Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Scoping Report

Title	Olmesartan Mono- and Combination Therapies in Patients with Essential Hypertension
Author/Affiliation	Ingrid Rosian-Schikuta, Daniela Antony, Isabella Röhrling, Heidi Stürzlinger, GÖ Forschungs- und Planungsgesellschaft mbH, Sophie Brunner-Ziegler, external medical Expert

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Technology	Olmesartan
Date	30/09/2019
Type of Technology	Pharmaceuticals
Keywords	Sartans, mono-preparations, fixed-dose preparations, Olmesartan, efficacy, effectiveness, safety, economics, legal, ethical, social, organisational, synthesis, evidence base, Scoping Report

Executive Summary:

Olmesartan belongs to the family of angiotensin II receptor blocker, one of the major drug classes recommended for essential hypertension treatment. The efficacy, effectiveness and safety of Olmesartan therapy in adult patients with essential hypertension compared to other available sartans have been questioned. This scoping report evaluates the feasibility of conducting a full HTA on this topic, based on a systematic literature search and analysis.

The size of the body of evidence for the domains efficacy, effectiveness and safety is substantial and of moderate quality. The evidence permits a meta-analytic evaluation for some critical and important outcome-comparisons, while more data from observational studies are required to analyse the remaining comparisons and to collect more long-term data.

The size of the body of evidence for the domains costs/cost-effectiveness is moderate and of moderate to low quality. Therefore, for conducting a full HTA a budgetary impact analysis will be performed. In addition, depending on the results of the efficacy and effectiveness domains two alternative health economic analyses are proposed: a cost-consequence analysis, or alternatively, a de-novo decision analytic model for a defined clinical outcome.

For conducting a full HTA, the literature search needs to be widened to obtain more data on legal, social, ethical and organisational aspects related to the technology.

Overall, the evidence base is considered sufficiently large to conduct a full HTA assessment, provided the literature search strategy is widened and additional data-analytic approaches are applied.

Zusammenfassung:

Olmesartan gehört zur Gruppe der Angiotensin-II-Rezeptorblocker, einer der wichtigsten Arzneimittelklassen, die für die Behandlung der essentiellen Hypertonie empfohlen wird. Die Wirksamkeit, Effektivität und Sicherheit der Olmesartan-Therapie bei erwachsenen Patientinnen und Patienten mit essentieller Hypertonie wurde im Vergleich zu anderen verfügbaren Sartanen in Frage gestellt. Dieser Scoping-Bericht bewertet die Durchführbarkeit einer vollständigen Gesundheitstechnologiebewertung (Health Technology Assessment, HTA) zu diesem Thema auf der Grundlage einer systematischen Literaturrecherche und -analyse.

Evidenz für die Bereiche Wirksamkeit, Effektivität und Sicherheit gibt es in beträchtlicher Menge und in mässiger Qualität. Die Evidenz ermöglicht eine meta-analytische Auswertung einiger kritischer und wichtiger Outcome-Vergleiche, wohingegen für die Analyse der restlichen Vergleiche mehr Daten aus Beobachtungsstudien benötigt werden. Damit lassen sich auch mehr Langzeitdaten sammeln.

Evidenz für die Bereiche Kosten/Kosteneffizienz gibt es in moderater Menge und in moderater bis niedriger Qualität. Daher wird in einem vollständigen HTA eine Budgetauswirkungsanalyse durchgeführt. Darüber hinaus werden je nach den Ergebnissen in den Bereichen Wirksamkeit und Effektivität zwei alternative gesundheitsökonomische Analysen vorgeschlagen: eine Kosten-Konsequenz-Analyse oder alternativ ein neues Entscheidungsanalysemodell für ein definiertes klinisches Ergebnis.

Für die Durchführung eines vollständigen HTA muss die Literaturrecherche erweitert werden, damit man mehr Daten zu rechtlichen, sozialen, ethischen und organisatorischen Aspekten der Technologie erhält.

Insgesamt wird die Evidenzlage als ausreichend erachtet, um eine vollständige HTA-Bewertung durchzuführen, sofern die Literaturrecherche erweitert und zusätzliche datenanalytische Ansätze angewendet werden.

Résumé:

Olmésartan appartient à la famille des antagonistes des récepteurs de l'angiotensine II, une des principales classes de médicaments pour le traitement de l'hypertension essentielle. L'efficacité, l´efficacité en conditions réelles (l'effectivité) et la sécurité de la thérapie avec Olmésartan pour des patients adultes souffrant d'une hypertension essentielle comparée avec d'autres sartans disponibles ont été questionnées. Ce rapport de scoping évalue la faisabilité de réaliser une évaluation des technologies

de la santé (HTA) complète sur ce thème, en se fondant sur une recherche et une analyse systématiques de la littérature.

Concernant l'efficacité, l'effectivité et la sécurité, l'ensemble des preuves est substantiel et de qualité modérée. Ces preuves permettent de procéder à une méta-analyse de quelques comparaisons critiques et importantes. Toutefois, l'analyse des autres comparaisons requièrent plus de données tirées des études d'observation. On peut ainsi récolter plus de données de longue durée.

Concernant les coûts et l'efficience des coûts, l'ensemble des preuves est de taille modérée et de qualité moyenne à basse. Par conséquent, une analyse de l'impact budgétaire sera menée afin de réaliser un HTA complet. De plus, en fonction des résultats concernant l'efficacité et l'effectivité, deux analyses alternatives en économie de la santé sont proposées: une analyse coût-conséquence, ou un nouveau modèle analytique de décision pour un résultat clinique défini.

Pour réaliser un HTA complet, la recherche littéraire doit être élargie afin d'obtenir plus d'informations sur les aspects légaux, sociaux, éthiques et organisationnels relatifs à la technologie.

Globalement, la base de preuves est considérée comme suffisamment large pour réaliser l'évaluation du HTA complet, la stratégie de recherche littéraire mise à disposition est élargie et des approches additionnelles d'analyse des données sont utilisées.

Table of Contents

Abbreviations and Acronyms

ACE inhibitors	Angiotensin converting enzyme inhibitors
AHRQ	Agency for Healthcare Research and Quality
ABPM	Ambulatory BP monitoring
AML	Amlodipin
ARBs	Angiotensin II receptor blockers
AZI	Azilsartan
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CAN	Candesartan
CCA	Cost-Consequences-Analysis
CCBs	Calcium channel blockers
CEA	Cost-Effectiveness-Analysis
CHEC	Consensus Health Economic Criteria (CHEC) Checklist
CLD	Chlortalidone
DALYs	Disability adjusted life years
EMA	European Medicines Agency
EPR	Eprosartan
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EUnetHTA – POP Database	European Network for Health Technology Assessment – Planned and Ongoing Projects (POP) database
FDA	Food and Drug Administration
FDC	Federal Drug Commission
FDHA	Federal Department of Home Affairs
FOPH	Federal Office of Public Health
GBD	Global Burden of Disease
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé
HBPM	Home-based BP measurements
HMOD	Hypertension-mediated organ damage
HCTZ	Hydrochlorothiazide

HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
ICD	International Statistical Classification of Diseases and Related Health Problems
INAHTA	International Network of Agencies for Health Technology Assessment
LMT	List of Medicines with Tariff
LOS	Losartan
IRB	Irbesartan
ISPOR	The International Society for Pharmaeconomics and Outcome Research
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MeSH	Medical Subject Headings
MHI	Mandatory Health Insurance
MSAC	Medical Services Advisory Committee (Australian government)
MSD	Merck Sharp & Dohme
N.A.	not applicable
NICE	National Institute for Health and Care Excellence
OLM	Olmesartan
PAD	Peripheral artery disease
PBAC	The Pharmaceutical Benefits Advisory Committee
PICO	Patient, Intervention, Comparator/Control, Outcome
QHES	Quality of Health Economic Studies
RCT	Randomised Controlled Trial
RePEc	Research Papers in Economics
SCORE	Systematic COronary Risk Evaluation
SL	Spezialitätenliste
TEL	Telmisartan
US/A	United States
VAL	Valsartan
WHO	World Health Organisation
WZW	W (Wirksamkeit: “effectiveness”), Z (Zweckmässigkeit: “appropriateness”), W (Wirtschaftlichkeit: “economic efficiency”)
ZIN	Zorginstituut Nederland/The National Health Care Institute

Objective of the HTA Scoping Report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of Olmesartan therapy in adult patients with essential hypertension because its efficacy, effectiveness and safety has been questioned.

The Transparency Committee of the Haute Autorité de Santé (HAS)[1] in France has decided not to recommend the continuation of the reimbursement of Olmesartan monotherapy, as well as of the Olmesartan/Hydrochlorothiazide and Olmesartan/Amlodipine combination therapies in 2015. The rationale for this recommendation was that the efficacy and effectiveness of Olmesartan compared to the majority of the other sartans has only been demonstrated for blood pressure reduction, and not for morbidity and mortality. Furthermore, it has been shown that Olmesartan leads to an increased risk of serious enteropathies compared to the other sartans, and to an increased risk of hospitalisation for intestinal malabsorption compared with angiotensin-converting enzyme (ACE) inhibitors. This increased risk of hospitalisation for intestinal malabsorption was also not found for the other sartans.

The process to evaluate health technologies involves multiple phases, 1) the pre-scoping phase, 2) the scoping phase, and 3) the HTA phase. This document represents the outcome of the scoping phase.

In the scoping phase, a health technology is examined and a central research question is presented based on a systematic review of the literature. In addition, key operational questions are formulated in order to determine the full scope of the HTA report. The target population, the appropriate comparator and the relevant health outcomes are defined.

The systematic literature search strategy guides the number and types of studies generated. Based on the quantity and quality of the extracted evidence, a decision is made as to whether an HTA report is commissioned. The objective of the HTA is to analyse the individual study outcomes.

1. Medical Background

Essential - also called primary, idiopathic or arterial - hypertension is described as elevated systemic arterial blood pressure (BP) for which no causal organic pathology can be identified. The aetiology of essential hypertension is multifactorial, including genetic factors, lifestyle and environmental conditions and metabolic risk factors such as obesity, impaired glucose or lipid metabolism. From a pathophysiological point of view, elevated BP may be the result of either cardiac volume overload or, more likely, of enhanced resistance in the blood vessel system, each exacerbating the other in a vicious circle. [2]

Arterial hypertension affects 30 to 40% of the world population.[2] Essential hypertension may be asymptomatic for many years and only a minority of affected patients complains about unspecific symptoms, such as morning cephalea, nausea, tinnitus, dyspnoea, fatigue and epistaxis. However, chronic arterial hypertension is associated with premature deaths, increased disability adjusted life years (DALYs), cardiovascular complications such as ischaemic heart disease and stroke and cognitive impairments.[3-5]

***Diagnosis**:* BP is measured in millimetres of mercury (mmHg) and is expressed as two numbers. The first number represents the systolic BP, which refers to the pressure in the arteries during the contraction of the heart muscle. The second number represents the diastolic BP, which refers to the pressure in the arteries when the heart rests between beats. A normal systolic BP is between 120 and 129 mmHg and a normal diastolic BP between 80 and 84 mmHg. Essential hypertension is defined as the elevation of systolic and diastolic BP to a cut-off value at which the benefit of diagnostic and therapeutic measures outweighs the risk of these measures.[6]

The diagnosis of essential hypertension pursues three major goals:

1. quantification of the severity grade of the disease,
2. systemic exclusion of potential secondary aetiological causes, such as sleep apnoea, stenosis of renal arteries, phaeochromocytoma and pregnancy- or drug-induced BP elevation,
3. classification of the patient's overall cardiovascular risk profile by assessing cardiovascular comorbidities and early hypertension-mediated organ damage.

