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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

BELFOR, film-coated tablets, 20mg/ 5mg, 40mg/ 5mg, 40mg/ 10mg

Menarini International Operations Luxembourg

Olmesartan medoxomil
Amlodipine besilate

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/1115/001-003/DC
Registration number in the Netherlands: RVG 100993, 100994, 100995

October 31rd, 2008

Pharmacotherapeutic group:	Angiotensin II antagonist (angiotensin Type I receptorblocker) and Calcium channel blocker.
ATC code:	C09DB02
Route of administration:	oral use
Therapeutic indication:	treatment of essential hypertension; Belfor is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy
Prescription status:	prescription only
Date of first authorisation in NL:	19 August 2008
Concerned Member States:	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 (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Belfor 20 mg/ 5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets from Menarini International Operations Luxembourg.
The date of authorisation was on 17 September 2008 in the Netherlands. The product is indicated for:

> Treatment of essential hypertension.
> Belfor is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy

A comprehensive description of the indications and posology is given in the SPC.
The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.

Belfor is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a calcium channel blocker, amlodipine besilate.
The olmesartan medoxomil component of Belfor is a selective angiotensin II type 1 (AT1) receptor antagonist. Olmesartan medoxomil is rapidly converted to the pharmacologically active metabolite, olmesartan. 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. In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure.
The amlodipine component of Belfor 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. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure.
The combination of these active ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

This application is made by the decentralised procedure. The marketing authorisation is granted based on article 10b of Directive 2001/83/EC, a so-called fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EU but not hitherto used in combination for therapeutic purposes. In these kind of applications the results of new pre-clinical tests or 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. In this case, the applicant refers to their own data for olmesartan. Because the data exclusivity for amlodipine is expired, reference can be made to the innovar dossier for amlodipine.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The reference member state (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.

Active substance

General information

The active substances are olmesartan medoxomil and amlodipine besilate, both established active substances. Amlodipine besilate is described in the European Pharmacopoeia. Amlodipine besilate is slightly soluble in water. Olmesartan medoxomil is practically insoluble in water.

For amlodipine besilate two CEPs are included. The CEP procedure is used for active substances. 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 suitablity 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU

For olmesartan medoxomil an ASMF procedure is used. 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/EMEA 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 the ASMF-holder via an eight stage route. A flow chart is provided in the dossier as is a reaction scheme. The manufacturing process is adequately described in the dossier. The route of synthesis, elemental analysis, IR spectrum ^{1}H and ^{13}C NMR spectra, mass and UV-spectra and single crystal X-ray data provide proof of the structure of olmesartan medoxomil.
Amlodipine besilate is manufactured by two different CEP-holders. The manufacture process is not included however the certificates of suitability of both manufacturers are included in the dossier.

Quality control of drug substance

The drug substance specifications are in line with the Ph.Eur. and the CEP or ASMF, with additional requirements for amlodipine besilate. For both manufactures of amlodipine besilate additional tests on related substances and on residual solvents are adapted. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for six full scaled or pilot scaled batches from each of the manufacturers.
For Olmesartan medoxomil the ASMF holder refers to Ph.Eur. methods. Non pharmacopoeial methods have been described and validated. The proposed limits for olmesartan and RNH-6373 exceed the qualification limit, but are considered to be qualified and acceptable.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for eight full scaled or pilot scaled batches.

Stability of drug substance

Stability data for amlodipine besilate have been provided for six batches at 25°C/60% RH (up to 60 months) three or six batches at 40°C/75% RH (six months) for both manufacturers. For the other manufacturer six batches were tested at both conditions for respectively up to 15 and nine months. All the batches were stored in airtight containers, protected from light.
Photostability was also tested on amlodipine besilate. Assay results show a slight decrease in amlodipine besilate. From the results it is considered that amlodipine is slightly light sensitive and therefore, moderate protection from light is required.
A claimed retest period of 2 years stored in airtight containers protected from light is granted.

Stability data for olmesartan medoxomil has been provided for eight batches at 25°C/60% RH (36 months) and at 40°C/75% RH (six months). All batches were stored in double layer of polyethylene bags in a well sealed steel drum.
Stress testing was done by the ASMF-holder showing that the drug substance was stable under light conditions and high temperature and high humidity when it was in solid state.
In solution olmesartan medoxomil is partially hydrolysed to olmesartan under alkaline conditions after one hour and is relatively unstable in acidic conditions and less stable in hydrogen peroxide solution.

Under light irradiation over 1 week, it is however stable, with no significant change in the assay. Olmesartan, the pharmacologically active metabolite, is the main degradation product in all cases.
The claimed retest period of 36 months when stored below 25°C is granted.

Medicinal Product

Composition
The drug product is called Belfor. The tablets are fixed dosage combination tablets consisting of two active ingredients, olmesartan medoxomil (OM) and amlodipine besilate (AML), for oral administration. The content of active substances is declared in terms of olmesartan medoxomil/ amlodipine base; 20/5 mg, 40/5 mg and 40/10 mg. The colour differs per tablet strength; 20/5 mg is a white tablet, 40/5 mg is cream coloured and 40/10 mg is brownish red tablet. All tablets, 20/5, 40/5 and 40/10, have debossing, C73, C75 and C77 respectively, on one side of the tablet.
The excipients are pregelatinised starch (maize), silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinylalcohol, talc, macrogol 3350, titanium dioxide (E171) and iron oxide yellow or red.
The tablets are packaged in laminated OPA/ aluminium/ polyvinyl chloride/ aluminium blisters.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Product containing olmesartan medoxomil or amlodipine besilate are currently registered as separate presentations. First compatibility of the two drug substances was tested. It showed good compatibility.
Amlodipine besilate as well as olmesartan medoxomil were tested in formulations with different excipients. The different formulations were tested in stability studies. After comparing the impurity profiles of each test formulation, a final test formulation was chosen.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing of the tablets consists of a direct compression of the excipients and the active substances followed by film-coating the tablets.
The manufacturing process has been adequately validated according to relevant European guidelines.

