value
OM40/AML10/HCTZ25 vs. OM40/AML10		-3.8 (0.53)		<0.0001
OM40/AML10/HCTZ25 vs. OM40/HCTZ25		-4.9 (0.53)		<0.0001
OM40/AML10/HCTZ25 vs. AML10/HCTZ25		-6.7 (0.54)		<0.0001

The LS mean reduction in SeSBP was 37.1 mmHg for the triple combination therapy group and ranged from 27.5 mmHg to 30.0 mmHg among the groups receiving dual combination therapy with significantly ($p < 0.0001$) greater reduction for the triple combination.

The percentage of subjects reaching blood pressure treatment goal at week 12 with LOCF ranged from 34.9% to 46.6% for the dual combination treatment groups compared to 64.3% for the triple combination treatment group.

Analysis of ambulatory blood pressure measurements in a subset of subjects conducted during the study confirmed the results observed using conventional blood pressure measurements.

Subjects who had their dose of OM/AML/HCTZ triple combination up-titrated during the open-label period benefited from further reductions in blood pressure

Subgroups

In general, the reduction in SeDBP and SeSBP with the triple combination therapy was statistically significantly greater compared to each of the component dual combination therapies in **subgroups** of age, gender, hypertension stage, hypertension severity, race, ethnicity, diabetic status, baseline body mass index (BMI) category, and renal impairment status.

In response to one of the questions, the MAH showed that at Week 52/Early Termination, for all triple combination therapy regimens, the blood pressures across the 3 age subgroups were similar.

Clinical safety

The main safety assessment was based on the **double-blind 12 week treatment period** of the pivotal CS8635-A-U301 study. The MAH provided in addition long-term safety data from the **open-label** portions of the CS8663-A-U301 and CS8663-A-E303 studies that were part of the dual FDC (OM+AML, Belfor application NL/H/1113-1115/001-003/DC). In that open label extension a sizeable proportion of patients was treated with the combination of OM, AML and HCTZ. In the second round, in answer to some of the questions, data of the open-label CS8635-A-U301 study were provided.

Double-blind period

Across the treatment groups, no important differences in the incidence of **AEs or drug-related AEs** between the triple combination treatment group (58.4% and 28.2%) and the dual combination treatment groups (51.7%-58.9%, 23.2%-29.7%) were observed [table S2].

Table S2: Overview of Adverse Events by Final Randomised Treatment – Number (%) of Subjects – Day 1 to Week 12 – CS8635-A-U301 – Safety Set 2

Category	OM40/ AML10 (N = 596) n (%)	OM40/ HCTZ25 (N = 580) n (%)	AML10/ HCTZ25 (N = 552) n (%)	OM40/ AML10/ HCTZ25 (N = 574) n (%)	Total (N = 2302) n (%)
Subjects with TEAEs					
Any TEAE	308 (51.7)	319 (55.0)	325 (58.9)	335 (58.4)	1287 (55.9)
Any drug-related [1] TEAE	138 (23.2)	121 (20.9)	164 (29.7)	162 (28.2)	585 (25.4)
Maximum severity of TEAEs					
Any TEAE					
Mild	160 (26.8)	177 (30.5)	160 (29.0)	183 (31.9)	680 (29.5)
Moderate	124 (20.8)	125 (21.6)	147 (26.6)	128 (22.3)	524 (22.8)
Severe	24 (4.0)	17 (2.9)	18 (3.3)	24 (4.2)	83 (3.6)
Drug-related [1] TEAEs					
Mild	84 (14.1)	78 (13.4)	104 (18.8)	103 (17.9)	369 (16.0)
Moderate	45 (7.6)	39 (6.7)	58 (10.5)	52 (9.1)	194 (8.4)
Severe	9 (1.5)	4 (0.7)	2 (0.4)	7 (1.2)	22 (1.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs					
Any SAE	9 (1.5)	7 (1.2)	9 (1.6)	10 (1.7)	35 (1.5)
Any drug-related [1] SAE	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Subjects with AE leading to study discontinuation [2]					
Any AE	7 (1.2)	12 (2.1)	11 (2.0)	23 (4.0)	53 (2.3)
Any TEAE	6 (1.0)	12 (2.1)	11 (2.0)	23 (4.0)	52 (2.3)
Any drug-related [1] TEAE	4 (0.7)	5 (0.9)	5 (0.9)	18 (3.1)	32 (1.4)
SAE	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	6 (0.3)

The patterns of observed adverse (drug) events were in line with the known safety profile of the individual components [table S3]. Overall, the **most common drug-related AEs** experienced by subjects occurred in the system organ classes nervous system disorders (9.1%) and general disorders and administration site conditions (8.9%). The incidence of **dizziness and drug-related dizziness** was highest in OM40/HCTZ25 and the triple combination (see also table S3).