It is recommended to base the diagnosis of hypertension on repeated BP measurements. The guidelines for the management of essential hypertension, published by the European Society of Cardiology (ESC) and European Society of Hypertension (ESH), recommend classifying BP as optimal, normal, high-normal, or hypertension grades 1 to 3, see *Table 1*.[6]

Table 1: Classification of hypertension grades, as recommended by the ESC/ESH-Guideline

Blood pressure classification	Systolic (mmHg)	Diastolic (mmHg)
Normal	120-129	80-84
High normal	130-139	85-89
Grade 1 hypertension	140-159	90-99
Grade 2 hypertension	160-179	100-109
Grade 3 hypertension	> 180	> 110

Treatment: In all patients with essential hypertension, patient education on the character and origin of the disease and motivation for lifestyle modifications are an integral part of first-line treatment. Most patients are prescribed antihypertensive drug treatment right after diagnosis or during the course of disease. The ESC/ESH Guidelines recommend on when to initiate antihypertensive drug treatment according to the severity grade of disease and cardiovascular risk stratification.[6] The Swiss Society of Hypertension[7] adheres to the recommendations published in the ESC/ESH Guidelines.[6]

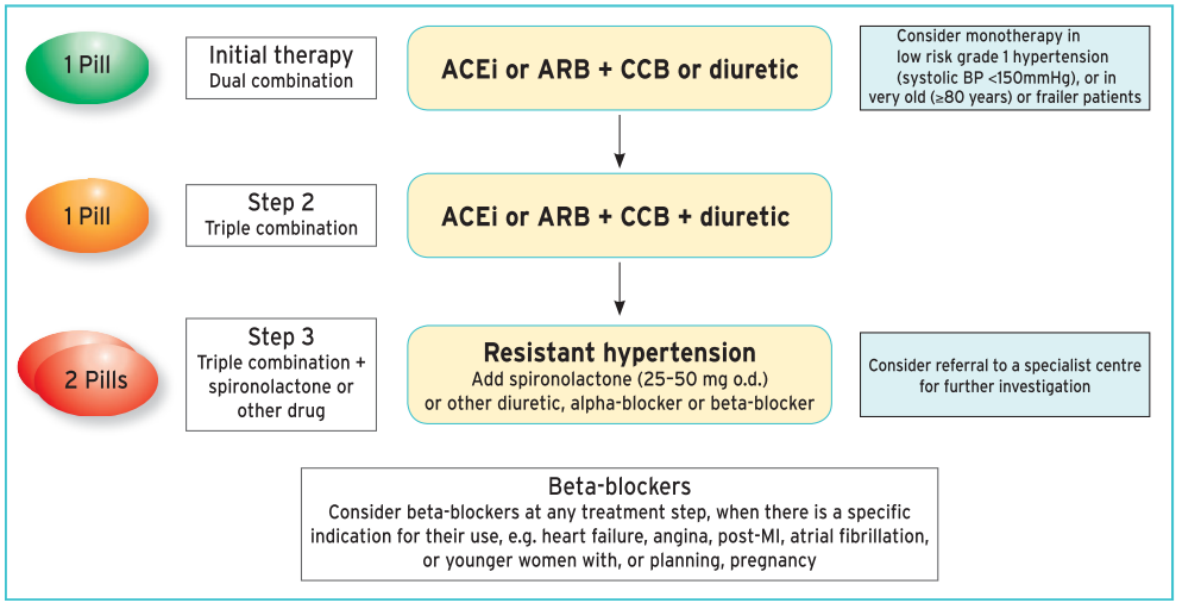
2. Technology

2.1 Technology Description

There are five major drug classes recommended for antihypertensive pharmacotherapy, including angiotensin II receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACE-inhibitors), beta-blockers, calcium channel blockers (CCBs) and diuretics (thiazides and thiazide-like diuretics).[8 9] ARBs and ACE-inhibitors are among the most widely used antihypertensive substances worldwide. The core treatment algorithm for “uncomplicated” hypertension, focusing on the five major antihypertensive drug classes, is presented in *Figure 1* and can be adapted for patients with concomitant coronary artery disease, chronic kidney disease, heart failure and arterial fibrillation.[6]

Combination therapy (two or more pharmaceutical agents in a single pill) is recommended in the current ESC/ESH Guideline for most hypertensive patients because the reduction of the number of pills taken on a daily basis improves adherence, and therefore, the control of blood pressure (this was supported by data from RCTs).[6]

Figure 1: Core drug treatment strategy for uncomplicated hypertension



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day)

Sartans: Sartans are ARBs that prevent the binding of angiotensin II by selectively blocking the AT1 subtype of angiotensin 2 receptors.[10] With respect to their BP-lowering effect, they mainly act by vasodilation (by antagonising the vasoconstrictive effect of angiotensin) and reducing the secretion of vasopressin and aldosterone.[11] [12]

In Switzerland, eight ARBs are approved for use in mono- or combination therapy: Olmesartan (OLM), Irbesartan (IRB), Losartan (LOS), Candesartan (CAN), Valsartan (VAL), Telmisartan (TEL), Eprosartan (EPR) and Azilsartan (AZI). Preparations containing ARBs in combination with the diuretic hydrochlorothiazide and/or the CCB amlodipine (AML) in fixed doses are also available.[13] Despite the fact that all ARBs share a common mechanism of action, they differ with respect to their pharmacologic and dosing profile.[14]

Olmesartan Medoxomil: Olmesartan Medoxomil (OLM) was developed in 1995[15] and approved in Switzerland in 2005 as mono- and combination therapy in patients with essential hypertension. OLM is administered as a prodrug that is converted to its active metabolite to achieve its BP-lowering effect. The half-life of OLM is between 10 and 15 hours. The antihypertensive effect of regular therapy starts within two weeks after the drug is first administered and reaches its maximum approximately eight weeks after the start of therapy. Important contraindications for treatment with OLM include pregnancy and biliary obstruction.[16] The most frequently reported adverse events include cephalea (7.7 %), influenza-like symptoms (4.0 %) and vertigo (3.7 %). Rare adverse events include sprue-like enteropathy characterised by severe, chronic diarrhea with significant weight loss, nausea, vomiting, abdominal pain and anaemia.

The recommended starting dose of OLM is 10 mg once daily. In patients whose blood pressure cannot be adequately controlled with a dose of 10 mg, the dose may be increased to 20 mg once daily. If a further reduction in blood pressure is desired, the dose can be increased to a maximum of 40 mg daily or an additional therapy with hydrochlorothiazide can be prescribed.[17]

Overview Reimbursed and Authorisation Status Sartans in Switzerland: In the group of sartans, eight monoactive substances with 39 different preparations (without differentiation by dosage and/or package size) are available for prescription (as of August 2018). LOS (Cosaar 50, holder of marketing authorisation MSD Merck Sharp & Dohme AG) was the first approved drug in 1997 and OLM (Olmetec, holder of marketing authorisation Daiichi Sankyo AG) was approved in 2005. Since 2016, generic drugs have been available for OLM (Olmesartan Spirig HC, Olmesartan Sandoz, Olmesartan Mepha Lactab). Reimbursed mono- and combination preparations of sartans are listed in the Swiss "Spezialitätenliste".[13]

Market Data: Sartans in Switzerland

Table 2 and 3 illustrate the turnover and quantity of packages sold in Switzerland of sartans at pharmacy retail prices, expressed as percentages between 2014 and 2018. Table 6 and 7 (*Appendix VI*) show the absolute figures. In 2017 and 2018 CAN has the largest market share, both in terms of the number of packages sold and turnover, followed by VAL (turnover and packages sold) and IRB (turnover). OLM is the fourth in line in terms of turnover. LOS is the third in line in terms of packages sold (Table 2).

Table 2: Sartan Mono-Preparations

	2014	2014	2015	2015	2016	2016	2017	2017	2018 [1]	2018 [1]
ATC Code/Substance	**Turn-over**	**Pack-ages**	**Turn-over**	**Pack-ages**	**Turn-over**	**Pack-ages**	**Turn-over**	**Pack-ages**	**Turn-over**	**Pack-ages**
C09CA01 Losartan	12 %	15 %	13 %	18 %	13 %	15 %	12 %	14 %	12 %	13 %
C09CA02 Eprosartan	1 %	1 %	1 %	0 %	1 %	0 %	1 %	0 %	1 %	0 %
C09CA03 Valsartan	14 %	15 %	15 %	15 %	15 %	16 %	16 %	16 %	16 %	16 %
C09CA04 Irbesartan	18 %	15 %	17 %	14 %	16 %	13 %	16 %	13 %	16 %	12 %
C09CA06 Candesartan	32 %	40 %	33 %	39 %	33 %	41 %	34 %	43 %	34 %	43 %
C09CA07 Telmisartan	8 %	5 %	7 %	5 %	7 %	5 %	6 %	4 %	6 %	4 %
C09CA08 Olmesartan medoxomil	14 %	9 %	13 %	9 %	14 %	9 %	14 %	9 %	14 %	10 %
C09CA09 Azilsartan medoxomil	1 %	1 %	1 %	1 %	1 %	1 %	2 %	1 %	2 %	1 %
Total	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**

[1] as of 1.1.2018 – 30.9.2018

Source 10.12.2018,Tarifpool: © SASIS AG, 2018

CAN and diuretics are the frontrunner among the combination preparations (turnover: 15.5 %; packages: 22.7 % in 2017). The market share of OLM fixed combination preparations in turnover is 4.9 % for OLM and diuretics, 6.5 % for OLM and AML and 7.8 % for OLM, AML and Hydrochlorothiazid. The market share in packs is 4.8 % for OLM and diuretics, 5.9 % for OLM and AML and 5.9 % for OLM, AML and Hydrochlorothiazid in 2017 (Table 3).

Table 3: Fixed Dose Combinations

	2014	2014	2015	2015	2016	2016	2017	2017	2018 [1]	2018 [1]
ATC Code/Substance	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**
C09DA01 Losartan and diuretics	6,8 %	7,8 %	8,0 %	9,1 %	7,9 %	9,0 %	7,7 %	8,9 %	7,6 %	8,4 %
C09DA02 Eprosartan and diuretics	0,6 %	0,6 %	0,6 %	0,5 %	0,5 %	0,4 %	0,5 %	0,4 %	0,4 %	0,4 %
C09DA03 Valsartan and diuretics	8,9 %	13,3 %	9,0 %	13,1 %	8,7 %	12,6 %	8,6 %	12,3 %	8,6 %	12,0 %
C09DA04 Irbesartan and diuretics	16,8 %	15,9 %	14,1 %	14,9 %	12,7 %	14,0 %	11,7 %	13,0 %	11,2 %	12,6 %
C09DA06 Candesartan and diuretics	18,0 %	24,8 %	17,4 %	24,0 %	16,8 %	23,5 %	16,5 %	23,4 %	16,3 %	23,3 %
C09DA07 Telmisartan and diuretics	4,8 %	3,5 %	3,8 %	3,1 %	3,5 %	3,0 %	3,2 %	2,8 %	3,1 %	2,7 %
C09DA08 Olmesartan medoxomil and diuretics	5,8 %	5,0 %	5,3 %	5,0 %	5,3 %	5,1 %	5,3 %	4,9 %	5,2 %	5,1 %
C09DA09 Azilsartan medoxomil and diuretics	0,0 %	0,0 %	0,2 %	0,2 %	0,8 %	0,9 %	1,1 %	1,1 %	1,2 %	1,1 %
C09DB01 Valsartan and Amlodipin	12,0 %	8,7 %	12,6 %	8,7 %	12,9 %	8,8 %	13,2 %	9,3 %	13,2 %	9,7 %
C09DB02 Olmesartan medoxomil and Amlodipin	5,5 %	5,2 %	6,1 %	5,5 %	6,6 %	5,9 %	6,9 %	6,1 %	7,1 %	6,4 %
C09DB04 Telmisartan and Amlodipin	0,7 %	0,7 %	0,8 %	0,7 %	0,8 %	0,7 %	0,8 %	0,7 %	0,8 %	0,7 %
C09DX01 Valsartan, Amlodipin and Hydrochlorothiazid	14,0 %	10,1 %	15,1 %	10,2 %	15,8 %	10,6 %	16,2 %	11,0 %	16,4 %	11,4 %
C09DX03 Olmesartan medoxomil, Amlodipin and Hydrochlorothiazid	6,1 %	4,4 %	6,9 %	4,9 %	7,8 %	5,6 %	8,3 %	6,0 %	8,8 %	6,1 %
Total	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**	**100.0 %**

[1] as of 1.1.2018 – 30.9.2018

Source: 10.12.2018,Tarifpool: © SASIS AG, 2018

2.2 Alternative Technologies

Alternative pharmaceuticals to OLM mono- or combination therapy include all other mono- or combination therapies with other ARBs, ACE-inhibitors, beta-blockers, CCBs and diuretics. Patients who cannot be controlled effectively by first-line pharmaceutical therapy, can be prescribed alpha-receptor blockers, spironolactone, centrally acting agents, mineralcorticoid receptor antagonists or minoxidil (second-line pharmaceutical therapy).[6 18]

3. Systematic Search Strategy

3.1 Databases

Evidence evaluated for all domains was obtained from a search of the MEDLINE, EMBASE, Cochrane Systematic Reviews, Cochrane Central Register of Controlled Trials and NHS Economic Evaluation databases.

