IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific discussion

Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20/12.5, 20/25, 40/12.5 and 40/25 milligram Film Coated Tablet
OLMESARTAN MEDOXOMIL

PA 593/039/001-004

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20/12.5, 20/25, 40/12.5 and 40/25 milligram Film Coated Tablet from STADA Arzneimittel AG Germany on 22/8/2-16 for Treatment of essential hypertension and is also indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil alone.

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC. In this decentralised procedure IE acted as the reference member state (RMS) with the following as concerned member states, DE, FR, BE, IT, LU and NL.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie .

Name of the product	Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG
Name(s) of the active substance(s) (INN)	OLMESARTAN MEDOXOMIL
Pharmacotherapeutic classification (ATC code)	C09DA08 Angiotensin II antagonists and diuretics
Pharmaceutical form and strength(s)	20/12.5, 20/25, 40/12.5 and 40/25 milligram Film Coated Tablet
MRP/DCP No. Reference Member State Concerned Member State	IE/H/461/001-004/DC IE BE DE FR IT LU NL
Marketing Authorisation Holder	STADA Arzneimittel AG

II QUALITY ASPECTS

II.1. Introduction

This application is for Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets.

II.2 Drug substance

The active substances olmesartan medoxmil and hydrochlorothiazide, established active substance described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specifications have been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer’s specifications.

P.5 Control of Finished Product

The Finished Product Specifications are based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. /EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Olmetec Plus 20 mg / 12.5 mg, 20 mg / 25 mg, 40 mg / 12.5 mg, 40 mg / 25 mg on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

The applicant has provided an abridged ERA consisting of consumption data of the active ingredients for the last 4 years in concerned Member States. This product is intended for generic substitution of existing products and as such, marketing of this product will not result in an increase in the environmental exposure to olmesartan

medoxomil/hydrochlorothiazide. This is acceptable.

III.6 Discussion on the non-clinical aspects

Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets is a generic formulation of Olmetec Plus 20 mg / 12.5 mg, 20 mg / 25 mg, 40 mg / 12.5 mg, 40 mg / 25 mg on the European market. No new preclinical data have been submitted as additional testing on animals would be repetitive and is therefore not required. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of abridged application.

IV CLINICAL ASPECTS

Olmesartan medoxomil is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no requirement to generate additional efficacy or safety clinical data, apart from the bioequivalence studies provided by the applicant.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Olmetec Plus marketed by Daiichi Sankyo Europe GmbH.

For this generic application, the applicant has submitted a pilot bioequivalence study and 3 pivotal bioequivalence studies, which are discussed below.

Bioequivalence studies

Pilot Bioequivalence Study
A single-dose, three-treatment, three-period pilot bioequivalence study of two batches of Olmesartan HCT 40/25 mg tablets and Olmetec Plus® was conducted.
12 healthy male subjects were randomised to receive either Test 1 or Test 2 or Reference after an overnight fasting. The subjects were confined to hospital from 13 hours prior to 12 hours after drug administration.

A 7-day washout period separated the treatment periods.

Olmesartan			
Pharmac-okinetic parameter	**Geometric Mean Ratio % T1/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	105.21	94.67 – 116.93	12.82
$AUC_{(0-\infty)}$	104.75	94.58 – 116.00	12.38
C_{max}	103.76	90.39 – 119.09	16.78
Pharmac-okinetic parameter	**Geometric Mean Ratio % T2/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	98.18	88.34 – 109.11	12.82
$AUC_{(0-\infty)}$	97.94	88.44 – 108.47	12.38
C_{max}	93.83	81.75 – 107.70	16.78
Hydrochlorothiazide			
Pharmac-okinetic parameter	**Geometric Mean Ratio % T1/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	99.20	89.91 – 109.46	11.93
$AUC_{(0-\infty)}$	98.67	89.39 – 108.90	11.97
C_{max}	105.41	92.02 – 120.76	16.54
Pharmac-okinetic parameter	**Geometric Mean Ratio % T2/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	99.20	89.90 – 109.45	11.93
$AUC_{(0-\infty)}$	98.96	89.66 – 109.22	11.97
C_{max}	101.77	88.83 – 116.58	16.54