The incidence of **hypotension** was highest on the triple combination. The incidence of drug-related hypotension was also highest in the triple combination (1.2%) compared to the other treatment groups (0.0% to 0.3%).

Peripheral oedema was highest in incidence for the treatment groups that used AML as one of their treatment components. This also applied to drug related peripheral oedema (5.0% to 6.1% (AML combinations) vs. 0.5% (non-AML combination)).

Hypokalemia had the highest incidence in the AML10/HCTZ25 treatment arm. Also drug-related hypokalemia and drug-related decreased blood potassium (3.4% and 2.4%, respectively) were highest in AML10/HCTZ25 compared to the other treatment groups (0.2% to 0.5%).

Table S3: Summary of Subjects with Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥1% in Any Treatment Group) . Day 1 to Week 12. Safety Set 2

System Organ Class Preferred Term	OM40/ AML10 (N = 596) n (%)	OM40/ HCTZ25 (N = 580) n (%)	AML10/ HCTZ25 (N = 552) n (%)	OM40/ AML10/ HCTZ25 (N = 574) n (%)	Total (N = 2302) n (%)
Subjects with drug-related TEAEs	138 (23.2)	121 (20.9)	164 (29.7)	162 (28.2)	585 (25.4)
Nervous system disorders	45 (7.6)	66 (11.4)	38 (6.9)	61 (10.6)	210 (9.1)
Dizziness	17 (2.9)	37 (6.4)	13 (2.4)	37 (6.4)	104 (4.5)
Headache	19 (3.2)	15 (2.6)	10 (1.8)	17 (3.0)	61 (2.6)
Lethargy	6 (1.0)	4 (0.7)	3 (0.5)	1 (0.2)	14 (0.6)
General disorders and administration site conditions	57 (9.6)	27 (4.7)	64 (11.6)	56 (9.8)	204 (8.9)
Edema peripheral	30 (5.0)	3 (0.5)	33 (6.0)	35 (6.1)	101 (4.4)
Fatigue	20 (3.4)	20 (3.4)	25 (4.5)	15 (2.6)	80 (3.5)
Gastrointestinal disorders	17 (2.9)	24 (4.1)	24 (4.3)	21 (3.7)	86 (3.7)
Nausea	4 (0.7)	8 (1.4)	5 (0.9)	6 (1.0)	23 (1.0)
Dry mouth	3 (0.5)	6 (1.0)	8 (1.4)	1 (0.2)	18 (0.8)
Musculoskeletal and connective tissue disorders	20 (3.4)	10 (1.7)	20 (3.6)	20 (3.5)	70 (3.0)
Joint swelling	13 (2.2)	0 (0.0)	11 (2.0)	7 (1.2)	31 (1.3)
Muscle spasms	5 (0.8)	6 (1.0)	6 (1.1)	9 (1.6)	26 (1.1)
Investigations	4 (0.7)	9 (1.6)	24 (4.3)	21 (3.7)	58 (2.5)
Blood potassium decreased	1 (0.2)	2 (0.3)	13 (2.4)	3 (0.5)	19 (0.8)
Blood creatinine increased	0 (0.0)	3 (0.5)	2 (0.4)	7 (1.2)	12 (0.5)
Metabolism and nutrition disorders	6 (1.0)	7 (1.2)	23 (4.2)	10 (1.7)	46 (2.0)
Hypokalemia	1 (0.2)	2 (0.3)	19 (3.4)	3 (0.5)	25 (1.1)
Renal and urinary disorders	14 (2.3)	10 (1.7)	9 (1.6)	9 (1.6)	42 (1.8)
Pollakiuria	8 (1.3)	7 (1.2)	5 (0.9)	8 (1.4)	28 (1.2)
Vascular disorders	2 (0.3)	5 (0.9)	4 (0.7)	12 (2.1)	23 (1.0)
Hypotension	0 (0.0)	2 (0.3)	0 (0.0)	7 (1.2)	9 (0.4)

Regarding AEs of special interest, the overall incidence of **hyperkalemia** was <1% in the triple combination and OM40/HCTZ25 treatment groups.

Gout, hyperuricemia, and increased uric acid events were highest in incidence for AML10/HCTZ25.