Websites of international organisations including AHRQ, CADTH, EMA, EUnetHTA, FDA, HAS, HTAi, INAHTA, ISPOR, IQWIG, MSAC, NICE, PBAC, RePEc, WHO, ZIN were searched for additional relevant reports. The US National Library of Medicine and EU clinical trial registries were searched to identify additional clinical trials.

3.2 Search Strategy and Selection of Relevant Publications

A two-step search strategy was applied to identify relevant studies. At first, titles and abstracts were searched applying general eligibility criteria:

a. Intervention: OLM mono- and combination therapy

b. Disease: Hypertension, essential hypertension

c. Type of Study: Randomised controlled trials (RCTs), economic evaluations, cost analyses, meta-analyses and systematic reviews. Meta-analyses and systematic reviews were hand searched to locate possible relevant primary RCTs that were missed in the single trial searches.

d. Language: English, German

e. Publication date: no restrictions

The selection was carried out by three independent reviewers. Studies identified by at least one reviewer were obtained in full-text format. More specific eligibility criteria were applied to the full-text records

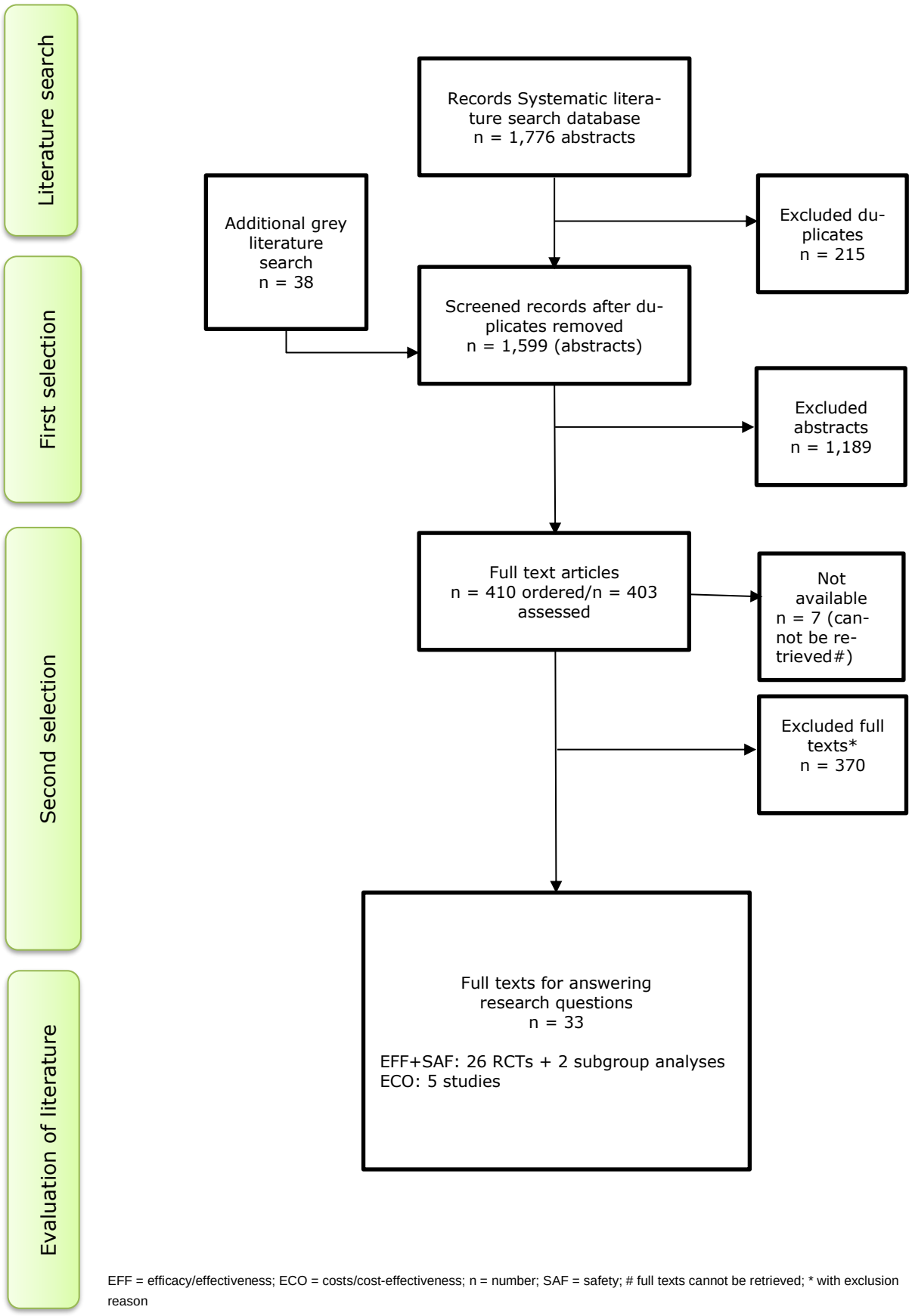
(*Table 4*). A final decision regarding inclusion was made and disagreements were resolved by consensus. Detailed search strategies are outlined in Appendix I.

Table 4: Eligibility Criteria

I 1	Patients (≥ 18 years) with essential (primary) arterial hypertension that requires antihypertensive pharmacotherapy (see Table PICO). The study focus is essential hypertension. However, comorbidities such as cardiovascular disease (coronary and cerebrovascular disease, peripheral artery disease, diabetes, dyslipidaemia), chronic kidney disease or malignant disease are considered.
I 2	Intervention: Olmesartan monotherapy, Olmesartan combination therapy with thiazide diuretics, Olmesartan combination therapy with calcium-channel blockers or Olmesartan combination therapy with thiazide diuretics and calcium-channel blockers (see Table PICO)
I 3	Control: all other sartans as monotherapy, all other sartans in combination with thiazide diuretics, all other sartans in combination with calcium-channel blockers, all other sartans in combination with thiazide diuretics and calcium-channel blockers (see Table PICO)
I 4	Including one or more of the critical or important outcomes as formulated in Table PICO
I 5	Study design for domain efficacy/effectiveness: randomised controlled trials (direct comparisons)
I 6	Study design for domain safety: randomised controlled trial (direct comparisons)
I 7	Study design for domain costs/cost-effectiveness: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-minimisation analysis (CMA), cost-consequence analysis (CCA), cost-benefit analysis (CBA), budget-impact analysis, economic models
I 8	Geographical aspects for domain economic evaluation: Switzerland and high-income economies as defined by the World Bank.[19]
I 9	Formal aspects: language (English, German), Search period: no restriction
I 10	Full publication available
I 11	Duration of treatment: 2 months and more (according to drug information: “The antihypertensive effect of Olmesartan medoxomil occurs essentially within 2 weeks after the start of treatment and reaches its maximum approximately 8 weeks after the start of therapy”.

The following PRISMA Flow Diagram shows the number of records identified.

3.3 PRISMA Flow Diagram



EFF = efficacy/effectiveness; ECO = costs/cost-effectiveness; n = number; SAF = safety; # full texts cannot be retrieved; * with exclusion reason

3.4 Available Evidence

The systematic literature search in the electronic databases identified 1,776 abstracts for the domains efficacy and effectiveness, safety and costs/cost-effectiveness. After excluding duplicates and including hand search-identified studies 1,599 abstracts remained. 410 full texts were ordered, of which 7 could not be retrieved. After application of the eligibility criteria defined in Table 4, 33 studies were selected (Appendix II + III).

To evaluate the risk of bias of the selected RCTs, quality criteria checklists were used (*Appendix IV*). Levels of risk of bias were defined and categorised as per Cochrane Handbook for Systematic Reviews of Interventions.[20]

Table 5: Risk of Bias -– Definitions

Low risk of bias	It is unlikely that the outcome of the study is significantly distorted by confounding factors. The confidence in the correctness of the results is high.
Moderate risk of bias	It is unclear to what extent the results of the study are distorted by confounding factors. Confounders are possible and could call the correctness of the results into question.
High risk of bias	It is very likely that the result of the study is significantly distorted by confounding factors. The confidence in the correctness of the results is very low.
Unclear risk of bias	The risk of bias cannot be evaluated because of missing information in the study.

The quality of economic studies was evaluated applying the Consensus Health Economic Criteria (CHEC)-Checklist[21 22] (*Appendix V*).

4. Synthesis of Evidence Base

4.1 Evidence Base Pertaining to Efficacy, Effectiveness and Safety

The literature search yielded 28 articles, reporting data on efficacy and safety of 26 RCTs. Punzi et al.[23] and Flack et al.[24] reported subgroup analyses of the RCT from Weir et al.[25]:

Of the 26 RCTs 19 assessed the efficacy of OLM monotherapy versus AZI, CAN, IRB, LOS, TEL, or VAL. Three RCTs assessed the efficacy of OLM (+/- CCB) vs. CAN (+/- CCB), OLM (+/- Hydrochlorothiazide, HCTZ) vs. LOS (+/- HCTZ) and OLM (+/- HCTZ) vs. TEL (+/- HCTZ). Four RCTs assessed the efficacy of OLM + HCTZ vs. TEL + AML, OLM + AML vs. LOS + HCTZ, OLM + HCTZ vs. AZI + Chlortalidone (CLD) and OLM + HCTZ vs. LOS + HCTZ.

RCTs assessing monotherapy and combination therapy included varying medication doses. The duration of treatment and follow-up was usually 12 weeks. Typical endpoints were blood pressure and other blood-pressure related clinical outcomes, such as heartrate or level of cholesterol. RCTs did not include endpoints on mortality.

19 out of 26 RCTs covered aspects of SAF. Appendix II gives an overview of the study characteristics for efficacy, effectiveness and safety.

Overall, the size of the body of evidence is substantial with a moderate to high risk of bias due to methodological limitations regarding randomisation, blinding, intention-to-treat analysis, patient populations and drop-out rate reporting and application. Of note, the majority of included RCTs were sponsored by pharmaceutical companies.

4.2 Evidence Base Pertaining to Costs, Budget Impact and Cost-Effectiveness

The literature search yielded 5 economic studies on OLM mono- or combination therapy. Two studies[26] [27] assessed the cost-effectiveness of OLM, LOS, VAL and IRB (monotherapy) for the treatment of hypertension using clinical trial data from Oparil et al..[28] Belsey et al. conducted a cost-effectiveness model for OLM or CAN (monotherapy) in a cohort of patients with moderate hypertension; effect data were taken from clinical trial data (indirect comparisons). [29] Miller et al. compared OLM, LOS, VAL and IRB (mono- and combination therapy with HCTZ) in 1600 randomly selected patients with medical chart data and administrative claims cost data (real world).[30] Maaza et al. compared OLM, CAN, IRB, LOS, TEL and VAL (mono- and fixed dose combinations with HCTZ) with effects based on retrospective cross sectional studies and pharmacy dispensing cost data.[31]

Two of the economic studies were conducted in the USA, one in the Netherlands, one in the United Kingdom and one in Italy. Two studies[26] [27] modelled cardiovascular events after 1 and 5 years. The other studies assessed BP lowering within a shorter time period (6 months up to 1 year). The characteristics and results of the studies are presented in Appendix III.

The size of the body of evidence for the domain costs/cost-effectiveness was moderate and its quality was moderate to low, due to heterogeneity in terms of study designs, outcomes and individual study quality. Of note: In four out of the five studies, the marketing authorisation holder of OLM was named as sponsor.

4.3 Evidence Base Pertaining to Legal, Social and Ethical Issues

No studies were identified that directly addressed legal, social or ethical issues related to OLM therapy in hypertensive patients in Switzerland.

4.4 Evidence Base Pertaining to Organisational Issues

The literature identified two studies that evaluated aspects of drug adherence, when switching from ACE inhibitors to ARBs or within ARB groups.[32] [33] Four studies regarded the effects of switching from mono-therapy to combination therapy.[34-37] One guideline reported possible effects of changing BP medication in general, stressing the importance of physician visit frequency.[6]

5. Central Research Question(s)

5.1 Central Research Question(s)

The central research questions for this report are:

- What is the efficacy, effectiveness and safety of OLM mono- and combination therapy in adult patients with essential hypertension compared to mono- and combination therapy with other available sartans?
- What are the costs, budget-impact and cost-effectiveness of OLM mono- and combination therapy in adult patients with essential hypertension compared to mono- and combination therapy with other available sartans?