Excipients
All compendial excipients are tested against individual Ph.Eur. monographs. Non compendial excipients will be tested for identity by a suitable method as specified in the dossier. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, water content, uniformity of dosage units, dissolution and microbial contamination.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three different strength full scaled batches demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on eight full scaled and seven pilot scaled batches stored at 25°C/60% RH (for 24 months) and at 40°C/75% RH (for six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed marketing packaging, i.e. laminated polyamide/ aluminium/ polyvinyl chloride/ aluminium blister packs. A fall in potency for amlodipine besilate was seen between the initial and the six months storage. Twelve-month storage data confirmed that analytical variation was responsible for the apparent fall in assay over the first six months.
The post-approval stability testing plan submitted in section 3.2.P.8.2 of the dossier of 60 months is indicated for the first two commercial batches of each approved strength. Test results will be reported to European Agencies should there be any unexpected findings (post-approval commitment).
A shelf-life of 36 months with no special storage conditions is proposed. Since 24 month data from pilot batches and 12 month data from scale up batches for both accelerated and long term tests are available and stayed well within the shelf-life specification the proposed shelf-life can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

Good Laboratory Practice
The repeat dose toxicology study was performed in accordance with GLP. The mechanistic studies were not performed in accordance with GLP. Because of the explorative nature of these studies which were used to determine a possible mechanism for the increased exposure to the metabolite of OM, this is acceptable.

Pharmacology
The pharmacological action of both substances has been well documented in the literature. No further studies have been submitted, which is acceptable. The effect of combination therapy with OM and AML was evaluated in a study using spontaneous hypertensive rats. There was an enhanced antihypertensive effect when OM and AML were given in combination to spontaneous hypertensive rats, as compared to both drugs alone.
This supports the intended clinical use of this fixed combination drug.

Pharmacokinetics
No new pharmacokinetic studies have been performed. This is acceptable; the pharmacokinetic profile of both drugs is well known and documented.

Toxicology
The toxicity profiles of both OM and AML are well known. To examine whether new emerging toxicity or synergistic toxic effect would be induced by the combination of OM and AML, an additional study was conducted in rats. Four groups of rats for each sex received either 30 mg/kg/day AML, 300 mg/kg/day OM, 330 mg/kg/day OM + AML (CS-8663), or 110 mg/kg/day CS-8663. An untreated group served as control group. In the CS-8663 group, major histopathological changes were observed in the kidney, intestines, adrenal, mammary gland and ovary and the changes were essentially the same as those observed in the AML or OM alone group.
It should be noted, that the combined dose group, 330 mg/kg/day of OM + AML (CS-8663) cannot be directly compared to the 30 mg/kg/day AML and 300 mg/kg/day OM groups, as the exposure to the active metabolite of OM in the combination group was much increased. The bioavailability to this metabolite in the 300 mg/kg/day group was comparable to the bioavailability in the 110 mg/kg/day CS-8663 group. As the effects seen in an exaggerated way in the CS-8663 group, dilatation of the intestinal lumina and hypertrophy of the ducts in mammary glands were at a dose of 330 mg/kg/day, and no synergistc effects were seen at the 110 mg/kg/day dosage, the cause of these effects might be the increased exposure to the metabolite of OM.
The applicant concludes that the results from this 3-month study demonstrated that combined administration of OM and AML did not augment any existing toxicities of the individual agents, nor induce any new toxicities and resulted in no toxicologically synergistic effects.
A mechanistic study was conducted to examine the increased exposure level of the active metabolite of OM. At co-administration of 100 mg/kg/day OM or higher and 10 mg/kg/day AML or higher, the exposure level of the active metabolite of OM, RNH-6270, is increased. The applicant suggests this is due to increased absorption of OM due to decreased motility of the digestive tract caused by AML, and that it is rat specific. Whether the same can happen at sufficiently high doses in humans cannot be excluded, but it has not been shown at therapeutic doses, and is therefore not likely to be of human concern.
No additional combination studies were conducted. As this product is a fixed combination of two known substances, this is acceptable. The applicant provided an overview of the genotoxicity, carcinogenicity and reproduction toxicology of the two substances, in which it was shown that neither substance is genotoxic or carcinogenic. There is a known risk of reproduction toxicology of OM, and a risk of prolonged delivery with the use of AML. This is adequately reflected in the SPC.

Environmental risk assessment

The environmental risk assessment for olmesartan is complete. For olmesartan, no potential environmental risks have been identified. For amlodipine further studies are necessary to complete the assessment (see post-approval commitments)

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The applicant states in the clinical overview that there were no unusual aspects of the research approaches used in the clinical development program and that all studies were conducted in accordance with Good Clinical Practice guidelines.

Clinical development Program
The clinical efficacy and safety program addressed the requirements of guideline CPMP/EWP/238/95 Rev 2 regarding fixed-dose antihypertensive combination products for use as second-line therapy. The overall program also addressed the general requirements of guideline CPMP/EWP/240/95 on fixed combination products. The clinical trial program was discussed on in two National Scientific Advice Meetings (June 2004 and December 2006) with the Reference Member State authority and was considered in principle acceptable.

Pharmacokinetics
The pharmacokinetics of olmesartan and amlodipine in combination therapy are well investigated.
The combination product to be marketed is bioequivalent with the combination of the reference products for olmesartan and amlodipine alone.This was shown in a bioequivalende study with the fixed combination product with commercial available innovator products. This study was conducted as a parallel-group, crossover study with two cohorts of 30 healthy male and female subjects (aged between 19 -45 years). In one cohort the 10/5 mg combination was tested in the other cohort the 40/10 mg combination. The following products were tested after administration in fasted state with 240 ml water:
Treatment A: One combination tablet with olmesartan medoxomil 10 mg/ amlodipine besylate 5 mg
Treatment B: one tablet olmesartan medoxomil 10 mg plus onre tablet amlodipine besylate 5 mg
Treatment C: One combination tablet with olmesartan medoxomil 40 mg/ amlodipine besylate 10 mg
Treatment D: one tablet olmesartan medoxomil 40 mg plus one tablet amlodipine besylate 10 mg
Blood samples were taken for olmesartan for 72 hours and for determination of amlodipine for 144 hours.