Increased blood creatinine was highest in incidence for the triple combination. Drug-related increased blood creatinine was also highest in the triple combination (1.2%) compared to the other treatment groups (0.0% to 0.5%).

The incidence of **renal impairment** was highest for the triple combination.

In total, 83 (3.6%) subjects had a **severe adverse event**, while for 22 (1.0%) subjects this was considered a **drug-related AE**: nine (1.5%) subjects in the OM40/AML10, four (0.7%) subjects in the OM40/HCTZ25, two (0.4%) subjects in the AML10/HCTZ25, and seven (1.2%) subjects in the triple combination. Four subjects discontinued from the study due to a severe drug-related AE.

No differences in **hepatic laboratory markers** were noticed between treatment groups. In **renal laboratory markers**, the incidence of marked elevations in potassium (>5.0 mmol/L) was higher in the treatment groups that used OM as 1 of their treatment components (4.9% to 7.6%) compared to the AML10/HCTZ25 treatment group (1.7%).

One subject died from alcohol poisoning during the double-blind treatment period prior to week 4.

Open-label period

In total, 106 (5.0%) subjects in the open-label cohort had a **serious adverse event (SAE)**: 40 (1.9%) subjects in OM40/AML5/HCTZ12.5, 11 (1.8%) subjects in OM40/AML5/HCTZ25, 17 (2.6%) subjects in OM40/AML10/HCTZ12.5, 38 (4.8%) subjects in OM40/AM10/HCTZ25 triple combination group. Three subjects on OM40/AML5/HCTZ12.5 and 2 subjects on OM40/AML5/HCTZ25 had an SAE considered by the investigator to be drug-related.

In **hepatic laboratory markers**, the incidence of marked elevations in ALT (>75 mU/mL) was 4.4% in the OM40/AML10/HCTZ25 triple combination compared to a range of 2.2% to 3.0% in the other treatment groups. The incidence of marked elevations in GGT (>87 mU/mL) was 10.4% in the OM40/AML10/HCTZ25 triple combination compared to a range of 4.6% to 5.6% in the other treatment groups.

Three subjects died during the open-label period of the study. None of the **deaths** were considered by the investigators to be related to study medication.

For the 40 week open-label period of study CS8635-A-U301, the following incidences of adverse events were found. No different safety issues emerge during this open-label period compared to the double-blind period (see table S4).

Table S4: Number (%) of Subjects With Adverse Events in Adverse Event Categories of Special Interest – Period III Safety Set

Adverse Event Category	OM40/ AML5/ HCTZ12.5 (N = 2112) n (%)	OM40/ AML5/ HCTZ25 (N = 627) n (%)	OM40/ AML10/ HCTZ12.5 (N = 652) n (%)	OM40/ AML10/ HCTZ25 (N = 790) n (%)	Total (N = 2112) n (%)
Edema	45 (2.1)	12 (1.9)	27 (4.1)	55 (7.0)	133 (6.3)
Hypotension	25 (1.2)	3 (0.5)	8 (1.2)	8 (1.0)	44 (2.1)
Headache	48 (2.3)	16 (2.6)	17 (2.6)	26 (3.3)	101 (4.8)
Dizziness and vertigo	108 (5.1)	24 (3.8)	25 (3.8)	47 (5.9)	194 (9.2)
Syncope	5 (0.2)	1 (0.2)	3 (0.5)	7 (0.9)	16 (0.8)
Renal impairment AEs	30 (1.4)	12 (1.9)	8 (1.2)	14 (1.8)	63 (3.0)
Hepatic-related AEs	51 (2.4)	10 (1.6)	7 (1.1)	18 (2.3)	85 (4.0)
Hyperkalemia	17 (0.8)	4 (0.6)	2 (0.3)	3 (0.4)	26 (1.2)
Hypokalemia	26 (1.2)	3 (0.5)	1 (0.2)	19 (2.4)	48 (2.3)
Glycemic control	67 (3.2)	5 (0.8)	12 (1.8)	31 (3.9)	112 (5.3)
Injury, falls, and fractures	29 (1.4)	3 (0.5)	10 (1.5)	23 (2.9)	64 (3.0)
Gout, hyperuricemia, and increased uric acid	49 (2.3)	9 (1.4)	6 (0.9)	22 (2.8)	84 (4.0)

Risk management plan

No new safety concerns have been observed during the non-clinical and clinical development of the OM/AML/HCTZ combination. The safety profile of combination therapy is as expected from the known safety profiles of the individual and dual components. Therefore, no action beyond routine pharmacovigilance is planned.