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC0- Area under the plasma concentration curve extrapolated to infinite time.
Cmax Maximum plasma concentration
tmax Time until Cmax is reached

1st Pivotal bioequivalence study:

Bioequivalence study of olmesartan and hydrochlorothiazide after single dose administration (fasting conditions) of Olmesartan/HCT 40/25 mg film-coated tablets (Test product) and Olmetec Plus® 40 mg/ 25 mg (Reference product) in 30 healthy subjects. There was a washout period of 7 days which is of sufficient duration

Results Olmesartan

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of olmesartan (N = 30)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	96.15	101.07	106.23	11.39
$AUC_{(0-\infty)}$	95.91	100.74	105.81	11.22
C_{max}	95.80	100.79	106.05	11.61

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

For the extent of absorption (AUC) and the rate of absorption (C_{max}) the confidence interval lies within the acceptance range of 80.00 % to 125.00 %.

Hydrochlorothiazide

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of hydrochlorothiazide (N = 30)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	89.08	94.55	100.35	13.62
$AUC_{(0-\infty)}$	89.30	94.74	100.50	13.50
C_{max}	77.62	84.31	91.57	18.99

LCL = lower 90 %-confidence limit
UCL = upper 90 %-confidence limit

In summary it is concluded that for the extent of absorption (AUC) bioequivalence could be accepted for both Olmesartan and hydrochlorothiazide, the rate of absorption (Cmax) could be accepted for Olmesartan, but for the rate of absorption (Cmax) bioequivalence could not be accepted for hydrochlorothiazide.
Further explanation was provided by the company as to the reasons for this bioequivalence failing to meet the Cmax limit in the 1st pivotal study conducted with the test formulation in the 40/25 mg strength. Following a review it was concluded that the reference batch used is to be considered as an extreme batch with regards to initial HCT dissolution. In line with the Bioequivalence guideline (CPMP/EWP/QWP/1040/98 Rev1) requirements it has to be ensured that a representative batch of the reference product should be used for the bioequivalence study.

Second Pivotal bioequivalence study 2
Bioequivalence study of olmesartan and hydrochlorothiazide after single dose administration (fasting conditions) of Olmesartan/HCT 40/25 mg film-coated tablets (Test product) and Olmetec Plus® 40 mg/25 mg (Reference product) in 42 healthy subjects.

Wash-out period: at least 7 days

Results
Olmesartan
Hydrochlorothiazide

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of olmesartan (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	93.26	99.47	106.09	17.68
$AUC_{(0-\infty)}$	93.18	99.26	105.74	17.34
C_{max}	92.73	99.43	106.61	19.16

LCL = lower 90 %-confidence limit
UCL = upper 90 %-confidence limit

Hydrochlorothiazide

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of hydrochlorothiazide n (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	94.60	99.24	104.10	13.08
$AUC_{(0-\infty)}$	94.67	99.14	103.83	12.61
C_{max}	91.57	97.66	104.16	17.68

LCL = lower 90 %-confidence limit
UCL = upper 90 %-confidence limit

The current Guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1041/98 Rev 1) defines the confidence limits as 80% to 125% for CMax and AUC values.

As the 90% confidence intervals of the test/reference ratio for the log transformed parameters C Max, AUC 0-∞ and AUC 0-t have been demonstrated to be within the pre specified limits bioequivalence has been demonstrated between the test product and the reference.

Third bioequivalence study:
This study was conducted to demonstrate bioequivalence for the Olmesartan 20 mg hydrochlorothiazide 25 mg formulation.

A single-dose, two-treatment, two-period pilot bioequivalence study of two batches of Olmesartan HCT 20/25 mg tablets and Olmetec Plus® was conducted.
42 healthy male subjects were randomised to receive either Test 1 or Test 2 or Reference after an overnight fasting with a wash out of 7 days.

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{wR} (%) from the OLS analysis of olmesartan (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{wR} (%)
$AUC_{(0-t)}$	94.58	99.48	104.63	13.81
C_{max}	90.35	96.72	103.54	18.71

LCL = lower 90 %-confidence limit
UCL = upper 90 %-confidence limit

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

HPRA has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of good clinical practice (GCP) and Good Laboratory Practice (GLP)

IV.2 Pharmacokinetics

Absorption and distribution

Olmesartan medoxomil
Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6 %.