The pharmacokinetic variables of interest were tested for bioequivalence after log transformation with ANOVA. The 90% confidence intervals were calculated for the fixed dose combinations versus individual components.

	Olmesartan		Amlodipine	
	10 mg	40 mg	5 mg	10 mg
	Point Estimate+90%CI	Point Estimate+90%CI	Point Estimate+90%CI	Point Estimate+90%CI
AUC_{0-t}	1.07 (0.99 – 1.16)	1.12 (1.03 – 1.21)	1.01 (0.99 – 1.04)	1.02 90.97 – 1.06)
AUC_{0-inf}	1.07 (0.99 – 1.16)	1.13 (1.04 – 1.23)	1.01 (0.99 – 1.04)	1.01 (0.97 – 1.06)
C_{max}	1.14 (1.06 – 1.22)	1.10 (1.02 – 1.18)	0.99 (0.95 – 1.02)	1.08 (1.03 – 1.13)

The results of this study indicate that the lower strength of the fixed combination as well as the highest strength is bioequivalent with the separate reference products. All 90% confidence intervals of the pharmacokinetic variables of interest are within the acceptance range for bioequivalence.

The bioequivalence study conducted with the 40/10 mg fixed combination tablet only can be extrapolated to the two other fixed dose combination strengths intended for marketing (20/5 and 40/5 mg fixed dose combinations) on the basis of the composition of the products. The pharmacokinetics of olmesartan and amlodipine are dose proportional after administration of the different strength as fixed combination tablets.
As the composition 20/5 mg combination tablet is fully dose proportional with the investigated 40/10 mg combination tablet, bioequivalence studies with these tablets can be waived.
The composition of the 40/5 mg combination tablet is with of course the exception of the amount of amlodipine besylate nearly the same as the 40/10 mg tablet. Only the amount of filler is less in the 40/10 mg tablet for compensation of the increased amount of amlodipine besylate. As the amount of

amlodipine besylate is less than 5% of the total weight of the tablets and the dissolution profiles of all of the dose strengths applied are similar under identical conditions for the additional strengths bioequivalence studies with the 40/5 mg tablets can be waived.

Food did not affect the bioavailability of olmesartan nor amlodipine from the combination tablets. The pharmacokinetics of olmesartan and amlodipine are not affected by co-administration of a high fat meal. There is no pharmacokinetic interaction between both compounds of the combination product, regardless of the proportion of the individual components.
The population pharmacokinetic analysis did not reveal any unexpected interactions of changes in the pharmacokinetics of either compound administered alone or in combination.

Pharmacodynamics
No specific studies were performed to evaluate the pharmacodynamics of the fixed dose combination, which is considered acceptable.

Clinical efficacy

One **factorial design** study (301) was conducted in the U.S., with the **objective** to determine if co-administration of olmesartan (OM) and amlodipine (AML) had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension and to identify the appropriate dosages.
Two add-on studies (studies 302 and 303)] were conducted in Europe with the **objective** to show additional antihypertensive efficacy in lowering DBP (diastolic blood pressure) by adding AML or OM in OM 20 mg non-responders and AML 5 mg non-responders, respectively, after 8 weeks of double-blind treatment. In study 303, this period of 8 weeks was followed by another 8-week double-blind (but non-randomised) period (Period III), in which the OM/AML dose was up-titrated in patients not responding to the initial add-on dosing.

Long-term treatment was evaluated in study 301 with a 44-week open-label follow-up (Period III) and study 303 with a 28-week long-term open-label treatment period (Period IV). This long-term treatment extension of study 303 was still ongoing at the time of the first submitted dossier; but the data until the end of the study extension (28 weeks) were submitted during the decentralised procedure.

Table 1: Summary of phase III efficacy studies

Study/ Period	Design	Dose (all once daily)	Full analysis set	Duration
301/ Period II	Randomised, double-blind, placebo-controlled factorial design	OM: 10, 20 and 40 mg AML: 5 and 10 mg OM/AML: 10/5, 10/10, 20/5, 20/10, 40/5 and 40/10 mg Placebo	1923 (157 – 163 per group)	8 weeks
301/ Period III	Open-label, long-term extension period	Initially OM/AML 40/5 mg increasing as required to OM/AML 40/10 mg, followed by addition of HCTZ 12.5 mg then 25 mg	1683	44 weeks
302/ Periods I and II	Randomised, double-blind, placebo-controlled (after OM run-in)	Monotherapy period (Period I): OM 20 mg Double-blind period (Period II): OM/AML 20/0, 20/5, 20/10	538 (177 – 182 per group)	Monotherapy period: 8 weeks Double-blind period: 8 weeks
303/ Periods I and II	Randomised, double-blind, placebo-controlled (after AML run-in)	Monotherapy period (Period I): AML 5 mg Double-blind period (Period II): OM/AML 0/5, 10/5, 20/5 40/5	746 (184 – 189 per group)	Monotherapy period: 8 weeks Double-blind period: 8 weeks
303/ Period III	Double-blind, non-randomised up-titration period (patients	OM/AML 0/5 → 20/5 mg OM/AML 10/5 → 20/5 mg OM/AML 20/5 → 40/5 mg	705 (57 – 107 in titrated groups; 68 – 118 in non-titrated	8 weeks

	with SeDBP ≥ 90 mmHg and SeSBP ≥ 140 mmHg)	OM/AML 40/5 → 40/10 mg Patients not requiring titration stayed on their Period II dose	groups)	
303/ Period IV	Open-label, long-term extension period	Initially OM/AML 40/5 mg increasing as required to OM/AML 40/10 mg, followed by addition of HCTZ 12.5 mg then 25 mg	692	28 weeks

AML = Amlodipine; HCTZ = Hydrochlorothiazide; OM = Olmesartan medoxomil; SeDBP = Seated diastolic BP; SeSBP = Seated systolic BP

No special dose-response studies were conducted,.

