CBG MEB

Public Assessment Report

Scientific discussion

Edarclor 40 mg/12.5 mg and 40 mg/25 mg, film-coated tablets

(azilsartan medoxomil and chlortalidone)

NL/H/3333/001-002/DC

Date: 18 September 2017

This module reflects the scientific discussion for the approval of Edarclor 40 mg/12.5 mg, film-coated tablets. The procedure was finalised on 8 October 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin-converting-enzyme
AEs	Adverse Events
ARB	Angiotensin II Receptor Blocker
ASMF	Active Substance Master File
AUC	Area Under the Curve
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CPN	Chronic Progressive Nephropathy
CRS	Clinical Research and Statistics
CYP	Cytogroom
DBP	Diastolic Blood Pressure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESRD	End-Stage Renal Disease
FDC	Fixed-Dose Combination
ICH	International Conference of Harmonisation
LTFU	Long-Term Follow-Up
MAH	Marketing Authorisation Holder
OECD	Organisation for Economic Co-operation and Develeopment
OLM/HCTZ	Olmesartan/Hydrochlorothiazide combination
PBO	Placebo
PBT	Persistent, Bioaccumulative and Toxic
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Package Leaflet
PPI	Proton-Pump Inhibitors
RH	Relative Humidity
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SmPC	Summary of Product Characteristics
SBP	Systolic Blood Pressure
TAK-491	Azilsartan medoxomil
TAK-491CLD	Azilsartan medoxomil-Chlortalidone fixed-dose combination
TAK-536	Azilsartan
TEAEs	Treatment-Emergent Adverse Events
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Edarclor 40 mg/12.5 mg and 40 mg/25 mg, film-coated tablets from Takeda Pharma A/S.

The product is indicated for the treatment of hypertension in adults. Edarclor is a fixed-dose combination and is indicated in adults whose blood pressure is not adequately controlled by azilsartan medoxomil monotherapy alone.

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

This decentralised procedure concerns an application for a fixed dose combination medicinal product where the individual active substances (monocomponents) have established clinical use as well as regulatory approval. For both azilsartan medoxomil and chlortalidone generic formulations are known substances.

Azilsartan medoxomil (TAK-491) is a prodrug that is rapidly metabolised to azilsartan (TAK-536). TAK-491 is currently approved under the name Edarbi 20 mg, tablet in the EEA through a centralised procedure (EU/1/11/734/001) by the same MAH since 7 December 2011, as well as the United Sates, Canada, Mexico, Switzerland, Russia and several Asian, Middle Eastern and Latin countries.
Chlortalidone is potent, long-acting diuretic comparable to thiazide, with a well-documented safety and efficacy profile for the treatment of hypertension, either alone or in combination with other antihypertensive agents. The substance has been widely available in Europe for many year (since 1959 in Switzerland and 1960 in the United kingdom).
The combination of TAK-491 and chlortalidone (TAK-491CLD) is currently approved in the United States, Canada, Mexico and some Asian, Middle Eastern and Latin America countries, with other global applications under review.

The concerned member states (CMS) involved in this procedure were Greece and Portugal.

A repeat-use procedure (NL/H/3333/001-002/E) was used to register the product in Ireland in 2017.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

To date, TAK-491CLD has been evaluated in 7 phase 3 studies and 5 phase 1 studies, and is supported by data from 3 TAK-491 monotherapy diuretic coadministration studies, the clinical pharmacology program for TAK-491 monotherapy, and the commercial labelling and scientific literature for chlortalidone.

Scientific advice was given by the European Medicines Agency (EMA) in 2008 and follow-up advices in 2009 and 2010.

No Paediatric Investigation Plan (PIP) has been submitted. A product specific waiver has been granted by the EMA for Edarclor for the treatment of hypertension in all subsets of the paediatric population, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients (EMEA-001294-PIP01-12).

II. QUALITY ASPECTS

II.1 Introduction

Edarclor 40 mg/12.5 mg is a pale red, round, biconvex, film-coated tablet with both “A/C” and “40/12.5” printed on one side. Each tablet contains 40 mg of azilsartan medoxomil (as potassium) and 12.5 mg chlortalidone.

Edarclor 40 mg/25 mg is a light red, round, biconvex, film-coated tablet with both “A/C” and “40/25” printed on one side. Each tablet contains 40 mg of azilsartan medoxomil (as potassium) and 25 mg chlortalidone.

The film-coated tablet are packed in desiccated or non-desiccated aluminium/aluminium blister packs.

The excipients are: mannitol (E421), fumaric acid (E297) for pH adjustment, sodium hydroxypropylcellulose (E463) for pH adjustment, crospovidone (type A), microcrystalline cellulose (E460), magnesium stearate (E572), titanium dioxide (E171), red iron oxide (E172), hypromellose 2910, talc and macrogol 8000.
For the grey printing ink (F1) are used: shellac and black iron oxide (E172).

II.2 Drug Substances

Azilsartan medoxomil
The active substance azilsartan medoxomil is a white to off-white crystalline powder and freely soluble in dimethyl sulfoxide, dimethylformamide and methanol. The solubility in water depends on pH. At a low pH the substance is practically insoluble and at pH 9.0-11.0 slightly soluble. The substance is hygroscopic, has no chiral centre and exists in one stable anhydrous form.

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
The manufacturing process has been described sufficiently. Information on the process, process controls and control of materials used in the synthesis has been provided in sufficient detail. The substance is manufactured in six steps from the starting material. The substances assigned as starting materials are acceptable.

Quality control of drug substance
The drug substance specification has been established in-house. Requirements have been set for appearance, identity, heavy metals, related substances, residual solvents, residual agents, water and assay. The methods have been described sufficiently and, where necessary, adequately validated. Omission of some other requirements has sufficiently been justified. 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 3 commercial-scale batches of azilsartan medoxomil.

Stability of drug substance
Stability data on the active substance have been provided for 8 batches in accordance with applicable European guidelines. The data shows the stability of the substance under long-term stability conditions (5ºC and 25ºC/60% RH) for 18 months as well as at accelerated conditions (40ºC/75% RH) for 6 months. Based on the data submitted, a retest period could be granted of 36 months. The storage instruction: “This drug substance does not require any special temperature storage conditions, keep the container tightly closed, protected from light and moisture.” is appropriate since the substance is sensitive to humidity and is photosensitive.

Chlortalidone
Chlortalidone is an established active substance and described in the European Pharmacopoeia (Ph. Eur.) The active substance is white or yellowish-white powder. It is very soluble in water, soluble in acetone and in methanol and practically insoluble in methylene chloride. Chlortalidone exhibits polymorphism.

The CEP procedure is used for this 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 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
A CEP has 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. with additional requirements for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches by the drug product manufacturer.

Stability of drug substance
As per CEP, a retest period could be granted of 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The compatibility of the active ingredient with excipients was evaluated.