The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7 %), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound coadministered active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 l).

Hydrochlorothiazide
Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing. Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 - 1.14 l/kg.

Biotransformation and elimination

Olmesartan medoxomil
Total plasma clearance of olmesartan was typically 1.3 l/h (CV, 19 %) and was relatively slow compared to hepatic blood flow (ca. 90 l/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10 - 16 % of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6 %, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca. 40 %) and hepato-biliary excretion (ca. 60 %). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

The terminal elimination half-life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 - 0.7 l/h and was independent of dose.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged active substance in urine. About 60 % of the oral dose is eliminated as unchanged active substance within 48 hours. Renal clearance is about 250 - 300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

Olmesartan medoxomil/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is reduced by about 20 % when co-administered with olmesartan medoxomil, but this modest decrease is not of any clinical relevance. The kinetics of olmesartan are unaffected by the co-administration of hydrochlorothiazide.

Pharmacokinetics in special populations

Older people (age 65 years or over)
In hypertensive patients, the olmesartan AUC at steady state was increased by ca. 35 % in older people (65 – 75 years old) and by ca. 44 % in very old people (≥ 75 years old) compared with the younger age group (see section 4.2).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive older people compared to young healthy volunteers.

Renal impairment
In renally impaired patients, the olmesartan AUC at steady state increased by 62 %, 82 % and 179 % in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2, 4.4).

The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

Hepatic impairment
After single oral administration, olmesartan AUC values were 6 % and 65 % higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26 %, 0.34 % and 0.41 %, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC was again about 65 % higher than in matched healthy controls. Olmesartan mean C_{max} values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2, 4.4).

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

Drug interactions

Bile acid sequestering agent colesevelam
Concomitant administration of 40 mg olmesartan medoxomil and 3,750 mg colesevelam hydrochloride in healthy subjects resulted in 28 % reduction in C_{max} and 39 % reduction in AUC of olmesartan. Lesser effects, 4 % and 15 % reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half-life of olmesartan was reduced by 50 – 52 % irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride.

IV.3 Pharmacodynamics

Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Once daily dosing with Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG provides an effective and smooth reduction in blood pressure over the 24 hour dose interval.

Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT_1) antagonist. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT_1 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 (AT_1) 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. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment.

The effect of olmesartan medoxomil on mortality and morbidity is not yet known.

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4,447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3.2 years, patients received either olmesartan or placebo in addition to other antihypertensive agents, except ACE inhibitors or ARBs.
For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2 % (178 of 2,160) of the patients in the olmesartan group and 9.8 % (210 of 2,139) in the placebo group developed microalbuminuria.
For the secondary endpoints, cardiovascular events occurred in 96 patients (4.3 %) with olmesartan and in 94 patients (4.2 %) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients (0.7 %) vs. 3 patients (0.1 %)), despite similar rates for non-fatal stroke (14 patients (0.6 %) vs. 8

patients (0.4 %)), non-fatal myocardial infarction (17 patients (0.8 %) vs. 26 patients (1.2 %)) and non-cardiovascular mortality (11 patients (0.5 %) vs. 12 patients (0.5 %)). Overall mortality with olmesartan was numerically increased (26 patients (1.2 %) vs. 15 patients (0.7 %)), which was mainly driven by a higher number of fatal cardiovascular events.

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) investigated the effects of olmesartan on renal and cardiovascular outcomes in 577 randomised Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3.1 years, patients received either olmesartan or placebo in addition to other antihypertensive agents including ACE inhibitors.

The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all cause death) occurred in 116 patients in the olmesartan group (41.1 %) and 129 patients in the placebo group (45.4 %) (HR 0.97 (95 % CI 0.75 to 1.24); p = 0.791). The composite secondary cardiovascular endpoint occurred in 40 olmesartan-treated patients (14.2 %) and 53 placebo-treated patients (18.7 %). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5 %) patients receiving olmesartan versus 3 (1.1 %) receiving placebo, overall mortality 19 (6.7 %) versus 20 (7.0 %), non-fatal stroke 8 (2.8 %) versus 11 (3.9 %) and non-fatal myocardial infarction 3 (1.1 %) versus 7 (2.5 %), respectively.