- **General inclusion/exclusion criteria**

The principal inclusion criterion for the **factorial** design study was that patients had a mean DBP of 95-120 mmHg with fluctuations ≤10 mmHg during the pre-randomisation visits. In the **add-on** studies SBP (systolic blood pressure) had to be ≥160 mmHg and mean sitting DBP ≥100 mmHg at pre-randomisation visits. These inclusion criteria are in line with the ESC/ESH guideline definitions for moderate to severe hypertension. The MEB considered that an inclusion criterion of DBP≥110 mmHg would have more appropriately reflected a population with moderate to severe hypertension than a population with a DBP≥100 mmHg as discussed in the scientific advice. Participants were considered non-responders to OM 20mg or AML 5 mg when DBP and SBP remained over ≥90 mmHg and ≥140 mmHg after eight weeks on respective monotherapy (goal for diabetics: DBP and SBP over ≥80 mmHg and ≥130 mmHg). They would then enter the second study 8-week period of combination therapy.

- **Outcomes/endpoints**

The **primary endpoint** was the mean change in sitting diastolic blood pressure (SDBP) (mmHg) from baseline to the end of a 8 week period. This is the known surrogate endpoint to establish the antihypertensive value of the product.
The most important **secondary endpoints** were

The mean change in sitting systolic blood pressure (SSBP) (mmHg) from baseline.

The number and percentage of patients achieving blood pressure goal (defined as blood pressure <140/90 mmHg for non-diabetics, or <130/80 mmHg for diabetic patients).

An automatic validated Omron **blood pressure monitoring** device (Model HEM-705CP) was used to assess the blood pressure in the factorial design study. Sphygmomanometers were used in the add-on studies. Following a 5-minute rest period, 3 separate seated blood pressures were measured at least 1 minute apart. The 3 results were averaged.

- **Statistical methods**

Analysis of the primary efficacy parameter was performed using an Analysis of Covariance (ANCOVA) model with treatment and pooled centre as effects and baseline DBP as a covariate. Comparisons of the combination therapies versus monotherapy were made using Hommel's multiple comparison procedure in study 301 and Dunnett's test in studies 302 and 303. Secondary endpoints were analysed in the same way, except that the Cochran-Mantel-Haenszel test was used to analyse the percentages of patients achieving SBP/DBP goal.

- **Results**

The **factorial** design study showed that combination versus monotherapy comparison reduced sitting diastolic blood pressure (mmHg) from baseline to week 8 significantly more for all combination treatments ($p<0.001$[1]). This was supported by a significantly higher number of patients reaching blood pressure goals on combination therapy (p-value ranging from 0.003 to <0.0001) (see table 2).

Table 2: Mean change in sitting systolic and diastolic blood pressure (mmHg) and number of patient (%) reaching blood pressure goal during the double-blind treatment period of studies 301, 302, and 303

Treatment group	**301 Period II** *Factorial design*	**302 Period II** *OM20 non-responders*	**303 Period II** *AML5 non-responders*

[1] p=0.002 for the OM10/AML10 combination therapy vs AML10 monotherapy

	ΔSDBP/SSBP	BPgoal	ΔSDBP/SSBP	BPgoal	ΔSDBP/SSBP	BPgoal
Placebo	-4.8/-3.1	8.8	-	-	-	-
OM10	-11.5/-8.3	20.0	-	-	-	-
OM20	-13.8/-9.2	26.4	-10.6/-7.8	28.5	-	-
OM40	-16.1/-10.2	36.3	-	-	-	-
AML5	-14.9/-9.4	21.1	-	-	-9.9/-5.7	29.9
AML10	-19.7/-12.7	32.5	-	-	-	-
OM10/AML5	-24.2/-13.8	35.0	-	-	-13.1/-7.4	39.2
OM10/AML10	-25.3/-8.3	49.1	-	-	-	-
OM20/AML5*	-23.6/-14.0	42.5	-16.2/-10.6	44.5	-15.3/-9.3	53.5
OM20/AML10	-29.2/-17.0	53.2	-16.5/-11.1	45.8	-	-
OM40/AML5*	-25.4/-15.5	51.0	-	-	-16.7/-9.5	50.5
OM40/AML10*	-30.1/-19.0	49.1	-	-	-	-

* Treatment group in **bold** are proposed to be licensed combinations.

Higher doses were associated with achieving increasingly greater mean reductions in DBP, for both monotherapy and the combination therapy (no significance shown). Only in the case of OM10/AML5 and OM20/AML5 combinations no difference in BP reduction was observed (see figure 1 and table 2) between the lower and the higher dose combination.

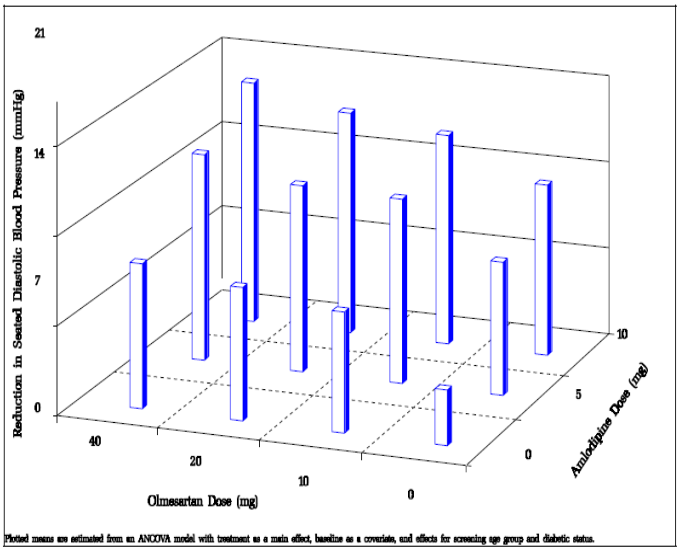

Figure 1: Mean reduction in SDBP (mmHg) from baseline to week 8 with LOCF (ITT): overall (up-left picture); age group: left ≥ 65, right <65 (up-right picture), diabetic subgroup: left diabetic, right non-diabetic (down-left picture), race-subgroup: left black, right non-black (down-right picture)

Subgroups

Approximately 13% of the patients with **diabetes** were included in each treatment group, these patients reached blood pressure goals less frequently than non-diabetic patients. This pattern was consistent across the different dosing groups.