5.2 Patients

The target population consists of adult patients (≥ 18 years) of any gender and ethnicity with essential hypertension. Patients with comorbidities such as cardiovascular disease (coronary and cerebrovascular disease, peripheral artery disease, diabetes, dyslipidaemia), chronic kidney disease or malignant disease are not systematically excluded.

5.3 Intervention

The intervention under assessment are all OLM mono-preparations and OLM combination-preparations (OLM with thiazide diuretics, CCB or thiazide diuretics and CCBs).

5.4 Comparator

All other sartans as monotherapy, all other sartans in double combination with thiazide diuretics or CCBs, all other sartans in triple combination with thiazide diuretics and CCBs.

5.5 Outcomes

Critical and important outcomes for the efficacy, effectiveness and safety domains include BP reduction, cardiovascular and cerebrovascular mortality, cardiovascular and cerebrovascular morbidity, health-related quality of life outcomes and adverse events such as sprue-like enteropathy, nausea, vertigo, influenza-like symptoms, fatigue, hyperkalaemia, gastrointestinal symptoms or muscular pain.

Critical and important outcomes for the costs/cost-effectiveness domain include direct and indirect costs, budget-impact and cost-effectiveness outcomes.

5.6 PICO

Table 5 presents the PICO with specifications on the patient population, interventions, comparators, and outcome parameters for the efficacy, effectiveness, safety and costs/cost-effectiveness domains.

Table 5: PICO

Population:	Patients (≥ 18 years at start of study) with essential (primary) arterial hypertension that requires antihypertensive pharmacotherapy
Intervention:	• OLM monotherapy • OLM combination therapy with thiazide diuretics • OLM combination therapy with CCBs • OLM combination therapy with thiazide diuretics and CCBs
Comparators:	• All other sartans as monotherapy (AZI, CAN, EPR, IRB, LOS, TEL, VAL) • All other sartans in combination with thiazide diuretics • All other sartans in combination with CCBs • All other sartans in combination with thiazide diuretics and CCBs
Outcomes:	**Domain Efficacy/Effectiveness:** • Cardiovascular morbidity (e.g. myocardial infarction, heart failure, cardiac arrhythmia) • Cardiovascular mortality (e.g. sudden heart death) • Cerebrovascular morbidity (e.g. transient ischaemic attack, ischaemic

stroke, haemorrhagic stroke, hypertensive dementia)

- Cerebrovascular mortality
- Reduction in blood pressure
- Health-related quality of life

Domain Safety:

- Treatment-associated adverse events (e.g. sprue- like enteropathy, nausea, vertigo, influenza-like symptoms, fatigue, hyperkalaemia, gastrointestinal symptoms, muscular pain)

Domain Costs/Cost-Effectiveness:

- Costs, budget-impact and cost-effectiveness outcomes

6. HTA Key Questions

Key sub-questions of relevance to OLM therapy have been informed by the European Network for Health Technology Assessment (EUnetHTA) HTA Core Model® (Version 3.0). All sub-questions related to the key assessment domains (i.e. efficacy/effectiveness, safety, costs/cost-effectiveness, ethical, social, legal, and organisational issues) were considered for inclusion; however, only those deemed relevant to OLM were included.

6.1 Key Questions Efficacy and Effectiveness

- What is the expected beneficial effect of the technology on mortality compared to its comparator(s)?
- How does the technology modify the magnitude and frequency of morbidity?
- How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition compared to its comparator(s)?
- How does the technology affect progression (or recurrence) of the disease or health condition?
- What is the effect of the technology on generic health-related quality of life?
- Were patients satisfied with the technology?

6.2 Key Questions Safety

- How safe is the technology in relation to its comparator(s)?
- Are the harms related to dosage or frequency of applying the technology?
- How does the frequency or severity of harms change over time or in different settings?

- What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

6.3 Key Questions Costs, Budget Impact and Cost-Effectiveness

- What types of resources are used?
- What are the volumes and monetary units for OLM and the compared sartans in Switzerland (e.g. incidence, prevalence hypertensive patients, number auf outpatient visits, number of inpatient stays, reimbursement prices for OLM and the compared sartans, costs for outpatient treatment, costs for inpatient stays)?
- What are the estimated differences in costs and outcomes between the technology and its comparator(s)?

6.4 Key Questions Legal, Social and Ethical Issues

- How are treatment choices explained to patients? What specific issues may need to be communicated to patients to improve adherence (e.g. after disinvestment/switching to another compound)?
- How does (a potential) withdrawal of OLM affect access (or adherence) to therapy? Are there (other) ethical consequences from switching to other sartans?

6.5 Key Questions Organisational Issues

- What consequences would a potential withdrawal of OLM have for patients, nurses?
- Do the patients have to have more medical checks when switching to another sartan?

7. Feasibility HTA

The size of the body of evidence for the domains efficacy, effectiveness and safety is substantial (26 RCTs). The overall quality of the evidence is moderate. Methodological limitations regarding randomisation, blinding, intention-to-treat analysis, patient populations and drop-out rate were reported. The available clinical data permit a meta-analytic approach for various short- and mid-term critical and important outcome comparisons. For more outcome-comparisons and for long-term outcomes additional observational studies will have to be included if a full HTA assessment was conducted.

The size of the body of evidence for the domain costs/cost-effectiveness was moderate and its quality was moderate to low. For a full HTA the available evidence is likely insufficient, due to heterogeneity between study design, outcomes and the models used, to serve as a basis for estimating costs/cost-

effectiveness for Switzerland. Moreover, the cost data used are in part outdated and most likely not applicable to Switzerland. For a full HTA a budgetary impact analysis with robust sensitivity analyses for uncertainties to investigate financial impact of removing OLM from the reimbursement list will be performed. In addition, depending on the results of the efficacy and effectiveness domains, two alternative health economic analyses are proposed. In case where no clear clinical outcome differences between OLM and other sartans can be observed a cost-consequence analysis listing all calculated costs and outcomes in tabular but not aggregated into quality-adjusted life-years or other cost-effectiveness ratios may be considered. The cost-consequence format may provide a comprehensive presentation of information describing the value of a drug therapy. Alternatively, a de-novo decision analytic model for a defined clinical outcome like achieved blood pressure reduction, implementing several treatment options and including safety aspects, can be considered. The economic analysis will be done from the perspective of the public payer (health insurance). The final decision which health economic analyses will be applied, will be decided during the course and development of the full HTA and in accordance with the FOPH.

For the legal, social, ethical and organisational domains the literature searches identified only a few references addressing key questions related to these issues. For conducting a full HTA, the search needs to be widened.

Overall, the evidence base is considered sufficiently large to conduct a full HTA, provided the literature search strategy is widened and additional data-analytic approaches are applied.

8. References

1. HAS. Olmetec. L'avis de la Commission de la transparence adopté le 18 février 2015 a fait l'objet d'une audition le 29 avril 2015. In: Haute Autrité de Santé, ed., 2015:37.
2. Chow CK, Teo KK, Rangarajan S, et al. PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA - Journal of the American Medical Association* 2013;310:968.
3. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115mmHg, 1990-2015. *JAMA - Journal of the American Medical Association* 2017;317:182.
4. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol* 2017;74:1254.
5. Rovio SP, Pahkala K, Nevalainen J, et al. Cardiovascular risk factors from childhood and midlife cognitive performance: the Young Finns study. *J Am Coll Cardiol* 2017;69:2289.
6. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39(33):3021-104. doi: 10.1093/eurheartj/ehy339 [published Online First: 2018/08/31]
7. Swiss Society of Hypertension. Arterielle Hypertonie 2015: Available from: http://www.swisshypertension.ch/ accessed 4.12.2018.
8. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA - Journal of the American Medical Association* 2015;313:615.
9. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis *Lancet* 2016;387:967.
10. Timmermans PB, Wong PC, Chiu AT, et al. Angiotensin II receptors and angiotensin II receptor antagonists. *Pharmacol Rev* 1993;45(2):251.
11. Thomopoulos C, Parati G, A. Z. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *J Hypertension Research* 2017;35:2160.
12. Thomopoulos C, Parati G, A. Z. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs - overview and meta-analyses. *J Hypertension Research* 2015;33 [published Online First: 1341]
13. Schweizerische Eidgenossenschaft. Spezialitätenliste: Eidgenössisches Department des Inneren EDI, Bundesamt für Gesundheit BAG; Available from: www.spezialitätenliste.ch accessed 15.11.2018.
14. Siragy HM. Comparing angiotensin II receptor blockers on benefits beyond blood pressure. *Advances in Therapy* 2010;27(5):257-84. doi: http://dx.doi.org/10.1007/s12325-010-0028-3
15. The Info List. The Info List - Olmesartan Medoxomil http://www.theinfolist.com/php/SummaryGet.php?FindGo=Olmesartan_%20Medoxomil: RxList Inc.; 2007; accessed 3.11.2018.
16. Hünseler C, Paneitz A, Friedrich D, et al. Angiotensin II receptor blocker induced fetopathy: 7 cases *Klin Padiatr* 2011;223(1):10.
17. swissmedic. Arzneimittelinformation; Available from: http://www.swissmedicinfo.ch/ accessed 15.11.2018.
18. NICE. Clinical guideline. Hypertension in adults: diagnosis and management. In: National Institute for Health and Care Excellence, ed., 2011:25.

19. World Bank Country and Lending Groups. World Bank list of economies https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups: World Bank; accessed 10.10.2018.

20. Higgins JG, S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Online]. http://handbook.cochrane.org/ 2011; accessed November 2018.

21. Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of Technology Assessment in Health Care* 2005;21(2):245.

22. Shemilt I, Mugford M, Byford S ea. Incorporating Economic Evidence. *Higgins JPT, Green S, eds Cochrane Handbood for Systematic Reviews of Interventions Version 502: The Cochrane Collaboration* 2009

23. Punzi HA, Lewin A, Li W, et al. Efficacy/safety of olmesartan medoxomil versus losartan potassium in naive versus previously treated subjects with hypertension. *Advances in Therapy* 2012;29(6):524-37. doi: https://dx.doi.org/10.1007/s12325-012-0029-5

24. Flack JM, Graff A, Li W, et al. Efficacy/safety of olmesartan medoxomil versus losartan potassium in patients by stage 1 or 2 hypertension. *Postgraduate Medicine* 2012;124(3):59-70. doi: https://dx.doi.org/10.3810/pgm.2012.05.2549

25. Weir MR, Punzi HA, Flack JM, et al. A randomized, double-blind, forced-titration study to compare olmesartan medoxomil versus losartan potassium in patients with stage 1 and 2 hypertension. *Postgraduate Medicine* 2011;123(1):80-7. doi: https://dx.doi.org/10.3810/pgm.2011.01.2248

26. Simons WR. Comparative cost effectiveness of angiotensin II receptor blockers in a US managed care setting: olmesartan medoxomil compared with losartan, valsartan, and irbesartan. *Pharmacoeconomics* 2003;21(1):61-74.

27. Boersma C, Voors AA, Visser ST, et al. Cost effectiveness of angiotensin receptor blocker monotherapy in patients with hypertension in the Netherlands: a comparative analysis using clinical trial and drug utilization data. *American Journal of Cardiovascular Drugs* 2010;10(1):49-54. doi: https://dx.doi.org/10.2165/11319570-000000000-00000

28. Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension.[Erratum appears in J Clin Hypertens (Greenwich) 2001 Nov-Dec;3(6):395]. *Journal of Clinical Hypertension* 2001;3(5):283-91, 318.

29. Belsey JD. Choice of angiotensin receptor blocker in moderate hypertension. A UK-based cost-benefit comparison of olmesartan- and candesartan-based regimens. *Journal of Medical Economics* 2011;14(5):553-61. doi: https://dx.doi.org/10.3111/13696998.2011.595463

30. Miller LA, Wade R, Dai D, et al. Economic evaluation of four angiotensin II receptor blockers in the treatment of hypertension. *Current Medical Research & Opinion* 2010;26(6):1307-20. doi: https://dx.doi.org/10.1185/03007991003711045

31. Mazza A, Sacco AP, Townsend DM, et al. Cost-benefit effectiveness of angiotensin-II receptor blockers in patients with uncomplicated hypertension: A comparative analysis. *Biomedicine & Pharmacotherapy* 2017;90:665-69. doi: https://dx.doi.org/10.1016/j.biopha.2017.04.008

32. Vegter S, Nguyen NH, Visser ST, et al. Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. *Am J Manag Care* 2011;17(9):609-16.