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

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

Clinical efficacy and safety

The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of each component.

In pooled placebo-controlled studies, administration of the 20/12.5 mg and 20/25 mg combinations of olmesartan medoxomil/hydrochlorothiazide resulted in mean placebo- subtracted systolic/diastolic blood pressure reductions at trough of 12/7 mmHg and 16/9 mmHg, respectively. Age and gender had no clinically relevant effect on response to treatment with olmesartan medoxomil /hydrochlorothiazide combination therapy.

Administration of 12.5 mg and 25 mg hydrochlorothiazide in patients insufficiently controlled by olmesartan medoxomil 20 mg monotherapy gave additional reductions in 24-hour systolic/diastolic blood pressures measured by ambulatory blood pressure monitoring of 7/5 mmHg and 12/7 mmHg, respectively, compared with olmesartan medoxomil monotherapy baseline. The additional mean systolic/diastolic blood pressure reductions at trough compared with baseline, measured conventionally, were 11/10 mmHg and 16/11 mmHg, respectively.

The effectiveness of olmesartan medoxomil/hydrochlorothiazide combination therapy was maintained over long-term (one-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension.

The effects of fixed dose combination of olmesartan medoxomil/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

Other information

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

IV.4 Clinical Efficacy

No additional efficacy studies were conducted which is acceptable for this application type.

IV.5 Clinical Safety

No new safety findings were noted during the bioequivalency studies and no additional safety studies were conducted which is acceptable for this application type.

The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country

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 Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20/12.5, 20/25, 40/12.5 and 40/25 milligram film coated tablets.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Renal impairment • Hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia • Moderate and severe hepatic impairment, cholestasis and biliary obstructive disorders • Foetotoxicity in the 2nd and 3rd trimester of pregnancy • Dual-blockade of the renin-angiotensin-aldosterone system (RAAS) resulting in increased risk of decreased renal function (including acute renal failure), hypotension, and hyperkalaemia

	• Lithium toxicity with concomitant use of olmesartan/hydrochlorothiazide • Sprue-like enteropathy • Exacerbation/activation of systemic lupus erythematosus
Important potential risks	• Potential interaction with medicinal products affecting potassium levels • Increased risk of fatal events from cardiovascular causes in patients with type 2 diabetes with additional cardiovascular risks • Acute myopia, secondary acute angle-closure glaucoma • Use in the subpopulations with renal artery, aortic, or mitral valve stenosis • Teratogenicity in the 1st trimester of pregnancy • Rhabdomyolysis
Missing information	• Use in paediatric patients • Exposure during breast-feeding • Use in patients with a recent kidney transplantation • Use in patients with severe hepatic impairment

For all safety concerns, routine pharmacovigilance activities and routine risk minimisation measures are acceptable.

With regard to PSUR submission, the MAH should take the following into account:

For medicinal products authorized under the legal basis of Article 10(1), 10a, 14, or 16a of Directive 2001/83/EC as amended, no routine PSURs need to be submitted, unless otherwise specified in the EURD list. This applies to this medicinal product. Marketing authorisation holders shall continuously check the European medicines web-portal for any changes to this.

IV.6 Discussion on the clinical aspects

Bioequivalence was demonstrated between the Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG and the reference product Olmetec Plus.

No new or unexpected safety concerns arose during assessment of this application.
There is extensive clinical experience with Olmesartan and Hydrochlorothiazide combination in the treatment of hypertension which has demonstrated the therapeutic value of this combination product.

V OVERALL CONCLUSIONS

Olmesartan/Hydrochlorothiazide STADA Arzneimittel AG 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets is a generic formulation of Olmetec Plus 20 mg / 12.5 mg, 20 mg / 25 mg, 40 mg / 12.5 mg, 40 mg / 25 mg on the European market.

Both active substances are well-known medicinal products when used in combination with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been demonstrated and to be in compliance with the CHMP guidance documents. No new non clinical or clinical safety concerns have been identified. The SmPC is consistent with that of the reference product.

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

On the basis of the data submitted and considering the extensive clinical experience of use the HPRA considers the benefit risk to be positive and therefore granted a marketing authorisation for Olmesartan/Hydrochlorothiazide STADA

Arzneimittel AG 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets.

VI REVISION DATE

18/08/2021