Reductions in diastolic blood pressure were similar for patient **< 65 years** (±80%) and patients **≥ 65 years** (±20%), while the proportion of patients ≥65 years reaching blood pressure goal were less for especially the high dose combination groups. Baseline diastolic blood pressure was similar in both age groups (SDBP was 102.0 mmHg for the subgroup <65 years of age and 100.3 mmHg for the subgroup ≥ 65 years of age).

In the **black** patients subgroup the BP lowering effect of olmesartan is smaller with both monotherapy and combination therapy compared to the non-black subgroup.

In both **add-on** studies only Caucasian patients were included. In both studies, approximately 75% of patients did not reach blood pressure goals on monotherapy and proceeded therefore into period II to receive combination therapy. Remarkably, in this second period approximately 30% of these patients reached blood pressure goals when they were randomised to placebo add-on, for another 8 weeks of monotherapy. The applicant argues that similar results were seen in other add-on trials. Also in the Exforge® (valsartan/amlodipine) application, both add-on studies showed a clinical relevant and

statistically significant decrease over time during the double blind treatment period and reached -6.6 and -10.0 mmHg at endpoint for valsartan and amlodipine in patients supposed to be non-responders. It can thus be questioned whether the monotherapy period to identify the non-responders was sufficiently long and whether the true non-responders actually were identified. Even though the add-on studies were not optimal, the guideline's requirement of "a significant and clinically relevant additional blood pressure reduction of the combination" in comparison to either monotherapy could be proven.

Both add-on studies show that combination therapy significantly further reduced systolic and diastolic blood pressure (p-value ranging from 0.020 to <0.0001) and resulted in more patients reaching blood pressure goal compared to monotherapy with either OM 20 mg or AML 5 mg (p-value ranging from 0.029 to <0.0001). However, in OM20 non-responders, there is hardly any difference in reduction in systolic and diastolic blood pressure or in reaching blood pressure goals between OM20/AML5 and OM20/AML10 treatment groups. Similarly in AML5 non-responders, OM20/AML5 and OM40/AML5 treatments showed comparable blood pressure reduction and percentages of patients reaching blood pressure goals (see table 2). Only in the factorial design study 301, there is a difference in mean BP reduction and proportion patients reaching blood pressure goal with the respective dose-increments in the mentioned treatment groups. In contrast, when comparing OM10/AML5 and OM20/AML5 a greater BP effect is observed in the AML5 non-responders (add-on study) than in the factorial design study.

In general, up-titrating from any combination therapy to a higher dose combination in non-responders to combination therapy resulted in further blood pressure reductions [period III of study 303]. Up-titration of patients from the OM20/AML5 (n=118) treatment to OM40/AML5 (n=58) treatment resulted in a further diastolic blood pressure reduction: -6.2 mmHg (SD 7.47) compared with -0.2 mmHg (SD 6.76) when the former dose was maintained. Also, up-titration from OM40/AML5 (n=118) to OM40/AML10 (n=57) resulted in a further decrease of -8.2 mmHg (SD 7.34) vs. -0.6 mmHg (SD 6.37) of DBP when the former dose was maintained. Changing from OM10/AML5 (n=97) to OM20/AML5 (n=82) resulted in a further decrease of -5.6 mmHg (7.02) vs. -0.7 mmHg (5.99) of DBP when the dose remained unchanged. Therefore, a stepwise dose increase in non-responders to respective mono- and then combination therapy seems to be the most rational antihypertensive strategy based on the submitted study findings.

Of the 2376 patients who entered the open-label long-term periods of study 301 (period III) and 303 (period IV) 83.1% (1400/1684 patients) and 97.3% (673/692 patients) completed respectively. Nearly half of the patients needed additional therapy with HCTZ in study 301, but in study 303 this was only 15%. These data indicate that treatment was well tolerated and that at least for study 303 treatment with the OM/AML combination was effective for the majority of the patients.

Clinical safety

The integrated analysis of safety was performed on the following 3 integrated analysis cohorts:

- Phase III double-blind cohort – All patients combined from double-blind portions of studies 301 Period II, 302 Period II, and 303 Periods II and III (3233 patients) [table 3]
- Phase III open-label cohort – Patients taking long-term open-label treatment (301 Period III and 303 Period IV) (2376 patients); and
- Phase III all patients cohort – All patients combined from the double-blind and open-label extension periods of studies 301, 302, and 303 (total 3233 patients) [table 4]

Table 3: Drug-related adverse events with ≥ 1% incidence in the OM/AML combined treatment group – Phase III all patients cohort

N (%) patients with:	Placebo (N=162)	OM (N=663)	AML (N=512)	OM/AML (N=2892)	OM/AML +HCTZ (N=755)
General Disorders and Administration Site Conditions	18 (11.1)	60 (9.0)	68 (13.3)	391 (13.5)	114 (15.1)
Oedema peripheral	9 (5.6)	35 (5.3)	45 (8.8)	252 (8.7)	85 (11.3)
Oedema	2 (1.2)	9 (1.4)	15 (2.9)	82 (2.8)	18 (2.4)
Fatigue	5 (3.1)	13 (2.0)	5 (1.0)	46 (1.6)	7 (0.9)
Pitting oedema	2 (1.2)	6 (0.9)	4 (0.8)	37 (1.3)	8 (1.1)
Nervous System Disorders	15 (9.3)	46 (6.9)	15 (2.9)	160 (5.5)	31 (4.1)
Dizziness	6 (3.7)	19 (2.9)	6 (1.2)	80 (2.8)	22 (2.9)
Headache	11 (6.8)	26 (3.9)	8 (1.6)	68 (2.4)	9 (1.2)
Vascular Disorders	9 (5.6)	11 (1.7)	1 (0.2)	40 (1.4)	15 (2.0)
Hypotension	0 (0.0)	1 (0.2)	0 (0.0)	25 (0.9)	10 (1.3)
Hypertension	7 (4.3)	5 (0.8)	0 (0.0)	2 (0.1)	0 (0.0)
Gastrointestinal Disorders	7 (4.3)	10 (1.5)	9 (1.8)	56 (1.9)	11 (1.5)
Nausea	3 (1.9)	2 (0.3)	2 (0.4)	12 (0.4)	4 (0.5)
Investigations	4 (2.5)	10 (1.5)	3 (0.6)	48 (1.7)	19 (2.5)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	9 (1.2)
Renal and Urinary Disorders	1 (0.6)	0 (0.0)	6 (1.2)	10 (0.3)	14 (1.9)
Pollakiuria	0 (0.0)	0 (0.0)	3 (0.6)	4 (0.1)	10 (1.3)