33. Ah YM, Lee JY, Choi YJ, et al. Influence of initial angiotensin receptor blockers on treatment persistence in uncomplicated hypertension: A nation-wide population-based study. *Clinical and Experimental Hypertension* 2016;38(3):325-30. doi: http://dx.doi.org/10.3109/10641963.2015.1116548

34. Kato H, Shiraishi T, Ueda S, et al. Blood pressure control and satisfaction of hypertensive patients following a switch to combined drugs of an angiotensin receptor blocker and a calcium channel blocker in clinical practice of nephrology. *Clinical & Experimental Nephrology* 2015;19(3):465-73. doi: https://dx.doi.org/10.1007/s10157-014-1017-7

35. Sakima A, Ohshiro K, Nakada S, et al. Switching therapy from variable-dose multiple pill to fixed-dose single-pill combinations of angiotensin II receptor blockers and thiazides for hypertension.

Clinical and Experimental Hypertension 2011;33(5):309-15. doi: http://dx.doi.org/10.3109/10641963.2010.549260

36. Weir MR, Shojaee A, Maa JF. Efficacy of amlodipine/olmesartan medoxomil +/- hydrochlorothiazide in patients aged >= 65 or, <65 years with uncontrolled hypertension on prior Monotherapy. *Postgraduate Medicine* 2013;125(2):124-34. doi: http://dx.doi.org/10.3810/pgm.2013.03.2646

37. Zemmrich C, Luders S, Gansz A, et al. Daytime systolic ambulatory blood pressure with a direct switch between candesartan monotherapy and the fixed-dose combination olmesartan/amlodipine in patients with uncontrolled essential hypertension (sevicontrol-1). *Journal of Clinical Hypertension* 2013;15(11):815-19. doi: http://dx.doi.org/10.1111/jch.12202

38. Kakio Y, Uchida HA, Umebayashi R, et al. Practical efficacy of olmesartan versus azilsartan in patients with hypertension: a multicenter randomized-controlled trial (MUSCAT-4 study). *Blood Pressure Monitoring* 2017;22(2):59-67. doi: https://dx.doi.org/10.1097/MBP.0000000000000229

39. Perez A, Cao C. The Impact of Azilsartan Medoxomil Treatment (Capsule Formulation) at Doses Ranging From 10 to 80 mg: Significant, Rapid Reductions in Clinic Diastolic and Systolic Blood Pressure. *Journal of Clinical Hypertension* 2017;19(3):312-21. doi: https://dx.doi.org/10.1111/jch.12895

40. Perez A, Cao C. Azilsartan in Patients With Mild to Moderate Hypertension Using Clinic and Ambulatory Blood Pressure Measurements. *Journal of Clinical Hypertension* 2017;19(1):82-89. doi: https://dx.doi.org/10.1111/jch.12873

41. Shiga Y, Miura SI, Motozato K, et al. Comparison of efficacy and safety of azilsartan and olmesartan in patients with essential hypertension: A randomized and prospective study (CANZONE study). *International Heart Journal* 2017;58(3):416-21. doi: http://dx.doi.org/10.1536/ihj.16-285

42. Brunner HR, Stumpe KO, Januszewicz A. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil assessed by 24-hour ambulatory blood pressure monitoring in patients with essential hypertension. *Clinical Drug Investigation* 2003;23(7):419-30.

43. Brunner HR, Arakawa K. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil in achieving 24-hour blood pressure reductions and ambulatory blood pressure goals. *Clinical Drug Investigation* 2006;26(4):185-93.

44. Daikuhara H, Kikuchi F, Ishida T. The combination of OLmesartan and a CAlcium channel blocker (azelnidipine) or candesartan and a calcium channel blocker (amlodipine) in type 2 diabetic hypertensive patients: the OLCA study. *Diabetes & Vascular Disease Research* 2012;9(4):280-6.

45. Tsutamoto T, Nishiyama K, Yamaji M, et al. Comparison of the long-term effects of candesartan and olmesartan on plasma angiotensin II and left ventricular mass index in patients with hypertension. *Hypertension Research - Clinical & Experimental* 2010;33(2):118-22. doi: https://dx.doi.org/10.1038/hr.2009.192

46. Morii J, Miura S, Shiga Y, et al. Comparison of the efficacy and safety of irbesartan and olmesartan in patients with hypertension (EARTH study). *Clinical & Experimental Hypertension (New York)* 2012;34(5):342-9. doi: https://dx.doi.org/10.3109/10641963.2012.683912

47. Giles TD, Oparil S, Silfani TN, et al. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *Journal of Clinical Hypertension* 2007;9(3):187-95.

48. Liau CS, Lee CM, Sheu SH, et al. Efficacy and Safety of Olmesartan in the Treatment of Mild-to-Moderate Essential Hypertension in Chinese Patients. *Clinical Drug Investigation* 2005;25(7):473-9.

49. Smith DH, Dubiel R, Jones M. Use of 24-hour ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan. *American journal of cardiovascular drugs* 2005;5(1):41-50.

50. Kalikar M, Nivangune K, Dakhale G, et al. Efficacy and tolerability of olmesartan, telmisartan, and losartan in patients of stage i hypertension: A randomized, open-label study. *Journal of*

Pharmacology and Pharmacotherapeutics 2017;8(3):106-11. doi: http://dx.doi.org/10.4103/jpp.JPP_39_17

51. Ball KJ, Williams PA, Stumpe KO. Relative efficacy of an angiotensin II antagonist compared with other antihypertensive agents. Olmesartan medoxomil versus antihypertensives. *Journal of Hypertension - Supplement* 2001;19(1):S49-56.

52. de Luis DA, Conde R, Gonzalez-Sagrado M, et al. Effects of telmisartan vs olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients. *Nutricion Hospitalaria* 2010;25(2):275-9.

53. Fogari R, Zoppi A, Mugellini A, et al. Effectiveness of hydrochlorothiazide in combination with telmisartan and olmesartan in adults with moderate hypertension not controlled with monotherapy: a prospective, randomized, open-label, blinded end point (PROBE), parallel-arm study. *Current Therapeutic Research - Clinical and Experimental* 2008;69(1):1-15. doi: http://dx.doi.org/10.1016/j.curtheres.2008.02.003

54. Nakayama S, Watada H, Mita T, et al. Comparison of effects of olmesartan and telmisartan on blood pressure and metabolic parameters in Japanese early-state type-2 diabetics with hypertension. *Hypertension Research* 2008;31(1):7-13. doi: http://dx.doi.org/10.1291/hypres.31.7

55. Destro M, Scabrosetti R, Vanasia A, et al. Comparative efficacy of valsartan and olmesartan in mild-to-moderate hypertension: results of 24-hour ambulatory blood pressure monitoring. *Adv Ther* 2005;22(1):32-43. [published Online First: 2005/06/10]

56. Ohishi M, Takeya Y, Tatara Y, et al. Strong suppression of the renin-angiotensin system has a renal-protective effect in hypertensive patients: high-dose ARB with ACE inhibitor (Hawaii) study. *Hypertension Research - Clinical & Experimental* 2010;33(11):1150-4. doi: https://dx.doi.org/10.1038/hr.2010.145

57. Ushijima K, Nakashima H, Shiga T, et al. Different chronotherapeutic effects of valsartan and olmesartan in non-dipper hypertensive patients during valsartan treatment at morning. *Journal of Pharmacological Sciences* 2015;127(1):62-8. doi: https://dx.doi.org/10.1016/j.jphs.2014.09.004

58. Jagodzinski A, Neumann JT, Ojeda F, et al. Cardiovascular Biomarkers in Hypertensive Patients with Medical Treatment-Results from the Randomized TEAMSTA Protect I Trial. *Clinical Chemistry* 2017;63(12):1877-85. doi: https://dx.doi.org/10.1373/clinchem.2017.275289

59. Khan BV, Merchant N, Rahman ST, et al. Changes in central aortic pressure, endothelial function and biomarkers in hypertensive African-Americans with the cardiometabolic syndrome: Comparison of amlodipine/olmesartan versus hydrochlorothiazide/losartan. *CardioRenal Medicine* 2013;3(4):221-31. doi: http://dx.doi.org/10.1159/000355136

60. Neutel JM, Cushman WC, Lloyd E, et al. Comparison of long-term safety of fixed-dose combinations azilsartan medoxomil/chlorthalidone vs olmesartan medoxomil/hydrochlorothiazide. *Journal of Clinical Hypertension* 2017;19(9):874-83. doi: https://dx.doi.org/10.1111/jch.13009

61. Rump LC, Ambrosioni E, Burnier M, et al. Initial combination therapy with olmesartan/hydrochlorothiazide in moderate-to-severe hypertension. *Journal of Human Hypertension* 2006;20(4):299-301.

9. Appendices

9.1 Appendix I: Search Strategies

Search strategy Medline via OVID

Search date: 24th October 2018

Databases: Ovid MEDLINE® ALL (1946 to Daily Update), Publisher, In-Data-Review, In-Process and PubMed-not-MEDLINE records from NLM

1	exp Essential Hypertension	2035	Search for disease (Mesh and free text)
2	exp Hypertensive Retinopathy/	152	
3	"essential hypertens*".ab,ti.	23338	
4	"Primar* Hypertens*".ab,ti.	1993	
5	"idiopathic* hypertens*".ab,ti.	84	
6	exp Hypertension/	241623	
7	exp Blood Pressure/	278331	
8	"hypertens*".ab,ti.	395922	
9	"blood pressur*".ab,ti.	276652	
10	"systemic* hypertens*".ab,ti.	4422	
11	"systolic* pressur*".ab,ti.	14092	
12	"diastolic* pressur*".ab,ti.	14984	
13	"arterial pressur*".ab,ti.	58731	
14	"bloodpressur*".ab,ti.	43	
15	exp Antihypertensive Agents/	245485	
16	"antihypertens*".ab,ti.	45580	
17	"anti hypertens*".ab,ti.	4249	
18	"spontan* hypertens*".ab,ti.	19332	
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	906957	Linking Search for disease with OR
20	exp Olmesartan Medoxomil/	402	Search for Intervention (Olmesartan as mono- and
21	"Olmesartan*".af.	1517	

			any combination therapy (Mesh and free text))
22	20 or 21	1517	Linking Search for Intervention with OR
23	19 and 22	1182	Intervention AND Disease
24	limit 23 to (English or German)	1140	Limit to English or German
25	exp Animals/	21858262	Exclude animal studies
26	humans.sh.	17349859	
27	25 not 26	4508403	
28	26 not 27	860	Total hits
29	from 28 keep 1-860	860	Total hits exported in Endnote
30	exp Randomised Controlled Trials as Topic/	121307	Search filter for RCTs excluding case reports, letters, historical articles
31	exp randomised controlled trial/	470739	
32	exp Random Allocation/	96305	
33	exp Double-Blind Method/	147990	
34	exp single-blind method/	25830	
35	exp clinical trial/	810025	
36	clinical trial, phase i.pt.	18433	
37	clinical trial, phase ii.pt.	29720	
38	clinical trial, phase iii.pt.	14283	
39	clinical trial, phase iv.pt.	1607	
40	controlled clinical trial.pt.	92722	
41	randomised controlled trial.pt.	470336	

42	multicentre study.pt.	240681	
43	clinical trial.pt.	512937	
44	exp Clinical Trials as Topic/	318582	
45	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	1260872	
46	(clinical adj trial*).tw.	318279	
47	((singl* or doubl* or treb* or tripl*) adj (blind* or mask*)).tw.	159764	
48	randomly allocated.tw.	25096	
49	(allocated adj2 random*).tw.	28183	
50	46 or 47 or 48 or 49	473432	
51	45 or 50	1456963	
52	case report.tw.	278351	
53	exp letter/	1004514	
54	exp historical article/	383676	
55	52 or 53 or 54	1651968	
56	51 not 55	1423446	
57	29 and 56	444	Hits for RCT
58	exp meta-analysis as topic/	16991	Search filter for systematic reviews and meta-analysis excluding comments, editorials, letters
59	exp meta-analysis/	93528	
60	"meta analy*".tw.	135331	
61	"metaanaly*".tw.	1881	
62	(systematic adj (review$1 or overview$1)).tw.	129746	
63	"Review Literature as Topic"/	7537	
64	58 or 59 or 60 or 61 or 62 or 63	240296	
65	cochrane.ab.	64682	
66	embase.ab.	69159	
67	(psychlit or psyclit).ab.	913	
68	(psychinfo or psycinfo).ab.	25326	
69	(cinahl or cinhal).ab.	21997	
70	science citation index.ab.	2820	
71	reference list$.ab.	15768	
72	bibliograph$.ab.	16165	
73	hand-search$.ab.	6082	
74	relevant journals.ab.	1074	