The pharmaceutical development studies and relevant bioequivalence studies were conducted using a product containing 80 mg of azilsartan medoxomil and 25 mg chlortalidone to create a worst case scenario. Sufficient details are provided on the development of the dissolution method for determination of both azilsartan medoxomil and chlortalidone. In the dissolution study 80/25 mg and 20/12.5 mg products are used. Although this application concerns the 40 mg azilsartan medoxomil in combination with 12.5 mg or 25 mg chlortalidone (and not the 80 mg product in combination with 25 mg chlortalidone as used in the bioequivalence studies), no biowaiver is applied for. This can be accepted from a clinical point of view as the 40 mg azilsartan medoxomil in combination with 12.5 mg or 25 mg chlortalidone is used in several phase 3 studies

In support of the application and in line with the bioequivalence guidance, dissolution data on the 80/25 mg product used in the bioequivalence studies as well as for relevant phase 3 batches in several pH's (i.e. pH 1.2, 4.5 and 6.8) and QC media were provided. The dissolution data is considered sufficient, as it is supportive in view of the bioequivalence studies, it sufficiently shows that dissolution of the 80 mg product ((in combination with 25 or 12.5 mg) is comparable to the 40 mg product (in combination with 25 or 12.5 mg).

Manufacturing process
The manufacturing process has been validated according to relevant ICH guidelines and consists of granulation of both active substances, blending with extragranular excipients, compression, film-coating and drying. The process and in-process controls are adequately described. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines and confirms reproducibility of the manufacturing process.

Control of excipients
The excipients comply with the requirements of the Ph. Eur., United States Pharmacopeia or National Formulary. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, related substances, assay, dissolution, content uniformity and microbiological contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data

for the analytical methods have been provided and is in line with ICH guidelines. Batch analytical data from the proposed production sites have been provided for 9 batches of the 40/12.5 mg strength and 7 batches of the 40/25 mg strength, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches of both strengths of the product stored at 25°C/60%RH (24-48 months) and 40°C/75%RH (6 months) in accordance with applicable European guidelines. The photostability studies showed a light increase in the amounts of related substances however, this was due to an increase of moisture. Based on the data submitted, a shelf life was granted of 48 months in the proposed packaging. The storage condition: "Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions." is acceptable.

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 Magnesium stearate is the only excipient of potential animal origin However, the manufacturer of the product has certified that the magnesium stearate will be of plant origin only. Therefore, a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Edarclor 40 mg/12.5 mg and 40 mg/20 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

No new non-clinical studies were submitted, apart from new Environmental Risk Assessment studies on chlortalidone. All studies on azilsartan and the fixed dose combination have been submitted and assessed previously for the medicinal product Edarbi 20 mg, tablet (azilsartan). Chlortalidone is a well known substance and therefore the dossier consists of literature references.

The non-clinical overview is adequate, providing an overview of available information on pharmacology, pharmacokinetics and toxicology of the active substances. Additional non-clinical studies are not needed since all the active substances were already tested for safety and efficacy, alone or in combination in similar already marketed products.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Azilsartan medoxomil
TAK-491 is administered as a pro-drug by the oral route. Under in vivo conditions the pro-drug is rapidly and quantitatively converted to the active pharmaceutical ingredient TAK-536 by hydrolysis.
TAK-536 is already marketed by the same MAH for patients with the same indication. An ERA has already been performed and assessed.

Fixed-dose combination
The fixed combination product does not include new indications. Because of this and because a lower maximum dosage is applied (maximum daily dose is one capsule of 40 mg TAK-491 (=32 mg TAK-536), instead of 80 mg TAK-491 (=64 mg TAK-536)), an increase in use of the active ingredient is not expected. Thus, an ERA does not need to be performed.

Chlorthalidone

Summary of main study results for chlorthalidone

Substance (INN/Invented Name): chlortalidone					
CAS-number (if available): 77-36-1					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	0.95			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.95			not B
Persistence	ready biodegradability	not readily biodegradable			
	DegT50 (system)	219, 277, 344, 402 d at 20°C			P
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥98 mg/L 32 mg/L 56 mg/L			not T based on aquatic toxicity
	CMR	not investigated			potentially T
PBT-statement	chlortalidone is considered not PBT, nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, refined F_{pen}, refined using STP simulation	3.99	µg/L			> 0.01 threshold: Y
Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 24.7, 26.1 L/kg $K_{oc\ soil}$ = 102, 143 and 130 L/kg			only K_{oc} in sludge determined
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT50_{water}$ 59 and 61 d for $U^{14}C$ labelled chlortalidone $DT50_{water}$ 31 and 23 d for ^{14}C labelled (waar) chlortalidone $DegT_{50\ system}$ 277 and 219 d for $U^{14}C$ labelled chlortalidone $DegT_{50\ system}$ 344 and 402 for ^{14}C labelled (waar) chlortalidone Sediment shifting: 30 and 42% at day 14 and higher thereafter.			All values determined at 20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *P. subcapitata*	OECD 201	NOEC	≥98	mg/L	growth rate
Daphnia magna. Reproduction Test	OECD 211	NOEC	32	mg/L	survival
Fish, Early Life Stage Toxicity Test / *P. promelas*	OECD 210	NOEC	56	mg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	≥4551	mg/kg	development rate and emergence.

					Mean measured concentration, normalised to 10% o.c.
Sediment dwelling organism / *C. riparius*	OECD 219	NOEC	58	mg/kg	development rate. Mean measured concentration, normalised to 10% o.c.

Conclusions on study
Chlortalidone is not a Persistent, Bioaccumulative and Toxic (PBT) substance. Considering the above data and the environmental risk assessment, chlortalidone is not expected to pose a risk to the surface water and groundwater compartment and the sewage treatment plant.

III.3 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Introduction
The clinical pharmacology program of the fixed dose combination consists of 3 *in vitro* studies, 5 phase 1 clinical studies, and 2 population pharmacokinetic studies (table 1). The application for the Fixed-Dose Combination (FDC) is also supported by the azilsartan medoxomil clinical pharmacology program, which was previously submitted and reviewed. This program included 22 *in vitro* and 2 *ex vivo* studies, 39 clinical studies, namely 18 phase 1 studies in which azilsartan medoxomil was administered and 20 phase 1 and 1 phase 2 study in which TAK-536 was administered.

Table 1 Pharmocology Program FDC

Study no.	Region	Description	N
TAK-491CLD Studies Using Human Biomaterials			
491-00272		Permeability of chlortalidone	
491CLD-00069		In vitro metabolism of chlortalidone	
491CLD-00068		CYP inhibition by chlortalidone	
TAK-491CLD Clinical Pharmacology Studies			
491CLD-102	(Europe)	Relative bioavailability of TAK-491CLD FDC pilot formulations (bilayer and monolayer tablets)	23
491CLD-103	(US)	Relative bioavailability of TAK-491CLD FDC phase 3 formulation (monolayer tablet); US-approved chlortalidone tablets	47
491CLD-104	(US)	Food-effect on TAK-491CLD (monolayer tablet) and on coadministered TAK-491 and chlortalidone monotherapy tablets	23
491CLD-105	(US)	Relative bioavailability of placebo TAK-491CLD FDC tablets (tablets contained either TAK-491 or CLD + placebo)	48
491CLD-106	(Europe)	Relative bioavailability of TAK-491CLD FDC phase 3 formulation (monolayer tablet): EU-approved chlortalidone tablets	48
Population Pharmacokinetics			

491CLD-302 Pop PK Report	(US, Europe [incl Russia], Latin America)	Population pharmacokinetic analysis in a factorial, efficacy, and safety study of TAK-491CLD FDC tablets in subjects with hypertension (phase 3 study)	1201, 1202, 1059
Pooled Pop PK Report	(US, Europe [incl Russia], Latin America)	Pooled Analysis to Evaluate the Population Pharmacokinetics of TAK-536, TAK-536 M-II, and Chlortalidone in Subjects with Varying Degrees of Renal Function (phase 1 and phase 3 studies)	1308, 1309, 1120

Methods

Overall the analytical methods were adequately validated and performed. The pharmacokinetic parameters analysed and statistical methods are acceptable

Absorption

Bioequivalence

The comparative bioavailability of the different formulations used throughout the development program of both TAK-491 and the TAK-491 / chlortalidone FDC is adequately demonstrated.