In the placebo-controlled study, frequency and severity of **adverse events** was not different between monotherapy or combination therapy and comparable to placebo. In the open-label periods the high dose regimen OM40/AML10 was associated with more severe adverse events than the low dose regimen with OM40/AML5 (2.9% vs. 2.0% respectively). High dose HCTZ further increases number of severe AEs. A similar pattern is observed for overall adverse events and or those events that were considered drug-related. The most common **drug-related adverse events** in the OM/AML group were 'general disorders and administration site conditions' among which oedema and 'nervous system adverse events', among which dizziness and headaches (see table 4).

Table 4: Number (%) of patients with adverse events of special interest – phase III double-blind cohort and phase III open-label cohort

Adverse event category	Placebo (N=162)	OM10 (N=161)	OM20 (N=340)	OM40 (N=162)	AML5 (N=349)	AML10 (N=163)	OM10/ AML5 (N=354)	OM20/ AML5 (N=721)	OM40 AML5 (N=407)	OM10 AML10 (N=162)	OM20 / AML10 (N=337)	OM40 / AML10 (N=219)	Total (N=3233)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lack of drug effect/Hypertension [1]	14 (8.6)	7 (4.3)	10 (2.9)	6 (3.7)	7 (2.0)	2 (1.2)	1 (0.3)	4 (0.6)	2 (0.5)	1 (0.6)	2 (0.6)	0 (0.0)	56 (1.7)
Oedema [2]	20 (12.3)	23 (14.3)	18 (5.3)	29 (17.9)	24 (6.9)	59 (36.2)	40 (11.3)	38 (5.3)	33 (8.1)	44 (27.2)	46 (13.6)	38 (17.4)	411 (12.7)
Hypotension [3]	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)	4 (1.0)	2 (1.2)	2 (0.6)	2 (0.9)	14 (0.4)
Headache	23 (14.2)	9 (5.6)	19 (5.6)	14 (8.6)	17 (4.9)	8 (4.9)	12 (3.4)	20 (2.8)	15 (3.7)	10 (6.2)	16 (4.7)	9 (4.1)	172 (5.3)
Dizziness [4] and vertigo	10 (6.2)	6 (3.7)	13 (3.8)	9 (5.6)	9 (2.6)	4 (2.5)	12 (3.4)	16 (2.2)	20 (4.9)	7 (4.3)	6 (1.8)	8 (3.7)	120 (3.7)
Syncope	0 (0.0)	1 (o.6)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (o.3)	0 (0.0)	3 (0.1)
Renal-related adverse events [5]	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.6)	0 (0.0)	4 (0.1)
Hepatic-related adverse events [6]	3 (1.9)	1 (0.6)	2 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	4 (1.1)	8 (1.1)	3 (0.7)	0 (0.0)	5 (1.5)	2 (0.9)	29 (0.9)

Adverse event category	OM10/AML5 (N=2371) n (%)	OM40/AML10 (N=1251) n (%)	OM10/AML5/HCTZ12.5 (N=742) n (%)	OM40/AML10/HCTZ25 (N=441) n (%)	Other (N=86) n (%)	Total (N=2376) n (%)
Lack of drug effect/Hypertension [1]	5 (0.2)	5 (0.4)	0 (0.0)	7 (1.6)	0 (0.0)	17 (0.7)
Oedema [2]	162 (6.8)	161 (12.9)	95 (12.8)	64 (14.5)	17 (19.8)	427 (18.0)
Hypotension [3]	17 (0.7)	9(0.7)	11 (1.5)	3 (0.7)	2 (2,.3)	40 (1.7)
Headache	49 (2.1)	27 (2.2)	22 (3.0)	10 (2.3)	2 (2.3)	101 (4.3)
Dizziness [4] and vertigo	69 (2.9)	35 (2.8)	23 (3.1)	24 (5.4)	2 (2.3)	146 (6.1)
Syncope	2 (0.1)	0 (0.0)	1 (0.1)	2 (0.5)	O (0.0)	5 (0.2)
Renal-related adverse events [5]	2 (0.1)	2 (0.2)	5 (0.7)	7 (1.6)	0 (0.0)	16 (0.7)
Hepatic-related adverse events [6]	24 (1.0)	4 (0.3)	5 (0.7)	3 (0.7)	0 (0.0)	35 (1.5)

Table 5: Incidence of oedema during double-blind treatment in studies 301 versus 302 and 303

	Study 301			Studies 302 and 303 combined		Phase III Double-blind Cohort	
Treatment group:	**Treated**	**N (%) with oedema[a]**	**Placebo subtracted**	**Treated**	**N (%) with oedema[a]**	**Treated**	**N (%) with oedema [a]**
Placebo	162	20 (12.3)	0.0	NA		162	20 (12.3)
OM 10	161	23 (14.3)	1.9	NA		161	23 (14.3)
OM 20	161	16 (9.9)	-2.4	179	2 (1.1)	340	18 (5.3)
OM 40	162	30 (18.5)	6.2	NA		162	29 (17.9)
AML 5	161	21 (13.0)	0.7	188	4 (2.1)	349	24 (6.9)
AML 10	163	60 (36.8)	24.5	NA		163	59 (36.2)
OM/AML 10/5	163	34 (20.9)	8.5	191	7 (3.7)	354	40 (11.3)
OM/AML 20/5	161	29 (18.0)	5.7	560	8 (1.4)	721	38 (5.3)
OM/AML 40/5	162	30 (18.5)	6.2	245	4 (1.6)	407	33 (8.1)
OM/AML 10/10	162	43 (26.5)	14.2	NA		162	44 (27.2)
OM/AML 20/10	160	41 (25.6)	13.3	177	5 (2.8)	337	46 (13.6)
OM/AML 40/10	162	38 (23.5)	11.1	57	1 (1.8)	219	38 (17.4)