75	selection criteria.ab.	27581	
76	data extraction.ab.	17020	
77	75 or 76	42493	
78	"review"/	2444155	
79	77 and 78	28391	
80	65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	131183	
81	exp comment/ or exp editorial/ or exp letter/	1667993	
82	64 or 79 or 80	288704	
83	82 not 81	277674	
84	29 and 83	35	Hits for systematic reviews, meta-analysis
85	Economics/	26962	Search filter for economy
86	"Costs and Cost Analysis"/	46487	
87	"Cost Allocation"/	1988	
88	Cost-Benefit Analysis/	74416	
89	"Cost Control"/	21261	
90	"Cost Savings"/	10930	
91	"cost of illness"/	24125	
92	"Cost Sharing"/	2376	
93	"Deductibles and Coinsurance"/	1683	
94	Medical Savings Accounts/	524	
95	Health Care Costs/	35782	
96	direct service costs/ or drug costs/ or employer health costs/ or hospital costs/	26168	
97	health expenditures/ or capital expenditures/	19899	
98	"Value of Life"/	5624	
99	exp Economics, Hospital/	23151	
100	exp Economics, Medical/	14059	
101	Economics, Nursing/	3982	
102	Economics, Pharmaceutical/	2808	
103	exp "Fees and Charges"/	29449	
104	exp Budgets/	13395	

105	(low adj cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	46156	
106	(high adj cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12388	
107	(health?care adj cost*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9372	
108	(fiscal or funding or financial or finance).tw.	126449	
109	(cost adj estimate*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2022	
110	(cost adj variable).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	39	
111	(unit adj cost*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2245	
112	(economic* or pharmacoeconomic* or price* or pricing).tw.	259902	
113	85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112	647046	
114	(cost adj effectiv*).tw.	116901	
115	(cost adj utility).tw.	3949	

116	(cost adj benefit*).tw.	10012	
117	(cost adj consequenc*).tw.	494	
118	"budget impact analys*".tw.	540	
119	113 or 114 or 115 or 116 or 117 or 118	715910	
120	29 and 119	33	Hits for economy

Search strategy Embase via OVID

Search date: 24th October 2018

Database:

1	exp essential hypertension/	26749	Search for disease (Mesh and free text)
2	exp hypertension retinopathy/	1123	
3	"essential hypertens*".ab,ti.	29535	
4	"Primar* Hypertens*".ab,ti.	2802	
5	"idiopathic* hypertens* ".ab,ti.	115	
6	exp hypertension/	648167	
7	exp blood pressure/	501268	
8	"hypertens*".ab,ti.	571010	
9	"blood pressur*".ab,ti.	384104	
10	"systemic* hypertens*".ab,ti.	5840	
11	"systolic* pressur*".ab,ti.	21613	
12	"diastolic* pressur*".ab,ti.	19766	
13	"arterial pressur*".ab,ti.	74110	
14	"bloodpressur*".ab,ti.	274	
15	exp antihypertensive agent/	640930	
16	"antihypertens*".ab,ti.	65335	
17	"anti hypertens*".ab,ti.	8306	
18	"spontan* hypertens*".ab,ti.	23637	
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1625784	Linking Search for disease with OR

20	exp olmesartan/	4254	Search for Intervention (Olmesartan as mono- and any combination therapy (Mesh and free text))
21	"Olmesartan*".af.	4557	
22	exp amlodipine plus olmesartan/	199	
23	exp hydrochlorothiazide plus olmesartan/	121	
24	exp amlodipine plus hydrochlorothiazide plus olmesartan/	60	
25	20 or 21 or 22 or 23 or 24	4557	Linking Search for Intervention with OR
26	19 and 25	4525	Intervention AND Disease
27	limit 26 to (English or German)	4351	Limit to English or German
28	exp animal/	23240067	Exclude animal studies
29	exp nonhuman/	5571333	
30	28 or 29	24845732	
31	exp human/	18921922	
32	30 not 31	5923810	
33	27 not 32	3704	Total hits
34	exp clinical trial/	1336406	Search filter for RCTs excluding case studies, case reports, abstract reports, Conference proceedings,
35	exp randomised controlled trial/	518611	
36	exp controlled clinical trial/	700352	
37	exp multicentre study/	197251	
38	exp phase 3 clinical trial/	36153	
39	exp phase 4 clinical trial/	3119	
40	exp randomisation/	79988	
41	exp single blind procedure/	32746	

42	exp double blind procedure/	154176	Conference abstracts, Editorials, Letters, Notes
43	exp crossover procedure/	56961	
44	"randomi?ed controlled trial*".tw.	188315	
45	rct.tw.	29824	
46	(random* adj2 allocat*).tw.	37858	
47	"single blind*".tw.	21754	
48	"double blind*".tw.	191476	
49	((treble or triple) adj blind*).tw.	855	
50	exp prospective study/	477113	
51	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	1928239	
52	exp case study/	56943	
53	case report.tw.	365037	
54	exp abstract report/	89733	
55	exp letter/	986850	
56	Conference proceeding.pt.	0	
57	Conference abstract.pt.	3185153	
58	Editorial.pt.	581540	
59	Letter.pt.	1038314	
60	Note.pt.	727894	
61	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	5941384	
62	51 not 61	1460374	
63	33 and 62	924	Hits for RCT
64	exp meta analysis/	150608	Search filter for systematic reviews and meta-analysis excluding letters, editorials
65	((meta adj analy*) or metaanalys*).tw.	177516	
66	(systematic adj (review$1 or overview$1)).tw.	158122	
67	64 or 65 or 66	305256	
68	cochrane.ab.	83470	
69	embase.ab.	87041	
70	(psychlit or psyclit).ab.	988	

71	(psychinfo or psycinfo).ab.	22371	
72	(cinahl or cinhal).ab.	25469	
73	science citation index.ab.	3269	
74	68 or 69 or 70 or 71 or 72 or 73	135091	
75	reference lists.ab.	17080	
76	"bibliograph*".ab.	20292	
77	"hand-search*".ab.	7244	
78	75 or 76 or 77	41461	
79	data extraction.ab.	20754	
80	selection criteria.ab.	33479	
81	79 or 80	52150	
82	review.pt.	2366281	
83	81 and 82	26064	
84	67 or 74 or 78 or 83	361019	
85	letter.pt.	1038314	
86	editorial.pt.	581540	
87	85 or 86	1619854	
88	84 not 87	352774	
89	33 and 88	185	Hits for systematic reviews, meta-analysis
90	exp socioeconomics/	338935	Search filter for economy
91	exp "cost benefit analysis"/	78913	
92	exp "cost effectiveness analysis"/	135934	
93	exp "cost of illness"/	17830	
94	exp "cost control"/	63172	
95	exp economic aspect/	1495791	
96	exp financial management/	386697	
97	exp "health care cost"/	267344	

98	exp health care financing/	12850	
99	exp health economics/	770030	
100	exp "hospital cost"/	33861	
101	exp "cost minimisation analysis"/	3195	
102	(fiscal or financial or finance or funding).tw.	162775	
103	(cost adj estimate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2978	
104	(cost adj variable*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	223	
105	(unit adj cost*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3890	
106	(cost adj effectiv*).tw.	157672	
107	(cost adj utility).tw.	6154	
108	(cost adj benefit*).tw.	13612	
109	(cost adj consequenc*).tw.	746	
110	budget impact analys*.tw.	1369	
111	90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110	1623974	
112	33 and 111	352	Hits for economy

Search strategy Cochrane Databases

Search date: 25th October 2018

Database: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials

ID	Search	Hits
#1	MeSH descriptor: [Essential Hypertension] explode all trees	118
#2	MeSH descriptor: [Hypertensive Retinopathy] explode all trees	2
#3	MeSH descriptor: [Hypertension] explode all trees	16457
#4	MeSH descriptor: [Blood Pressure] explode all trees	26369
#5	MeSH descriptor: [Antihypertensive Agents] explode all trees	7573
#6	(essential hypertens*):ti,ab,kw (Word variations have been searched)	6776
#7	(Primar* Hypertens*):ti,ab,kw (Word variations have been searched)	10656
#8	(idiopathic* hypertens*):ti,ab,kw (Word variations have been searched)	489
#9	(hypertens*):ti,ab,kw (Word variations have been searched)	49837
#10	(blood pressur*):ti,ab,kw (Word variations have been searched)	78135
#11	(systemic* hypertens*):ti,ab,kw (Word variations have been searched)	2722
#12	(systolic* pressur*):ti,ab,kw (Word variations have been searched)	27038
#13	(diastolic* pressur*):ti,ab,kw (Word variations have been searched)	20749
#14	(arterial pressur*):ti,ab,kw (Word variations have been searched)	26133
#15	(bloodpressur*):ti,ab,kw (Word variations have been searched)	486
#16	(antihypertens*):ti,ab,kw (Word variations have been searched)	16494
#17	(anti hypertens*):ti,ab,kw (Word variations have been searched)	2603
#18	(spontan* hypertens*):ti,ab,kw (Word variations have been searched)	577
#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	109292
#20	MeSH descriptor: [Olmesartan Medoxomil] explode all trees	127
#21	(olmesartan*) (Word variations have been searched)	612
#22	#20 OR #21	612
#23	#22 AND #19	550

Search strategy NHS Economic Evaluation Database (NHS EED

Search date: 29th October 2018

((Hypertens*) AND (Olmesartan*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	3