In order to bridge pharmacokinetic literature data of both compounds to this FDC formulation, comparable bioavailability needs to be de shown. In the pivotal bioequivalence study (TAK-491CLD_106), bioequivalence was shown except for the chlortalidone component to the Hygroton 25 mg chlortalidone formulation by MIBE GmbH Arzneimittel, Germany. However, it is agreed to bridge chlortalidone pharmacokinetic literature data to the FDC formulation, as the difference in C_{max} is limited and therefore not expected to be of major influence on the safety, efficacy or the interaction potential of chlortalidone.

Influence of food

Following administration of the TAK-491CLD FDC tablets after a high fat meal, a significant food effect was observed. A reduction of the extent and rate of absorption of 21-25% was observed for TAK-536 and TAK-536 M-II. Furthermore, for chlortalidone a 24% reduction of the rate of absorption was observed. These differences are clinically not relevant and therefore the posology recommendation (irrespective of food) is supported.

Bioavailability

The bioavailability of an oral dose of 50mg chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, C_{max} values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively.

The absorption of TAK-491 has been characterised adequately. After oral administration of TAK-491, it is hydrolysed to the active substance TAK-536. TAK-536 is absorbed, and has a t_{max} of approximately 3 hours, with a Cmax and AUC of approximately 5.7 µg/mL and 34 µg.hr/mL after administration of the highest tablet strength (80mg). The estimated absolute oral bioavailability of azilsartan medoxomil based on plasma levels of azilsartan is approximately 60%.

The estimated bioavailability of chlortalidone is approximately 64%, after 8 to 12 hours post dose. On repeated daily doses of 50 mg, mean steady state blood concentration of 7.2 µg/ml (21.2 µmo/L), measured at the end of the 24 hour dosage interval, is reached after 1 to 2 weeks.

Distribution

The volume of distribution of azilsartan is approximately 16 litres. Azilsartan is highly bound to plasma proteins (>99%), mainly serum albumin. Protein binding is constant at azilsartan plasma concentrations well above the range achieved with recommended doses.

In whole blood, chlortalidone is predominantly bound to erythrocyte carbonic anhydrase. *In vitro*, plasma protein binding of chlortalidone is approximately 76%, with the major binding protein being albumin. Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50 mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood were about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Elimination

Excretion

After oral administration of TAK-491 approximately 42% of the radioactivity dosed was recovered in the urine with 15% of the dose identified as TAK-536, which indicates TAK-536 was available systemically. The remaining radioactivity (55%) that appeared in feces after oral administration of TAK-491 could be attributed either to biliary excretion of TAK-536 and its metabolites or microbial metabolism of unabsorbed TAK-536 (converted from TAK-491) in the gastrointestinal tract.
Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Metabolism

Following oral administration, azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan in the gastrointestinal tract and/or during absorption. Based on in vitro studies, carboxymethylenebutenolidase is involved in the hydrolysis in the intestine and liver. Metabolism of TAK-536 after TAK-491 administration is extensive, and 2 metabolites are formed in humans: TAK-536 M-I, a minor decarboxylated metabolite, and TAK-536 M-II, a major O-dealkylated metabolite, which is formed via CYP2C9.
Metabolism and hepatic excretion into bile constitute a minor pathway of the elimination of chlorthalidone. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form. In addition to literature, an additional study was performed indicating chlortalidone was hardly metabolised by human hepatic microsomes and individual human CYP isoform expressing microsomes.

Dose proportionality and time dependency

Dose proportionality of exposure to TAK-536 and TAK-536 M-II, the major human metabolite, was established at doses from 20 to 320 mg using data from several single and multiple dose studies. No accumulation of TAK-536 and TAK-536 M-II was observed.
For chlortalidone doses up to 100mg there is a proportional increase in AUC.

Special populations

renal impairment

Total exposure (AUC) to TAK-536 after a single dose of TAK-491 tended to be higher in subjects with renal impairment than in healthy subjects, with increases of 30%, 25%, 96% in subjects with mild, moderate, and severe renal impairment. Subjects with end-stage kidney disease (ESRD) are dialysed and cannot be compared to the other groups. In subjects with renal impairment a 2-5 fold increase of the TAK-536-M-II exposure was observed. This observed increase of TAK-536-M-II is not clinically relevant. Based on the results of study TAK491_103, caution is needed in patients with severe renal impairment and ESRD. The pharmacokinetics (PK) of unbound TAK-536 and its metabolites (M-I and M-II) were similar to the PK of total drug concentrations in subjects with renal impairment.

hepatic impairment

Clinical experience treating patients with any type of hepatic impairment is extremely limited. One hepatic impairment study was conducted including 8 patients with mild and 8 patients with moderate hepatic impairment (study 491-102). Steady-state total exposures to TAK-536 were approximately 28% and 64% greater in subjects with mild and moderate hepatic impairment, respectively. Steady state total exposures to TAK-536 M-II were 27% and 36% greater respectively. Since the individual values for the Child-Pugh scores were not recorded in the case report form, it was not possible to assess properly whether the study population was appropriate. This deficiency does not call for a new study, however caution is needed and a starting dose of 20 mg could be considered in subjects with mild and moderate hepatic impairment. The PK of unbound TAK-536 and its metabolites (M-I and M-II) were similar to the PK of total drug concentrations in subjects with hepatic impairment. TAK-491 or TAK-491CLD has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group.

gender, race and weight

No clinically meaningful differences in exposure to TAK-536 related to gender, race (white versus black) were observed (study 491-003). The magnitude of the effects identified in the population PK

study (study 491CLD_302) resulting in variability of exposure to TAK-536 of >30% is considered not clinically relevant.

elderly population
The mean age of the elderly subjects was 68.7 ± 4.77 years. No clinically meaningful differences in exposure to TAK-536 related to age (<45 years of age vs >65 years of age) were observed. Caution should be exercised and close medical monitoring is recommended in the very elderly (aged >75 years) who may be at increased risk of adverse events.

paediatric population
The use of TAK-491 was not evaluated in children. The absence of data in children is acceptable as the application concerns use in the adult population only.