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are considered adequate to monitor the safety of the fixed dose combination. No risk minimisation activities are needed.

Conclusion

In conclusion, the benefit/risk of the triple combination in the proposed substitution indication can be considered as positive, because bioequivalence has sufficiently been shown.

In addition, a clear additional blood pressure lowering effect is demonstrated for the high dose triple FDC compared to the high dose dual FDCs. This was associated with some additional adverse events that can be attributed to the new component that is introduced by switching from dual to triple therapy. However, no unexpected safety issues emerged.

Product information

SmPC

The content of the SmPC approved during the decentralised procedure was adapted as required by the member states. The MAH committed to include a statement on fertility for amlodipine in the SmPC, if such statement is included in the next update of the CSP for amlodipine.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

There were 2 test phases with 10 subjects each. The test persons were volunteers aged from 18 to 80 years. There were 8 males and 12 females. People currently taking the medicine for the leaflet being tested or who had taken it in the previous 6 months, as well as people currently taking a medicine from the same therapeutic class have been excluded.

The leaflet on the highest strength (40 mg/10 mg/25 mg) was tested. The key points reflect specific safety and compliance issues for the product when it is used to treat hypertension. After pilot testing of the questionnaire and leaflet, 20 eligible participants from the target group for this product were interviewed individually.

The test included 15 questions on the text of the leaflet and 1 open question regarding general impressions of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections.

No amendments were proposed between the two rounds. The scores of both rounds were not analysed separately. The results for both rounds taken together were satisfactory, i.e. at least 90% of the participants were able to find the information and at least 90% were able to express the information in their own words.

Although the package leaflet passes the user test successfully, some amendments were introduced to deal with the three questions which seemed more difficult to answer. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Belfor HCT 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg and 40 mg/10 mg/25 mg, film-coated tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Belfor HCT film-coated tablets have a proven chemical-pharmaceutical quality.

Non-clinical aspects of all three single compounds, olmesartan medoxomil, amlodipine and hydrochlorothiazide, were sufficiently reviewed and discussed based on literature. A 3-month repeated dose toxicity study was conducted in rats, which showed no effects relevant to humans other than the ones known for the separate components.

In support of the application, the MAH submitted a number of pharmacokinetic studies, including comparative bioavailability studies versus Benicar HCT® (olmesartan and hydrochlorothiazide) plus Norvasc® (amlodipine) or Antacal® (amlodipine). As a study demonstrating bioequivalence of the mono components was not performed, the indication of the fixed dose triple combination is limited to substitution therapy for patients that are adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component and a single-component formulation. One pivotal study provides information on the efficacy of the triple combination of OM, AML, and HCTZ on blood pressure. These data support the bioequivalence pharmacokinetics studies for the substitution indication.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC contains sufficient information on the separate components, as well as the combination. The SmPC, package leaflet and labelling are in the agreed templates and have been adapted in accordance with requirements laid down during the procedure.

In the Board meetings of 1 April 2010 and 2 September 2010, the application was discussed. The most important issues were related to pharmacokinetics. Ultimately the Board considered the product approvable.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that a favourable benefit/risk profile has been established, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 December 2010. Belfor HCT 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg and 40 mg/10 mg/25 mg, film-coated tablets were authorised in the Netherlands on 21 December 2010.

The PSUR submission cycle is based on the Harmonised Birth date of olmesartan (25 April 2002). PSURs will be submitted as follows:

- 6-monthly PSUR submissions will be continued until two full years of marketing experience in the EU has been gained;
- thereafter yearly PSURs for the following two years;
- thereafter PSURs should be submitted at 3-yearly intervals.

The date for the first renewal will be: 16 December 2015.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to test the first three commercial batches of the five marketed tablet strengths packed in each marketing pack.
- The MAH committed to continue the stability studies according to the accepted protocols through the proposed shelf life.
- The MAH committed carry out stability studies on commercial batches and annual batches, at the appropriate time intervals and to report any unexpected findings to national authorities.
- The MAH committed to review the water content limits at the end of the stability study and to revise them if appropriate.

Product information

- The MAH committed to include a statement on fertility for amlodipine in the SmPC, if such statement is included in the next update of the CSP for amlodipine.

List of abbreviations

AE	Adverse Event
AML	Amlodipine Besilate
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCTZ	Hydrochlorothiazide
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OM	Olmesartan Medoxomil
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _½	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Grouped IA variations.	NL/H/1859/001/IA/001-005/G	IA/G	21-3-2011	28-4-2011	Approval	N