9.2 Appendix II: Evidence Table Efficacy/Effectiveness, Safety

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM) vs. Azilsartan (AZI)											
Kakio et al. 2017[38]	RCT	84 40 vs. 44 Hypertensive patients who did not achieve target BP levels (140/90 mmHg) with conventional ARBs for more than 3 months BP > 140/90 mmHg (patients with CKD, DM, CI: >130/80 mmHG) Mean age: 66.6 OLM 68.7 AZI	OLM 20 mg/daily Increase to 40mg if necessary	AZI 20 mg/daily Increase to 40mg if necessary	Japan, Multicentre	16 weeks[1] 0-16	▪ BP ▪ Renal function (estimated glomerular filtration rate, serum potassium level, soluble fms-like tyrosine kinase-1, urinary albumin/Cr ratio, urinary L-type fatty acid binding protein ▪ Serum lipid profiles (total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol levels, brain natriuretic peptide, haemoglobin A1c) ▪ Adverse events	Mean ± SD	n.a.	High	EFF, SAF
Perez et al. 2017 (a)[39]	RCT	449 randomised 442 analysed 65 vs. 63 vs. 64 vs. 62 vs. 64 vs. 63 (OLM) vs. 61 (Placebo) Patients with essential hypertension DBP ≥ 95 and ≤ 114 mmHG Mean age: between 53.5 and 56.5	OLM 20 mg/day or placebo/day	AZI 5, 10, 20, 40 or 80 mg/day	USA, Mexico, Argentina, Peru, Multicentre	8 weeks 0-8	▪ BP (clinic, ambulatory) ▪ Clinical laboratory tests ▪ Adverse events	Mean ± SD	Takeda Development Center Americas, Inc. Absolute Healthcare Communications Ltd	Moderate	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Perez et al. 2017 (b)[40]	RCT	574 randomised 555 analysed 78 vs. 80 vs. 80 vs. 79 vs. 81 vs. 80 (OLM) vs. 77 (Placebo) Patients with essential hypertension DBP ≥ 95 and ≤ 114 mmHG Mean age: between 52.6 and 55.2	OLM 20 mg/day or placebo/day	AZI 2.5, 5, 10, 20, 40 mg/day	USA, Argentina, Multicentre	8 weeks	▪ BP (clinic, ambulatory) ▪ Clinical laboratory tests ▪ Adverse events	Mean ± SD	Takeda Development Center Americas, Inc.	Moderate	EFF, SAF
Shiga et al. 2017[41]	RCT	64 randomised 56 patients analysed 28 vs. 28 Patients with essential hypertension BP ≥ 140/90 mmHg (≥ 130/80 mmHg in patients with diabetes mellitus and/or chronic kidney disease) Mean age: 70 OLM 72 AZI	OLM 20mg/day	AZI 20mg/day	Japan, single centre	12 weeks 0-4-8-12	▪ BP ▪ Biochemical parameters in blood and urine ▪ Body weight	Mean ± SD	N.a.	Unclear	EFF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM) vs. Candesartan (CAN)											
Brunner et al. 2003[42]	RCT	645 Patients with essential hypertension Mean sitting DBP 100-120 Mean sitting SBP > 150 Mean age: 51.7	OLM 20mg/day	CAN 8mg/day	Germany, Poland and Czech Republic, Multicentre	8 weeks 0-1-2-8	▪ BP ▪ Smoothness index ▪ Adverse events	Mean ± SD	Sankyo Europe GmbH	Unclear	EFF, SAF
Brunner & Arakawa[2] 2006[43]	RCT	645 Patients with essential hypertension Mean sitting DBP 100-120 Mean sitting SBP > 150 Mean age: 51.7	OLM 20mg/day	CAN 8mg/day	Germany, Poland and Czech Republic, Multicentre	8 weeks 0-1-2-8	▪ BP ▪ Smoothness index ▪ Adverse Events	Mean ± SD	Sankyo GmbH	Unclear	EFF, SAF
Daikuhara et al. 2012[44]	RCT	300 150 vs. 150 Or 115 vs. 121 (adding CCB) Patients with essential hypertension and type 2 diabetes mellitus SBP ≥ 130 mmHg DBP ≥ 80 mmHg Mean Age: 59.2 OLM 60.0 CAN	OLM 20mg/day Adding CCB azelnidipine 16mg/day if BP ≥ 130/80 mmHg	CAN 8 mg/day Adding CCB amlodipine 5mg/day if BP ≥ 130/80 mmHg	Japan, single centre	12 weeks or 24 weeks (if BP ≥ 130/80 mmHg) 0-4-8-16-24	▪ BP ▪ Heart rate ▪ Clinical laboratory tests (blood tests, urinalysis) ▪ Fasting blood glucose level ▪ HbA1c ▪ eGFR ▪ Urinary albumin level ▪ Adverse events	Mean ± SD	No funding or sponsoring	High	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Tsutamoto et al. 2009[45]	RCT	50 25 vs. 25 Patients with essential hypertension receiving CAN for more than 1 year 17 patients with CHF BP not mentioned in inclusion or exclusion criteria Mean age: 67.7 CAN, 68.2 OLM	OLM 20 mg	CAN 8 mg	N.a.	52 weeks[1] 0-12-26-52	▪ BP ▪ Heart rate ▪ Left ventricular ejection rate ▪ Left ventricular diastolic dimension ▪ Intraventricular septum ▪ Left ventricular posterior wall ▪ Left ventricular mass index ▪ Creatinine ▪ eGFR ▪ Serum potassium ▪ Brain natriuretic peptide ▪ Plasma renin concentration ▪ Aldosterone ▪ Angiotensin II	Mean ± SD	N.a.	Unclear	EFF
Comparison Olmesartan (OLM) vs. Irbesartan (IRB)											
Morii et al. 2012[46]	RCT	62 randomised 31 vs. 31 54 analysed 27 vs. 27 Patients with essential hypertension BP ≥ 140/90 mmHg Mean age: 71 OLM, 70 IRB	OLM 10-20mg/day Switching to higher dose or medication if necessary	IRB 50-100mg/day Switching to higher dose or medication if necessary	Japan, single centre	12 weeks 0-4-8-12	▪ BP ▪ Biochemical parameters ▪ Adverse events	Mean ± SD	n.a.	High	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM) vs. Losartan (LOS)											
Giles et al. 2007[47]	RCT	696 199 OLM, 200 LOS, 197 VAL, 100 Placebo Seated DBP > 100 and < 115 Mean age: 52.2 OLM, 51.3 LOS, 52.2 VAL, 52.4 Placebo	OLM 20 mg/day; After week 4 titrated to 40 mg	LOS 50 mg/day, VAL 80 mg/day, Placebo; After week 4 titrated to 100 mg (LOS), 160 mg (VAL) After week 8 titrated to 50 mg (LOS, twice daily), 320 mg (VAL, once daily)	N.a., Multicentre	12 weeks 0-2-4-8-12	▪ BP ▪ DBP (2-4-6-8-10-12) ▪ Adverse events	Mean ± SD	Daiichi Sankyo, Inc.	Unclear	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Liau et al. 2005[48]	RCT	126 62 vs.64 Chinese patients with essential hypertension DBP between 95 and 114 mmHg Mean age: 48.5 OLM 48.1 LOS	OLM 20 mg/day	LOS 50 mg/day	Taiwan, Multicentre	12 weeks 0-4-8-12 Follow up 4 and 12 weeks after treatment	▪ BP ▪ Laboratory examinations (electrocardiography, blood chemistry, blood count, urinalysis) ▪ Adverse events	Mean ± SD	Taiwan Sankyo Pharmaceutical Co. Ltd.	Moderate	EFF, SAF
Oparil et al. 2001[28]	RCT	588 147 OLM, 150 LOS, 145 VAL, 146 IRB Patients with essential hypertension Average cuff DBP ≥ 100 and ≤ 115 Mean daytime DBP ≥ 90 and < 120 Mean age: 52.4 OLM, 51.6 LOS, 51.7 VAL, 51.9 IRB (not based on number of randomised patients)	OLM 20mg/day	LOS 50mg/day VAL 80mg/day IRB 150mg/day	USA, Multicentre	8 weeks 0-2-4-8	▪ BP (0-8) ▪ DBP (0-8) ▪ DBP (2-4) ▪ SBP (0-2-4-8) ▪ Adverse events	Mean ± SD	N.a.	Unclear	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Smith [1,3] et al. 2005[49]	RCT	588 147 OLM, 150 LOS, 145 VAL, 146 IRB Patients with essential hypertension Average cuff DBP ≥ 100 and ≤ 115 Mean age: 52.3 OLM, 52.0 LOS, 51.9 VAL, 52.1 IRB (not based on number of randomised patients)	OLM 20mg/day	LOS 50mg/day VAL 80mg/day IRB 150mg/day	USA, Multicentre	8 weeks 0-2-4-8	▪ BP (0-8) ▪ DBP (0-8) ▪ DBP (2-4) ▪ SBP (0-2-4-8) ▪ Adverse events	Mean ± SD	Sankyo Pharma Inc.	Unclear	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Weir et al. 2011[25]	RCT	941 465 (420 + 52) vs. 469 Patients with stage 1 or 2 essential hypertension SeDBP ≥ 95 and ≤ 115 mmHg SeSBP ≤ 180 mmHg Mean age: 51.7 Combined OLM 52.1 LOS	Combined OLM group (= OLM group and placebo/OLM group): OLM 20 mg/day (weeks 1-4) OLM 40 mg/day (weeks 5-8) Placebo/OLM (placebo for 2 weeks; 20 mg OLM/day for 2 weeks; 40 mg/day OLM for 4 weeks)	LOS 50 mg/day (weeks 1-4) LOS 100 mg/day (weeks 5-8)	USA, Multicentre	8 weeks 0-2-4-8	▪ BP ▪ Compliance ▪ Adverse events	Mean ± SD	Daiichi Sankyo, Inc.	Moderate	EFF, SAF
Punzi et al. 2012[23]	Subgroup analysis of Weir et al. 2011[25]	See Weir et al., 2011 Subgroup analysis of previously treated patients (752) and treatment of naïve subjects (189) with stage 1 or 2 essential hypertension for OLM, placebo/OLM, combined OLM and LOS group	See Weir et al. 2011	See Weir et al. 2011	See Weir et al. 2011	8 weeks 0-4-8	▪ See Weir et al., 2011 Endpoints separated by previously treated and treatment of naïve patients In addition: ▪ Ambulatory BP measurement	See Weir et al. 2011	See Weir et al. 2011	High	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Flack et al. 2012[24]	Subgroup analysis of Weir et al. 2011[25]	See Weir et al., 2011 Subgroup analysis of hypertension severity (i.e. stage 1 or stage 2 hypertension)	See Weir et al., 2011	See Weir et al., 2011	See Weir et al., 2011	8 weeks 0-4-8	▪ See Weir et al., 2011	See Weir et al. 2011	See Weir et al. 2011	Moderate	EFF, SAF
Kalikar et al. 2017[50]	RCT	60 20 vs. 20 vs. 20 Patients with stage 1 hypertension SBP 140 – 159 mmHG DBP 90 – 99 mmHG Mean age OLM: 46.2 TEL: 48.26 LOS: 49.94	OLM 20 mg	TEL 40 mg LOS 50 mg	India, single centre	12 weeks 0-2-4-8-12	▪ BP ▪ Fasting blood glucose level ▪ Serum lipids ▪ Adverse events	Mean ± SD	None	High	EFF, SAF
Ball K. J. et al. 2001[51]	RCT	316 Allocation intervention vs. control: n.a. Patients with mild to moderate essential hypertension DBP 95-114 mmHG Mean age: n.a.	OLM 10 mg If necessary dose doubling and combination with HCTZ 12.5 or 25 mg HCTZ	LOS 50 mg If necessary dose doubling and combination with HCTZ 12.5 or 25 mg HCTZ	N.a., Multicentre	24 weeks 2-4-8-12-16-20-24	▪ BP ▪ Clinical laboratory tests ▪ Adverse Events	Mean ± SD	Sankyo Europe GmbH	Unclear	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM) vs. Telmisartan (TEL)											
De Luis et al. 2010[52]	RCT	65 34 vs. 31 Obese patients with mild to moderate hypertension BP > 140/90 mmHg Mean age: 56.2 TEL, 59.8 OLM	OLM 40 mg	TEL 80 mg	N.a	12 weeks[1] 0-12	▪ BP ▪ Weight ▪ BMI ▪ Basal glucose ▪ Insulin ▪ Total cholesterol ▪ LDL-cholesterol ▪ HDL-cholesterol ▪ Triglycerides ▪ Leptin ▪ Adiponectin levels	Mean ± SD	N.a.	High	EFF
Fogari et al. 2008[53]	RCT	126 Monotherapy: 63 vs. 63 Combination therapy: 52 vs. 49 Patients with essential hypertension not adequately controlled by monotherapy DBP ≥ 99 mmHg and < 110 mmHg SBP <2 00 mmHg Mean age: 60.1 OLM/HCTZ 59.9 TEL/HCTZ	OLM 20mg Treatment with OLM/HCTZ 20mg/12.5mg /day if DBP ≥ 90 mmHg	TEL 80mg Treatment with TEL/HCTZ 80mg/12.5 mg/day if DBP ≥ 90 mmHg	Italy, single centre	Monotherapy 8 weeks Combination therapy 8 weeks	▪ BP (clinic and ABPM) ▪ Adverse events	Mean ± SD	N.a.	High	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Nakayama, S. et al. 2008 [54]	RCT	20 Allocation intervention vs. control: n.a. Patients with hypertension and type 2 diabetes, treated with Valsartan 80mg/day BP ≥ 130/85 mmHg Mean age 63.7	OLM 20 mg/day Switching after 8 weeks	TEL 40 mg/day Switching after 8 weeks	Japan, two centres	16 weeks 0-8-16	▪ BP ▪ Metabolic parameters ▪ Inflammatory parameters	Mean ± SD	N.a.	Unclear	EFF
Comparison Olmesartan (OLM) vs. Valsartan (VAL)											
Destro et al, 2005 [55]	RCT	114 55 vs. 52 (initial number of patients randomised to intervention and control group not stated) Patients with mild-moderate essential hypertension DBP > 95 and < 110 mmHg Mean age of patient population not stated; age: 35-70	VAL 160 mg/day	OLM 20 mg/day	N.a.	8 weeks 0-2-8	▪ BP (+24h ambulatory) ▪ Heart rate	Mean ± SD	N.a.	High	EFF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Ohishi et al. 2010[56]	RCT	37 19 vs. 18 Hypertensive patients without CKD taking 160 mg VAL BP not explicitly stated Mean age: 64	VAL 160 mg + Imidapril (2.5 mg/ 5 mg/ 7.5 mg/ 10 mg 19 patients switched from VAL 160 mg to 40 mg OLM 18 patients received 2.5-10 mg Imidapril (2.5 mg increment per month) additional to VAL 160 mg	OLM 40 mg	Japan	16 weeks[1] 0-4-8-12-16	▪ BP ▪ Pulse rate ▪ Serum creatinine ▪ Urinary protein reduction ▪ eGFR	Mean ± SD	N.a.	Unclear	EFF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Ushijima et al. 2015[57]	RCT	(92 overall study population) 40 randomised (only non-dippers; patients were divided beforehand into dippers and non-dippers) Hypertensive patients with VAL morning dose including diabetic patients dippers (52) vs. non-dippers (40) BP ≥ 140/90 mmHg Mean age: 64.6 (VAL-M), 63.2 (VAL-E), 64.3 (OLM-M), 66.2 (OLM-E)	VAL-M 40, 80 or 160 mg/day	VAL-E 40, 80 or 160 mg, OLM-M 20, 40 or 80 mg, OLM-E 20, 40 or 80 mg/day	N.a. Multicentre	16 weeks[1] 0-16	▪ 24 h BP ▪ Serum creatinines ▪ eGFR	Mean ± SD	Japan Research Foundation for Clinical Pharmacology (KU) & Ministry of Education, Culture, Sports, Science and technology of Japan	High	EFF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM)/Hydrochlorotiazide (HCTZ) vs. Telmisartan (TEL)/Amlodipine (AML)											
Jagodzinski et al. 2017[58]	RCT	577 randomised 481 analysed 230 vs. 251 Patients with treated uncontrolled or controlled hypertension and ≥ 3 cardiovascular risk factors and/or metabolic syndrome and/or diabetes mellitus and/or end-organ damage Controlled: BP < 140/90 mmHg (< 130/80 mmHg for renal impaired and/or diabetic patients) Uncontrolled: BP 20/10mmHg above target BP < 140/90mmHg (< 130/80 mmHg for renal impaired and/or diabetic patients) Mean age: 60.6 OLM/HCTZ 60.3 TEL/AML	OLM/HCTZ 40mg/12.5mg Uptitrated after 2 weeks to 40mg/25mg	TEL/AML 80mg/5mg Uptitrated after 2 weeks to 80mg/10mg	Single centre	26 weeks 0-26	▪ BP ▪ Heart rate ▪ Laboratory tests ▪ Adverse events	Mean ± SD	Boehringer Ingelheim Pharma GmbH. S. Blankenberg, Abbott, Abbott Diagnostics, Bayer, Boehringer Ingelheim, SIEMENS, Thermo Fisher	Unclear	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM)/Amlodipine (AML) vs. Losartan (LOS)/Hydrochlorotiazide (HCTZ)											
Khan et al. 2013[59]	RCT	66 Hypertensive (stage 1 or stage 2) African-Americans with cardiometabolic syndrome BP < 180/110 mmHg Mean age: 50.0	AML/OLM 5mg/20mg/day for 2 weeks Titrated to AML/OLM 10mg/40mg/day for 12 weeks; then switching or maintaining current regimen	LOS/HCTZ 50mg/12.5 mg/day for 2 weeks Titrated to LOS/HCTZ 100mg/25 mg/day for 12 weeks; then switching or maintaining current regimen	USA, Multicentre	20 weeks 0-2-8-14-20	▪ BP ▪ Central aortic pressure ▪ Endothelial function	Mean ± SD	Daiichi Sankyo, Inc.	High	EFF, SAF
Comparison Olmesartan (OLM)/Hydrochlorotiazide (HCTZ) vs. Azilsartan (AZI)/Chlorthalidone (CLD)											
Neutel et al. 2016[60]	RCT	837 418 vs. 419 Patients with stage 2 essential hypertension Clinic SBP 160-190 Mean age: 58.5 AZI/CLD, 57.6 OLM/HCTZ	FDC AZI/CLD 40/12,5mg; Uptitration week 4-52 to 80/25mg if necessary	FDC OLM/HCTZ 20/12,5mg; Uptitration week 4-52 to 40/25mg (US) or 20/25mg (EU) if necessary	USA; Germany, Poland, United Kingdom and Netherlands, Multicentre	52 weeks	▪ BP (0-2-4-8-12-16-24-32-42-52) ▪ Clinical safety laboratory tests ▪ 12-lead electrocardiographic findings ▪ Vital signs ▪ Creatinine ▪ Adverse events	Mean ± SD	Takeda Development Center Americas, Inc.	High	EFF, SAF