Interactions
In vitro studies TAK-491 and TAK-536
The potential of TAK-491 and TAK-536 to induce CYP3A is low. The potential of TAK-491 to inhibit cytochrome P450 was investigated for the most relevant CYP enzymes (CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) and TAK-536 has been evaluated (CYP2C8, CYP2C9) *in vitro* using human liver microsomes and B-lymphoblastoid-derived microsomes. From these *in vitro* studies it can be concluded that CYP2C9 and CYP2C8 might be relevant for drug-drug interactions. The permeability and involvement of Pgp has been investigated sufficiently. The permeability of TAK-491 and TAK-536 is low and TAK-491 had an inhibitory effect on Pgp-mediated efflux activity *in vitro*. TAK-536 does not inhibit the hepatic uptake of either pravastatin or atorvastatin, TAK-536 is unlikely to have any inhibitory effect on OATP1B1-mediated uptake activity *in vivo*. Results from these studies can be extrapolated to other transporters and it can be concluded that no interaction between TAK-491 and statins is expected via uptake transporters.

In vivo studies with TAK-491
Following co-administration of TAK491 with an aluminium-magnesium hydroxide antacid (study TAK-491_107) a decreased exposure to TAK-536 of 18% was observed. This decrease is not clinically meaningful. In population PK data study 491CLD-302 the co-administration of TAK491 with Proton Pump Inhibitors (PPIs) was evaluated. The study shows that the median exposure to TAK-536 in subjects who received concomitant PPIs is comparable with the median exposure in subjects who did not receive concomitant PPIs. Concomitant administration of TAK-491 with either chlortalidone, amlodipine or digoxine had no clinically significant effect on the pharmacokinetics of TAK-491 or the respective medicinal product. The interaction between TAK-491 and multiple cytochrome P450CYP probes was investigated. A cocktail of midazolam (3A4), caffeine (1A2), tolbutamide (2C9), dextromethorphan (2D6), and fexofenadine (PgP-probe) was administered, following multiple dose administration of TAK 491. Coadministration of TAK491 and the drug combination did not have a clinically relevant effect on any of the tested cytochrome P450 probes, the exposure to the P-glycoprotein (PgP) probe was slightly decreased (by 16%). It is expected that this interaction is not clinically relevant, as no interaction with digoxin was observed in study TAK-491_104. No drug interaction studies were conducted between TAK-491 or TAK-536 and lithium, non-steroidal anti-inflammatory drugs (NSAIDs), or potassium-sparing diuretics because clinical evidence already informs the potential risks associated with concomitant administration of these drugs and other drugs in the same class as TAK-491. Literature references were provided and this was considered acceptable.

In vivo studies with TAK-536
Several studies were conducted with TAK-536 the active metabolite. Most of the drug-drug interaction studies conducted with TAK-536 can be extrapolated to TAK-491. In study 536-006, no interaction between TAK-536 and the CYP2C8 substrate pioglitazone was observed. Negligible inhibition of CYP2C8 activity was observed in *in vitro* studies with TAK-536. However, *in vitro* tests suggest that TAK-491 has a potential for drug-drug interactions with CYP2C8 substrates. As TAK-491 appears to be hydrolysed pre-systematically to TAK-536 entirely and CYP2C8's expression in the GI tract is very small, no first pass interaction is expected. No new drug interaction study with TAK-491 and pioglitazone is therefore required. In study TAK-536_004 the same drug combination as in study TAK-491_013 was administered. Coadministration of TAK-536 and the drug combination did not have a clinically relevant effect on any of the tested cytochrome P450 probes, but also the exposure to the P-glycoprotein (PgP) probe was also not affected. The results of this support the findings of study TAK-

491_013. Co-administration of the CYP2C9 inhibitor fluconazole and TAK-536 (study TL-536-005) resulted in a 42% increase in TAK-536 AUC(0-inf), a 14% increase in TAK-536 C_{max}, and a 48% increase in XU(0-24) (total estimated amount of analyte in the urine collected over a 24 h postdose period divided by the total volume of urine collected) relative to administration of TAK-536 alone. Plasma clearance of TAK-536 was reduced with co-administration (0.87 L/hr versus 1.25 L/hr), but renal clearance was not (0.17 L/hr versus 0.16 L/hr) affected, furthermore, T1/2 and T_{max} were not affected. Co-administration of the CYP 3A4 inhibitor ketoconazole and TAK-536 (study TL-536-005) did not result in an increase of exposure of TAK-536 as expected, but resulted in a decrease in TAK-536 AUC0- inf (by 21%), C_{max} (by 32%) and urinary excretion (by 17%) and delayed T_{max} values (3.21 vs 2.06 hr). Neither plasma clearance nor renal clearance nor T1/2 of TAK-536 was affected. This is possibly due to reduced absorption of TAK-536 by ketoconazole. Co-administration of TAK-536 and metformin (study TL-536-011) did not significantly alter the steadystate concentrations of plasma TAK-536 and M-I or the respective medicinal product. In study 536-009 the drug-drug interaction of TAK-536 and warfarin was evaluated. Warfarin is used as a probe for CYP2C9 ((S)-warfarin) and CYP1A2 ((R)-warfarin) Multiple doses of TAK-536 did not affect the steady-state pharmacokinetics and pharmacodynamics of warfarin. The pharmacokinetic profile of glyburide (CYP2C9 probe) was not affected by multiple-dose administration of TAK-536 (study TL-536-010).