Incidence of **oedema** was higher in study 301 than in both add-on studies. According to the applicant, the reason is the actively questionnaire for oedema events in the protocol of the study. In the add-on studies this was passively monitored. This could indeed explain the difference. Table 5 shows generally higher incidences of oedema with AML10 dose, and less when AML10 is combined with OM. Furthermore, oedema in the factorial design study is in all combination groups with AML5 higher than in the AML5 monotherapy group. Furthermore, in contrast to the AML10 combination, an amelioration with higher doses of OM in combination with AML5 could not been shown .

The same is the case when **other adverse events of special interest** (hypotension, headache, dizziness and vertigo, and syncope) are taken into account (see table 5). Also, in the combination groups more infections and infestations were observed, 7.2 to 9.6% in monotherapy groups, 16.6% in OM/AML group and 19.3% in the OM/AML/HCTZ group. This large increase can however be explained by the difference in duration of follow-up that was longer in patients on fixed dose combination than monotherapy.

Three patients **died** for non-drug-related reasons: One patient in study 301 (on placebo) was murdered, another patient in study 303 (on OM 40/AML5) died from a cerebral haemorrhage, and one patient during open-label cohort was shot in the head. In the Phase III double-blind cohort, one patient from the 301 study on OM 20 mg experienced a **drug-related adverse event** (cerebrovascular accident, probably related due to poor blood pressure control). One patient experienced non-cardiac chest pain in the open-label cohort (possible related).

There were no clinically meaningful changes in these key **laboratory parameters** (ALT, AST, BUN, creatinine, sodium and potassium) among patients in the phase III double-blind cohort. For the Phase III open-label cohort, the triple combination (OM/AML + HCTZ) appeared to be associated with larger decreases in sodium and potassium, and larger increases in ALT, AST, blood urea nitrogen (BUN), creatinine, glucose and total protein than the dual (OM/AML) combination. Many of these trends are typical for HCTZ treatment.

- **Special population**.

The incidence of adverse events in the OM/AML combination group was slightly higher in female patients (54.1%) compared to male (47.6%), also the incidence of peripheral oedema appeared higher in females (15.0%) than males (8.4%). The incidence of adverse events in the OM/AML combination group was lower in Caucasian (48.8%) than non-Caucasian patients (58.1%). There were no large differences in other subgroups (age, diabetic status). No clear pattern could be noticed for an increased risk of susceptible patients (older age, comorbid heart disease) for hypotension-related adverse events. No specific studies with OM/AML combination therapy have been conducted in patients with renal or hepatic impairment, or in children and adolescents below 18 years of age.

- **Discontinuation due to adverse events**.

A total of 23 (0.7%) patients discontinued due to hypertension: 10 patients on placebo, 5 patients on OM20, 2 patients each on OM10, OM40 and AML5, and 1 patient each on OM20/AML5 and OM40/AML5. Discontinuation due to oedema occurred in 6 patients in OM10/AML10, 5 patients in AML10 and 5 patients in OM40/AML10. The most common adverse event leading to patient discontinuation in the open-label cohort was dizziness. A total of 9 (0.4%) patients discontinued due to dizziness: 7 patients on OM40/AML5, and 1 patient each on OM40/AML10 and OM40/AML10/HCTZ25.

Pharmacovigilance System and Risk Management System

Concerning the Pharmacovigilance System of Menarini:
The applicant has provided documents that set out a detailed description of the system for pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services in place of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reactions.

Concerning the Risk Management Plan:
No safety issues, or potential risk can be identified from the available data. Therefore, the RMS agrees with the MAH and consider routing pharmacovigilance and routine risk minimisation activities currently sufficient.

Readability test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test process involved two rounds with 10 participants each. The test included 15 questions on the text of the leaflet and one open question regarding general impressions of the leaflet. These questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections. Scoring was not separately analysed for the two test rounds. No amendments were proposed between the two rounds. The results were satisfactory, i.e. 100% of the participants were able to find the information, and 100% were able to express the information in their own words. The readability test has been adequately performed.

III BENEFIT-RISK ASSESSMENT

Hypertension is a risk factor for development of cardiovascular disease and should therefore be treated adequately. Treatment with only one antihypertensive drugs is often not sufficient to reach treatment goal, especially in patients with moderate to severe hypertension. Anti-hypertensive drugs are therefore often combined to give further blood pressure reduction to reach treatment goals. Olmesartan and amlodipine are both antihypertensive drugs with well-known different modes of action. No special pharmacodynamic studies were performed, but synergistic mechanisms of action between an angiotensin-receptor blocker (ARB) and dihydropyridine calcium-channel blocker (CCB) can be postulated that should lead to increased BP control and improved tolerability (less oedema). The European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines on the clinical management of hypertension published in 2003 recognise ARB/CCB combination treatment as an therapeutic option (ESH/ESC Guidelines Committee, 2003). The usefulness of ARB and CCB combination therapy has been recognised in the EU through the recent authorisation of a fixed-dose combination of valsartan and AML (Exforge®). These PD considerations are valid and are

appropriately tested in the clinical efficacy and safety trials submitted.
The applicant has conducted a factorial design study in the U.S. and two add-on studies in Europe to support a second-line indication for olmesartan (OM) or amlodipine (AML) non-responders.