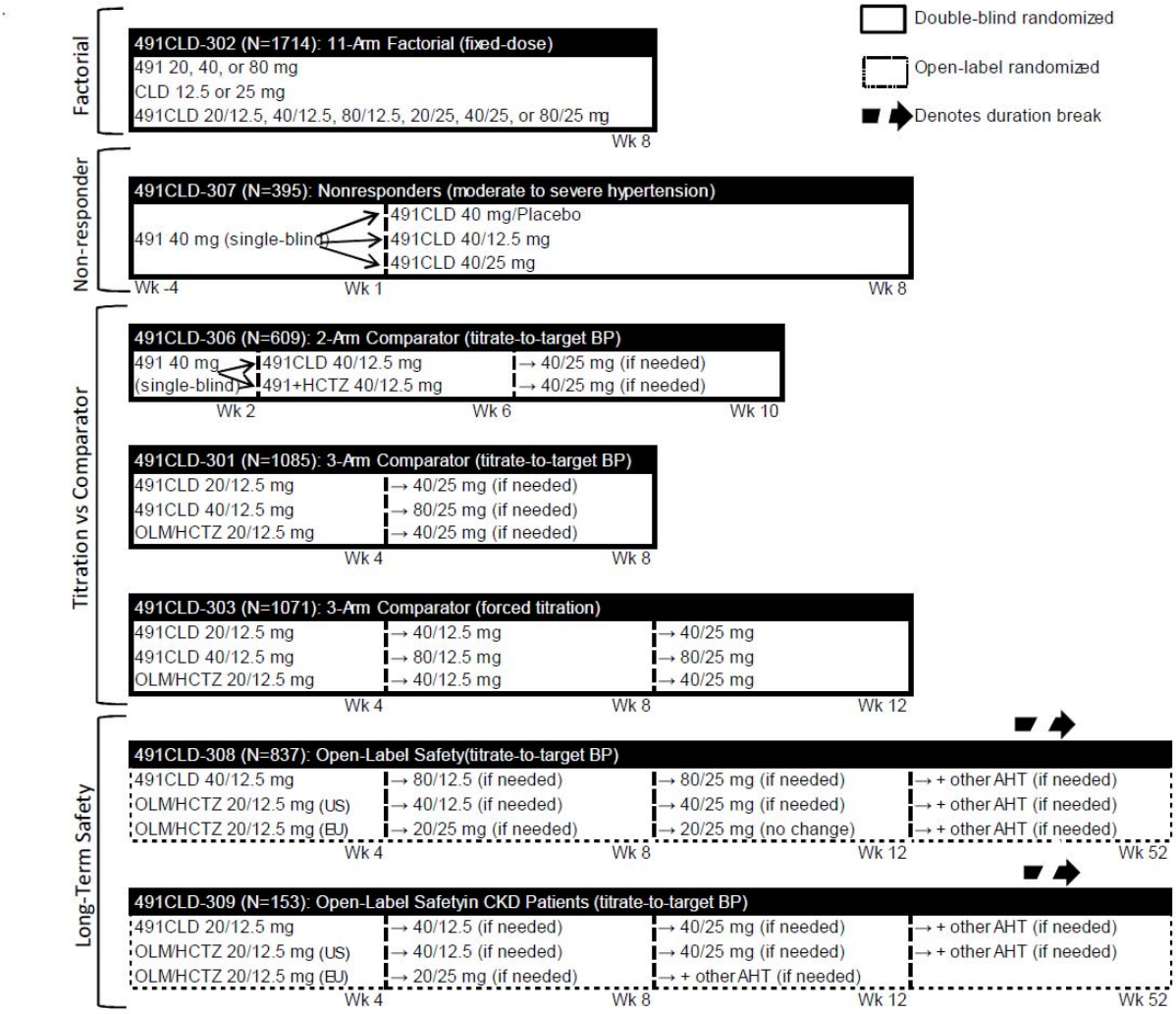
In vitro studies chlortalidone
Chlortalidone has no substantial inhibitory effects on CYP activities as was investigated using microsomes.

Conclusion
Overall the pharmacokinetics of TAK-491CLD have been adequately characterised. It has been substantiated that a clinically relevant interaction between azilsartan medoxomil and chlortalidone is absent. Supported by the provided studies, the pharmacokinetic characteristics of azilsartan medoxomil monotherapy are applicable to the applied for FDC formulation.
The interaction potential of TAK/491CLD has sufficiently been characterised. No clinically significant interactions have been reported in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, digoxin, fluconazole, glyburide, ketoconazole, metformin, and warfarin.
No specific dose recommendations for special populations are necessary, however the following specifics are noted: caution should be exercised with patients with severe renal impairment, due to the 96% increase in exposure of TAK-536. Caution should be exercised with mild and moderate hepatic impairment and is not recommended with severe hepatic impairment due to absence of data.
No dose adjustment of TAK-491CLD is required based on age, gender, or race, although caution should be exercised and close medical monitoring is recommended in the very elderly (aged >75 years) who may be at increased risk of adverse events.

IV.2 Clinical efficacy

Main clinical studies
Seven phase 3 studies for demonstrating the add-on efficacy of adding chlortalidone to azilsartan were performed: two pivotal, three comparator and two long term studies. The two pivotal studies were a factorial design study and non responders study. In figure 1, the overview of the seven studies can be found.

Figure 1. Overview of the phase 3 studies.



Study participants

The phase 3 FDC studies included adult subjects of 18 years and older with primary hypertension. Exclusion criteria were a Diastolic Blood Pressure (DBP) >119 mm Hg or of an Estimated Glomerular Filtration rate <30 mL/min/1.73 m^2. Other exclusion criteria were known or suspected unilateral or bilateral renal artery stenosis, hyperkalaemia, hypokalaemia, active liver disease or jaundice. In the short-term efficacy studies subjects receiving other medication classes known to have blood pressure-altering effects were excluded.

Primary endpoints

The primary efficacy endpoints of the two pivotal studies (491CLD-302 and 491CLD-307) were changes from Baseline in trough Systolic Blood Pressure (SBP) by ambulatory blood pressure monitoring (ABPM) and sitting clinic SBP, respectively. The primary endpoint of the titrate-to-target blood pressure studies (491CLD-306 and 491CLD-301) and the forced titration study (491CLD-303) was through sitting clinic SBP, while trough SBP by ABPM was included as a secondary endpoint.

Results

A total of 4874 subjects were randomised in the short-term FDC studies: 491CLD-302 (N=1714), 491CLD-307 (N=395), 491CLD-306 (N=609), 491CLD-301 (N=1085), and 491CLD-303 (N=1071) (table 2).

Table 2. Disposition across phase 3 studies.

Study Treatment Arm	Dose (mg)	n (%) Com-pleted	Discon-tinued	Discontinued Due to: Adverse Event	Protocol Deviation	LTFU	Voluntary Withdrawal	Lack of Efficacy	Other
491CLD-302									
CLD	25	141 (88.1)	19 (11.9)	6 (3.8)	1 (0.6)	3 (1.9)	4 (2.5)	2 (1.3)	3 (1.9)
TAK-491	40	139 (90.8)	14 (9.2)	6 (3.9)	1 (0.7)	0	5 (3.3)	1 (0.7)	1 (0.7)
TAK-491CLD	20/12.5	135 (86.5)	21 (13.5)	10 (6.4)	2 (1.3)	0	5 (3.2)	3 (1.9)	1 (0.6)
	40/12.5	131 (89.1)	16 (10.9)	6 (4.1)	2 (1.4)	1 (0.7)	3 (2.0)	0	4 (2.7)
	40/25	125 (80.1)	31 (19.9)	19 (12.2)	1 (0.6)	1 (0.6)	8 (5.1)	1 (0.6)	1 (0.6)
491CLD-307									
TAK-491 +Pbo	40	123 (92.5)	10 (7.5)	1 (0.8)	3 (2.3)	0	3 (2.3)	2 (1.5)	1 (0.8)
TAK-491CLD	40/12.5	122 (96.1)	5 (3.9)	2 (1.6)	2 (1.6)	0	0	0	1 (0.8)
	40/25	123 (91.1)	12 (8.9)	7 (5.2)	3 (2.2)	0	2 (1.5)	0	0
491CLD-306									
TAK-491CLD	40/12.5 → 40/25	252 (83.2)	51 (16.8)	28 (9.2)	2 (0.7)	3 (1.0)	16 (5.3)	0	2 (0.7)
TAK-491 +HCTZ	40+12.5 → 40+25	260 (85.0)	46 (15.0)	19 (6.2)	2 (0.7)	2 (0.7)	14 (4.6)	2 (0.7)	7 (2.3)
491CLD-301									
TAK-491CLD	20/12.5 → 40/25 (a)	317 (85.2)	55 (14.8)	20 (5.4)	5 (1.3)	8 (2.2)	11 (3.0)	1 (0.3)	9 (2.4)
	40/12.5 → 80/25	308 (86.3)	49 (13.7)	30 (8.4)	4 (1.1)	2 (0.6)	11 (3.1)	1 (0.3)	1 (0.3)
OLM/HCTZ	20/12.5 → 40/25	323 (90.7)	33 (9.3)	11 (3.1)	0	5 (1.4)	9 (2.5)	2 (0.6)	6 (1.7)
491CLD-303									
TAK-491CLD (b)	20/12.5→ 40/25	300 (84.5)	55 (15.5)	28 (7.9)	0	4 (1.1)	17 (4.8)	0	6 (1.7)
	40/12.5→ 80/25	275 (78.1)	77 (21.9)	51 (14.5)	2 (0.6)	5 (1.4)	14 (4.0)	1 (0.3)	4 (1.1)
OLM/HCTZ (c)	20/12.5→ 40/25	317 (87.1)	47 (12.9)	26 (7.1)	1 (0.3)	5 (1.4)	11 (3.0)	1 (0.3)	3 (0.8)
491CLD-308									
TAK-491CLD (b)	40/12.5→ 80/25	287 (68.7)	131 (31.3)	75 (17.9)	6 (1.4)	14 (3.3)	31 (7.4)	0	5 (1.2)
OLM/HCTZ (c)	20/12.5→ 20/25 (EU) or 40/25 (US)	330 (78.8)	89 (21.2)	37 (8.8)	7 (1.7)	16 (3.8)	20 (4.8)	2 (0.5)	7 (1.7)
491CLD-309									
TAK-491CLD (b)	20/12.5→ 40/25	61 (79.2)	16 (20.8)	10 (13.0)	0	0	5 (6.5)	0	1 (1.3)
OLM/HCTZ (c)	20/12.5→ 20/25 (EU) or 40/25 (US)	60 (78.9)	16 (21.1)	11 (14.5)	1 (1.3)	0	4 (5.3)	0	0

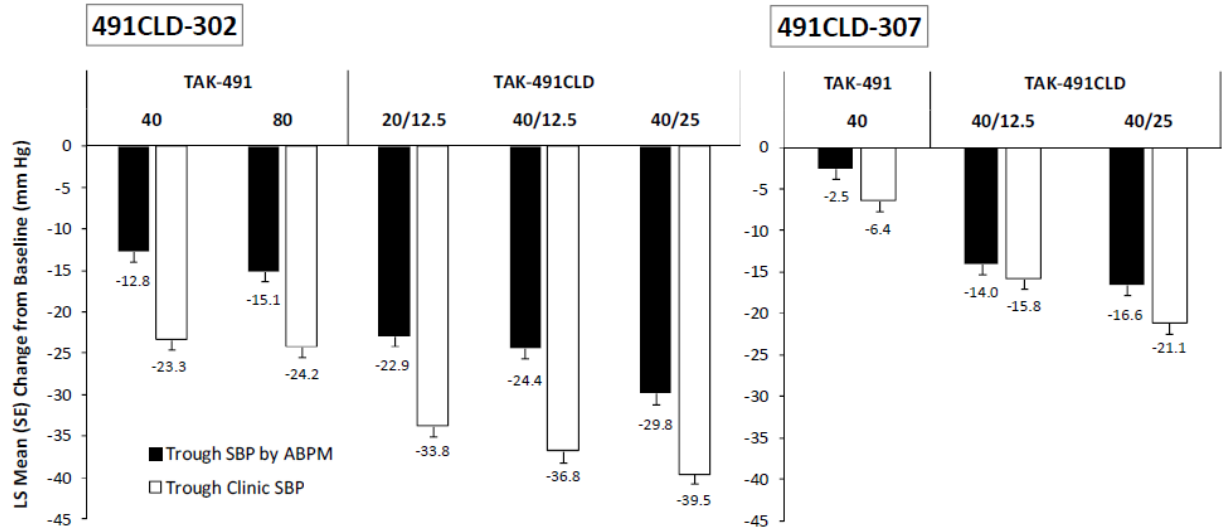
LTFU= lost to follow-up NA= not applicable Pbo= placebo
(a) In lower TAK-491CLD titration group, 1/317 subject (0.3%) discontinued due to pregnancy.
(b) Only starting and final doses are shown; see original CSRs for full titration steps.
(c) Only starting and final doses per region are shown; see orginal CSRs for full titration steps, which are region-specific.

Factorial design study 302 - There were statistically significant reductions at Week 8 in trough SBP by ABPM (28.9 mm Hg) and sitting clinic SBP measurements (39.8 mm Hg) in the treatment groups receiving the highest doses of the TAK-491CLD FDC (40/25 mg+80/25 mg pool) compared with the treatment groups receiving the highest doses of TAK-491 (80 mg) or chlortalidone (25 mg) monotherapy. In addition, each of the 6 individual TAK-491CLD dose strengths (20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, and 80/25 mg) led to clinically and statistically significantly greater reductions in SBP and DBP compared with their respective monotherapy components, as assessed by both clinic and ABPM trough blood pressure measurements.
In 491CLD-302, the sensitivity analyses using multiple imputation methodology for change from Baseline in trough SBP as measured by ABPM and clinic SBP at Week 8 also yielded results consistent with the primary analysis.

Non-responders study 307 - Statistically significant and dose-dependent reductions in trough, sitting, clinic SBP were observed at Week 8 in the TAK-491CLD 40/12.5 and 40/25 mg groups compared with the TAK 491 40 mg monotherapy group. Statistically significantly greater reductions of 15.8 mm Hg

and 21.1 mm Hg were achieved with TAK-491CLD 40/12.5 and 40/25 mg, respectively, relative to the 6.4 mm Hg reduction observed with TAK-491 40 mg monotherapy (p<0.001 for both comparisons).
In 491CLD-307, the sensitivity analyses using multiple imputation methodology for change from Double-Blind Baseline in trough, clinic SBP and in trough SBP as measured by ABPM at Week 8 also yielded results consistent with the primary analysis.

Figure 2. Change from baseline in clinic SBP and trough SBP by ABPM at week 8 in 491CLD-302 and 491CLD-307.



.
For the short term comparison studies, an additional blood pressure (BP) lowering effect could be observed after each dose step. The BP lowering effect was generally significantly lower in the FDC in comparison to the olmesartan/hydrochlorothiazide combination (OLM/HCTZ). However, the value of these comparisons for the proposed indication may be questioned.
In the long term study 308, the BP lowering effect was generally significantly greater in the chlortalidone-TAK FDC in comparison to the OLM/HCTZ combination. In addition, less up titrations were needed with the FDC compared to the OLM/HCTZ combination. However, the dose steps as proposed in the posology of the SmPC have not been evaluated in this study, thus questioning the relevance in terms of efficacy of this study.
In the smaller 309 study in patients with moderate renal impairment, relevant long-term effects on BP were observed, although in this population there were no obvious differences between the LCD-TAK FDC versus OLM/HCTZ.