Efficacy
The **factorial** design study clearly demonstrated additive dose- and combination-related reductions in diastolic blood pressure after 8 weeks of treatment (primary endpoint). These findings were generally supported by similar profiles for systolic blood pressure and patients reaching blood pressure goals, except for the OM10/AML5 vs. OM20/AML5 treatment arms. Also the **add-on** studies generally showed additive responses when OM was combined with AML, both in non-responders to OM and to AML. The applicant's proposal not to license the OM10/AML5, OM20/AML10 and OM10/AML10 combinations is considered appropriate.

OM20/AML5 is the optimal initial dose combination when up-titrating from monotherapy based on efficacy in those patients whose blood pressure is not adequately controlled by 20 mg OM. Titration from AML5 to OM20/AML5 instead of OM10/AML5 is a dose step which can be supported based on higher efficacy, and there were no signs that this dose step is not a safe treatment option for a patient subgroup at high risk for hypotensive effects (e.g. higher age, comorbid heart disease). In contrast to the factorial design study, a higher dose of OM did not have an additional effect in AML5 non-responders and a higher dose of AML did not have an additional effect in OM 20 non-responders.

The proposed treatment algorithm is adequate. OM40/AML5 combination has been shown to be of benefit in patients whose blood pressure is not adequately controlled by the OM20/AML5 combination (period III, study 303). Titration from AML5 immediately to a high dose OM40/AML5 instead of OM20/AML5 is not supported by the data. Besides similar efficacy in the AML non-responders study, this dose step could lead to unnecessary exposure to high dose OM, with approximately 75% already reaching blood pressure goal on the lower OM20/AML5 dose.
OM40/AML10 combination has been shown to be of benefit only in patients whose blood pressure is not adequately controlled by the OM40/AML5 combination (period III, study 303). Titration from OM40 to OM40/AML10 instead of OM40/AML5 is not supported by the data as incidence of oedema is – as expected – increased further.

Results reported on subgroups showed that, in the factorial design study, black patients responded less to OM than non-blacks. This difference in response for the black subgroup is reflected in the SPC. For the age-subgroup, results show that in the factorial design study and the add-on studies in AML non-responders patients <65 and patients ≥65 years experienced similar blood pressure reductions, although fewer patients ≥65 years seemed to reach the pre-defined blood pressure goals. No final conclusion can however be drawn based on the results as observed in elderly patients (>65 years) due to small numbers of patients in these subgroups.
In the long-term treatment period after 44 weeks, 83.1% (1400/1684 patients) and 97.3% (673/692 patients) completed resp in study 301 and 303. Nearly half of the patients needed additional therapy with HCTZ in study 301, but in study 303 this was 15% only. These data indicate that treatment was well tolerated and that at least for study 303 treatment with the OM/AML combination was effective for the majority of the patients.

Safety
Differences in adverse events or drug-related adverse events when comparison is made between the fixed dose combination and the monocomponents do not appear to be large, also when comparison is made with the small placebo comparison arm. A higher frequency of infections is observed in the combination treatment arms versus monotherapy, which could be explained by the longer duration of exposure to combination therapy. Furthermore, differences in safety (and as discussed in efficacy), especially oedema and amelioration of oedema, do appear when single treatment arms are considered. This may be relevant when the various treatment arms are discussed in terms of efficacy.
For the most adverse events of special interest (hypotension, headache, dizziness and vertigo, and syncope) and key laboratory parameters (ALT, AST, BUN, creatinine, sodium and potassium) no large differences appear. Additional treatment with HCTZ does show some more safety issues, but with hardly any drug-related adverse events leading to discontinuation, it is shown that this concerns mainly a high risk treatment resistant population.

In conclusion, it is shown that addition of AML to OM or OM to AML in a fixed dose combinations leads to additional blood pressure reduction without major safety concerns. Olmesartan/ amlodipine fixed dose combination is considered approvable for a second-line antihypertensive indication as add-on or

replacement therapy.

IV OVERALL CONCLUSION

The first assessment report of the MEB was discussed in the Board meeting of 6 December 2007. The Board decided to follow the advice of the assessors.
During the Decentralised Procedure a number of changes were introduced in the product-information because of the comments raised by the RMS in their assessments, but also because of the comments of the Concerned Member States. The major issue for discussion was the proposed treatment algorithm.

Finally it was concluded to approve the following **posology**
BELFOR 20 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil or 5 mg amlodipine alone.
BELFOR 40 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by BELFOR 20 mg/5 mg.
BELFOR 40 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled by BELFOR 40 mg/5 mg.

At Day 210 agreement was reached between the Member States and the applicant on product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling. The Decentralised procedure was finished on 30 July 2008.

In conclusion, it is shown that addition of AML to OM or OM to AML in a fixed dose combinations leads to additional blood pressure reduction without major safety concerns. Olmesartan/ amlodipine fixed dose combination is considered approvable for a second-line antihypertensive indication as add-on or replacement therapy.
On the basis of the data submitted, the concerned member states have granted a marketing authorisation. Belfor 20 mg/ 5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets from Menarini International Operations Luxembourg was authorised in the Netherlands on 17 September 2008.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.
The MAH has provided written confirmation that systems and services are in place to ensure ompliance with their pharmacovigilance obligations.

The PSUR submission cycle is 6-monthly during the first 2 years. Thereafter once a year for the following two years and thereafter at 3-yearly intervals. The data lock point for the first PSUR is based on the Harmonised Birth date of olmesartan, i.e. 25 April 2002.

The date for the first renewal be 30 August 2013.

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

Product-information:
The wording regarding pregnancy and lactation will be amended, if necessary, by way of a Type II variation, following the conclusion of the still ongoing discussions in the PhVWP.

Quality - Stability
Post Approval Stability Commitment for Studies that are ongoing in accordance with the Protocol in Module 3.2.P.8.2.

Non-clinical - Environmental Risk Assessment:
- Two additional studies will be performed to complete the risk assessment for amlodipine.

List of abbreviations

AML	amlodipine
ARP	angiotensin-receptor blocker
ASMF	Active Substance Master File
AT1	Angiotensin II type 1
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CCB	calcium-channel blocker
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
DBP	Diastolic blood pressure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMS	Reference Member State
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPC	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