Conclusion
The factorial study 302 has been performed to compare the BP lowering response for all dose combinations possible. In this study significant and clinically relevant reductions in the primary endpoint of clinical SBP and ABPM SPB were observed for all FDCs in comparison to the respective monocomponents (10.3 mmHg to 17.0 mmHg additional BP lowering). A dose dependent reduction was observed for all strengths up to the 40/25 mg combination. For the highest doses (80/12.5 mg and 80/25 mg) in comparison to the 40/12.5 mg and 40/25 mg doses, respectively, the additional BP reduction seems less clear.
The non-responder study 307 has been chosen as the dose strength to compare the FDC with. An significant additional BP reduction was observed with the combination of either 12.5 or 25 mg CHLORTALIDONE after 8 weeks of treatment on the primary endpoint of clinical SBO reduction (9.4 mmHg to 15.1 mmHg additional BP lowering).

Special populations
Some inconsistencies with respect to the BP effect can be observed in subgroups. For instance, a different effect between male and female can be observed. However, it may be disputed whether these are clinically meaningful. At least all FDC combinations demonstrate a significant effect for both male and female. For the Black population, it is known that less effect can be observed with RAS blockers. This is confirmed for the monotherapy response in the pivotal studies. However, effects are

approximately similar when these patients are treated with the FDC in comparison to the White subgroup. For the comparator studies, this effect remains however slightly less for the Black subgroup. The company explored the treatment effect of BP reduction in the elderly categories of older than 65 and 75 years of age. Although some differences appear with the younger population, these are not consistent, thus any conclusions on this remain difficult.

IV.3 Clinical safety

Patient exposure

Across the TAK-491CLD development program and the TAK-491 monotherapy studies in which chlortalidone was co-administered, 4240 unique subjects with hypertension received at least 1 dose including more than 787 subjects who were treated for at least 6 months and 396 subjects who were treated for at least 1 year. In the phase 3 TAK-491CLD clinical studies, 3421 subjects received at least 1 dose of TAK-491CLD at various dose combination; of these, 381 were treated for at least 6 months and 225 were treated for at least 1 year. Mean treatment duration was approximately 13.1 weeks (93 days), while the median duration was approximately 8.3 weeks (58 days). The total number of patients treated with the FDC can be considered sufficient. The number of patients treated for at least 3 months and 6 months is limited though sufficient. In addition, the safety profile of the mono components is already known from initial submission and the use in clinical practice.

Adverse events

An overview of the number of adverse events (AEs) observed in the pivotal studies (302 and 307) is provided below.

Table 3. Adverse events overview in the factorial design study 302

	Number (%) of Subjects										
	TAK-491 (mg)			CLD (mg)		TAK-491CLD (mg)					
Event Category	20 N=155	40 N=153	80 N=162	12.5 N=156	25 N=160	20/12.5 N=156	40/12.5 N=146	80/12.5 N=153	20/25 N=154	40/25 N=156	80/25 N=161
Any TEAE	70 (45.2)	75 (49.0)	70 (43.2)	82 (52.6)	92 (57.5)	92 (59.0)	83 (56.8)	84 (54.9)	88 (57.1)	106 (67.9)	100 (62.1)
Related (a)	32 (20.6)	34 (22.2)	29 (17.9)	42 (26.9)	54 (33.8)	50 (32.1)	41 (28.1)	52 (34.0)	49 (31.8)	68 (43.6)	66 (41.0)
Intensity (b)											
Mild	36 (23.2)	43 (28.1)	38 (23.5)	46 (29.5)	50 (31.3)	56 (35.9)	43 (29.5)	45 (29.4)	45 (29.2)	59 (37.8)	47 (29.2)
Moderate	31 (20.0)	31 (20.3)	26 (16.0)	34 (21.8)	38 (23.8)	33 (21.2)	39 (26.7)	33 (21.6)	38 (24.7)	44 (28.2)	45 (28.0)
Severe	3 (1.9)	1 (0.7)	6 (3.7)	2 (1.3)	4 (2.5)	3 (1.9)	1 (0.7)	6 (3.9)	5 (3.2)	3 (1.9)	8 (5.0)
Leading to discontinuation (c)	3 (1.9)	6 (3.9)	7 (4.3)	3 (1.9)	6 (3.8)	10 (6.4)	5 (3.4)	14 (9.2)	12 (7.8)	22 (14.1)	23 (14.3)
SAEs	2 (1.3)	2 (1.3)	3 (1.9)	0	2 (1.3)	3 (1.9)	1 (0.7)	2 (1.3)	0	2 (1.3)	2 (1.2)
Related (a)	0	0	0	0	0	0	1 (0.7)	1 (0.7)	0	1 (0.6)	0
Deaths	0	0	0	0	0	0	0	0	0	0	1 (0.6)

Table 4: Adverse events overview in the non-responders study 307

	DB Treatment Period		
	TAK-491CLD 40 mg N=133	TAK-491CLD 40/12.5 mg N=127	TAK-491CLD 40/25 mg N=135
	Number (%) of Subjects		
Any TEAE	37 (27.8)	30 (23.6)	43 (31.9)
Related (a)	11 (8.3)	14 (11.0)	23 (17.0)
Intensity (b)			
Mild	21 (15.8)	21 (16.5)	25 (18.5)
Moderate	13 (9.8)	9 (7.1)	17 (12.6)
Severe	3 (2.3)	0	1 (0.7)
Leading to discontinuation (c)	3 (2.3)	3 (2.4)	9 (6.7)
SAEs	2 (1.5)	0	0
Related (a)	0	0	0
Deaths	0	0	0

The majority of all treatment-emergent adverse events (TEAEs) were considered mild or moderate in intensity and the incidence of serious adverse events (SAEs) was low. The most frequently occuring TEAEs are blood creatinine increased, dizziness and headache. Blood creatinine and dizziness may be pharmacological dose related adverse events, while a dose relationship for headache seems not to appear. Furtermore, attenuation of the hypokalemic effect of Chlortalidone can also be observed when azilsartan is added as combination. During the long term studies a similair safety patern can be observed, with the exception that nasopharyngitis was also frequently observed. If AEs are shown clustered, the incidence of the hypotension cluster becomes more apparent, although a dose related frequency is less clear.

Serious adverse events and deaths

Renal related SAEs

Ten renal-related SAEs were reported, of which 6 occurred in the FDC TAK-491CLD. None of these events was associated with severe clinical complications. Of these 6 subjects, 1 subject had already completed the study prior to the SAE (renal failure acute), 1 subject continued with no change in dose (blood creatinine increased concurrent with blood urea increased), 1 subject had a dose interruption and continued treatment (real failure acute concurrent with gastroenteritis salmonella) and the SAEs (blood urea increased, blood creatinine increased and renal failure chronic concurrent with blood creatinine increased) for 3 subjects resolved after discontinuation. Renal related SAEs were also reported for 1 subject who received TAK-491+HCTZ (renal failure acute, event resolved after study drug was discontinued) and 3 subjects who received OLM/HCTZ (renal failure acute, two with blood creatinine increased).

Hypotension related SAEs

Eleven hypotension-related SAEs were reported; of these, 8 subjects received the FDC TAK-491CLD. Of these 8 subjects, 1 subject had already completed the study prior to the SAE (hypotension), 2 subjects were previously withdrawn from the study prior to the SAE (hypotension, cardiogenic shock), 1 subject continued with no change in dose (syncope), and the SAEs for 4 subjects resolved after discontinuation (hypotension, syncope concurrent with hypotension, loss of consciousness concurrent with syncope, orthostatic hypotension). Hypotension-related SAEs were also reported for 1 subject who received TAK-491+HCTZ (syncope, resolved after study drug was discontinued) and 2 subjects who received OLM/HCTZ (hemodynamic shock, resolved after study drug was discontinued; presyncope, dose not changed).

Deaths

A total of 8 deaths (3 from short-term double-blind and 5 from long-term open-label studies) were reported during active treatment: 1 in a subject who received TAK-491 40 mg (subject randomised to TAK-491+HCTZ treatment arm), 4 in subjects who received TAK-491CLD, and 3 in subjects who received OLM/HCTZ; the percentage of subjects who died in each of the treatment arms were 0.16%,

0.17%, and 0.25%, respectively, suggesting that there were no increase in fatality for TAK-491CLD treatment arm when compared with a comparator. The majority of fatal cases were due to cardiovascular events, as would be expected from a population with hypertension. Although 2 sudden deaths were reported in the short term comparison study 306, there were no common characteristics (eg, time of onset, subject demographics, or baseline characteristics) among the fatal events, and autopsies were not performed. Due to the lack of a definitive diagnosis in 1 subject, the event was recorded as possibly related to study drug in the absence of adequate information. For the other deaths, no common characteristics were noted.

Laboratory findings
Decreased in hemoglobin and hematocrit were observed, a known effect associated with ARB treatment. Meaningful decreases were only observed in approximately 1.5% of the patients, and thus the effect may be considered marginal.
A known effect of some antihypertensive drugs and ACE inhibitors and ARBs in particular is the initial increase in serum creatinine upon start of treatment. This occurred most with the combination of TAK491CLD and seemed to be dose dependent with 4.5% on the 20/12.5 mg and 15.7% on the 80/25 mg combination for >30% in serum creatinine elevation. In the non responders study this effect only occurred in 9 patients due to the more gradient dose increase. In accordance with a supposed hemodynamic effect, most of these effects were transient. Supporting this mechanism, serum creatinine elevations are related to the BP lowering effect, with a likelihood increased when BP reduction in larger.

Safety in special populations
A slightly higher incidence of adverse events occurred in patient older than 65 years of age compared to the younger population. However, when divided according to clusters of adverse events, no consistent increased number of adverse events were found for renal events and hypotension in the factorial design study. In the non-responders study, these events seem higher for the 65 years and older patients, however, numbers were very limited.
According to the company, no clear pattern of increased adverse events could be observed for the very elderly (>75 years) compared to younger patients in the whole study set. However, based on limited number of events in the factorial design study, a higher incidence of dizziness, hypotension and discontinuations in the >75 years of age group could be observed for the FDC not observed for the monocomponents. Although such pattern can be expected, definite conclusions cannot be drawn considering such limited number of patients and the inconsistency in findings.

Discontinuation due to adverse events
The incidence of discontinuation due to adverse events was dose related with the highest doses showing the highest discontinuation (1.9% to 14.3%). Overall, the frequency of discontinuation due to AEs was acceptable with only a slightly higher incidence in the long term safety study 491CLD-308 (18.9%). In this study, the FDC was compared to a olmesartan medoxomil/hydrochlorthiazide combination. The discontinuation for the TAK491CLD was higher (10.3%) but may be explained by the larger BP lowering effect. Overall, the most discontinuations were related to serum creatinine increase, hypotension and dizziness, typically dose dependent effects. In addition, a slower up-titration was associated with far less discontinuations.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Edarclor.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Elevated Serum Creatinine - Hypotension - Diarrhoea - Foetotoxicity - Angioedema
Important potential risks	- Electrolyte imbalance - Metabolic effects - Hypersensitivity

	- Interaction with: o Lithium o Non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3g/day), and non-selective NSAIDs o Aliskiren or other hypertension medications that work through the RAAS
Missing information	- Use in patients with severe renal impairment and/or ESRD - Use in patients with severe hepatic impairment - Use in patients with congestive heart failure - Use in patients with congestive heart failure - Use in patients with renal artery stenosis - Use in patients with kidney transplantation - Use in elderly persons >= 75 years old - Use in pregnant females - Use in nursing mothers - Off-label use

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

The combination of azilsartan and chlortalidone is considered clinically and pharmacologically plausible. Both components are from well known pharmaceutical classes, although experience with azilsartan within the class of ARBs is still limited. Additional blood pressure lowering efficacy for the specific 40/12.5 mg and the 40/25 mg FDC of azilsartan and chlortalidone has been demonstrated in comparison to monotherapy with 40 mg and 80 mg azilsartan. These data provide support for an indication of treatment with the fixed-dose combination in adults whose blood pressure is not adequately controlled on azilsartan monotherapy alone. As can be expected based on the mechanism of action, dose related adverse events occur at a higher incidence with the FDC in comparison to the monocomponents, mainly 'serum creatinine increased', dizziness and to a lesser extent hypotension. These were also the main reasons of the higher incidence of discontinuations, although these may be limited by a more conservative step wise up-titration as proposed in the SmPC. Severe adverse events seem to occur sporadically which is reassuring. The long term studies support the long term use in both the general population as patients with moderate renal impairment. As known from these type of medications, elderly seem to be more prone to experience adverse events. Other known subgroup differences were also observed. Overall, the clinical program can be accepted.

V. USER CONSULTATION

A focus test was performed instead of a full user test. A full user test was conducted on the package leaflet (PL) for Edarbi 20 mg and 80 mg tablets (azilsartan medoxomil) in April 2011. The PL for Edarclor is similar to that for Edarbi in many respects, but there are some differences in key safety messages due to the addition of the second active ingredient chlortalidone. Therefore, a focused user testing was required to address these differences. This test focusses on the information in the PL in section 1,2 and 4.
There were two rounds of each ten participants and a pilot of 1 participant. Although the majority of subjects were female (15/20, 75%), this is not expected to be of any influence on this user test.
There were 6 questions about the package leaflet on issues which are specific to this presentation. and the participants were also asked to provide feedback in terms of their own impressions.
The test criterion was that at least 90% of the participants must be able to find the information in the leaflet and of those 90% should be able to understand it correctly. This test criterion has been met.
The conclusions are clear, concise and clearly presented. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Edarclor 40 mg/12.5 mg and 40 mg/12.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Both azilsartan medoxomil and chlortalidone are well known, established substances, which are used as a combination in clinical practice.

A positive benefit risk profile for the fixed-dose combination can be concluded with demonstration of additional efficacy in comparison to azilsartan monotherapy while maintaining an acceptable safety profile.

The Board followed the advice of the assessors.

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 essential similarity has been demonstrated for Edarclor with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 October 2015.

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
Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Change in the Manufacturing Authorisation Holder's European QPPV	NL/H/3333/ 1-2/IA/001	IA	15-01-2016	22-01-2016	approved	No
Repea-use procedure used to register the product in Ireland	NL/H/3333/ 1-2/E/001	E	20-01-2017	20-04-2017	approved	Yes