Study	Study design	Number of patients (randomised)	Intervention	Control	Setting	Duration of treatment, Time of measurement	Relevant outcomes	Effect estimate	Sponsor	Risk of bias	Domain
Comparison Olmesartan (OLM)/Hydrochlorotiazide (HCTZ) vs. Losartan (LOS)/Hydrochlorotiazide (HCTZ)											
Rump et al. 2006[61]	RCT	629 315 vs. 314 Patients with moderate to severe essential hypertension DBP ≥ 100 - ≤ 120 mmHg SBP ≥ 160 mmHg (or inadequate controlled DBP 90-110 mmHg despite using ≥ 1 antihypertensive) Mean age:	OLM/HCTZ 20/12.5 mg	LOS/HCTZ 50/12.5 mg	9 European countries	12 weeks	▪ BP ▪ Puls pressure ▪ Adverse events	Mean ± SD	N.a.	unclear	EFF, SAF

AML = Amlodipine; AZI = Azilsartan; BMI = Body Mass Index; BP = blood pressure; CAN = Candesartan; CCB=Calcium channel blocker; CHF = chronic heart failure; CI = cerebral infarction; CKD = chronic kidney disease; CLD = Chlorthalidone; DBP = diastolic blood pressure; DM = diabetes mellitus; E = evening; EFF = efficacy/effectiveness; eGFR = Estimated glomerular filtration rate; FDC = fixed dose combination; HCTZ = Hydrochlorothiazide; HDL = high-density lipoprotein; IRB = Irbesartan; LDL = low-density lipoprotein; LOS = Losartan; M = morning; OLM = Olmesartan; OLM-E = Olmesartan evening; OLM-M = Olmesartan morning; SAF = safety; SBP = systolic blood pressure; SD = standard deviation; TEL=Telmisartan; USA = United States of America; VAL = Valsartan; VAL-E = Valsartan evening; VAL-M = Valsartan morning

[1] Duration of treatment was stated in months and converted to weeks

[2] No separate study; publication based on study of Brunner et al., 2003; going to be analysed jointly

[3] No separate study; publication based on study of Oparil et al., 2001; going to be analysed jointly

Source: GÖ FP

9.3 Appendix III: Evidence Table Costs/Cost-Effectiveness

Study/Country	Methods	Population	Source clinical /cost data	Comparators	Perspective	Time/ cost data year	Main results	Sponsor	CHEC checklist
Belsey, J. D. 2011[29], UK	Cost-effectiveness, Monte-Carlo Simulation Model linked blood pressure targets Budget impact	Parent cohort patients with normally distributed blood pressures about mean values of 170 mmHg and 105 mmHg No subclasses for age, sex or co-morbidity	Clinical trial data: – indirect comparison: Karlson, B. W. et al. 2009; Chrysant, S. G. et al. 2008, Oparil, S. et al. 2010 Drug Tariff and British National Formulary	OLM CAN	Payer: National Health Service	1 year 2010	*Lowering BP* *Mean cost per patient/year* *Systolic Target:* 150 mmHg: OLM/CAN: £171.36/189.91 *Systolic Target 140 mmHg: OLM/CAN* £304.50/441.96 Diastolic Target: 90 mmHg); *OLM/CAN* £156.11/189.13	Daiichi-Sankyo UK	Appendix V
Boersma, C. et al. 2010 [27], NL	Cost-effectiveness Simulation Model, Extrapolation 1/5 years; BP control: < 140/90 mmHg)	Hypothetical cohort with essential hypertension combined with daily-practice prescription data No subclasses	Clinical trial data: Oparil, S. et al. 2001 Dutch drug prices	OLM LOS VAL IRB	Payer	1 and 5 years 2006	Net costs/cardiovascular complication, averted for cohort of 100,000 (compared with do-nothing); 1/5 years OLM: €39,100/38,900 LOS: €77,100/78,600 VAL: €70,700/69,700 IRB: €50,900/52,100	Daiichi-Sankyo NL	Appendix V

Study/Country	Methods	Population	Source clinical /cost data	Comparators	Perspective	Time/ cost data year	Main results	Sponsor	CHEC checklist
Miller, L. et al. 2010[30], USA	Cost-effectiveness Modelling (Decision analytic model)	Patients selected randomly from real distribution cohort with > 140/90 mmHg for uncomplicated hypertension and > 130/80 mmHG for patients with diabetes; Average age 57.1 years 53.5 % females	Medical chart data Administrative claims cost data	OLM/OLM HCTZ LOS/LOS HCTZ VAL/VAL HCTZ IRB/IRB HCTZ	Payer	9 months? 2006	Cost per patient reaching BP goal: all cause/hypertension attributable OLM: $8,964/2,704 LOS: $10,484/3,291 VAL: $10,557/3,577 IRB: $13,335/4,325	Daiichi-Sankyo, USA	Appendix V
Mazza A. et al. 2017[31], I	"Cost-benefit-analysis" stated by author, however no values cost/benefit/effectiveness shown Retrospective cross-sectional study 114 people with essential hypertension	114 patients (> 18 years) with essential hypertension – target: < 140 mmHG (excluded severe hypertension >180/110 mmHG) and cardiovascular events severe obesity, dementia)	Retrospective cross-sectional study Pharmacy dispensing records	OLM CAN IRB LOS TEL VAL Mono- and FDC with HCTZ	N/R	6 months N/R	Blood pressure lowering Drug acquisition cost per day/cost per year, no combination with "effects" Authors' conclusion: "treatment of BP with candesartan appears to be the most favourable option in terms of cost-effectiveness" Data and conclusions partly contradictory and not comprehensible	N/R	Appendix V

Study/Country	Methods	Population	Source clinical /cost data	Comparators	Perspective	Time/ cost data year	Main results	Sponsor	CHEC checklist
Simons, W. R. 2003[26], USA	Cost-effectiveness Budget impact (health expenditure savings)	Costs: administrative data set, population with hypertension; Effects: trial	Clinical trial data: Oparil, S. et al. 2001 Predicting CV: Framingham Heart Study Cost: managed care database	OLM LOS VAL IRB	Payer	1 and 5 years 1997/1999	Incremental benefit 5 years for 100,000 patients: **OLM vs LOS** CVD: $15,149,000 CHD: $11,107,000 MI: $1,437,000 Stroke: $1,437,000 **OLM vs. VAL** CVD: $16,231,000 CHD: $11,955,000 MI: $ 14,505,000 Stroke: $1,741,000 **OLM vs IRB** CVD: $5,410,000 CHD: $3,975,000 MI: $2,430,000 Stroke: $497,000	Sankyo Pharma Inc.	Appendix V

BP = blood pressure; CAN = Candesartan; CHD = coronary heart disease, CVD = cardiovascular disease; CKD = chronic kidney disease; FDC = fixed dose combination; HCTZ = Hydrochlorothiazide; I = Italy, IRB = Irbesartan; LOS = Losartan; OLM = Olmesartan; MI = myocardial infarction, NL = Netherlands; N/R = not reported, TEL=Telmisartan; UK = United Kingdom; USA = United States of America; VAL = Valsartan

Source: GÖ FP

9.4 Appendix IV: Assessment of Risk of Bias for Efficacy/Effectiveness and Safety

1. Ball, K. J. et al., 2001

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (Allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Sponsor: Sankyo Europe GmbH
- General drop-out rate: 14.2 %
- Differential drop-out rate: no detailed information on number of people in intervention and control groups and drop-outs given
- ITT: no information given on number of patients in intervention and control groups and how many patients were analysed.

* unclear because of missing information in the study.

Source: GÖ FP

2. Brunner et al., 2003

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding by Sankyo Europe GmbH
- Double blinded, clinical trial, but nothing was mentioned about randomisation and allocation concealment
- General drop-out rate: 4.81 %; it was not possible to calculate the drop-out rates of the intervention and control groups as the initial number of patients assigned to the intervention and control groups is not mentioned in the paper

* unclear because of missing information in the study.

Source: GÖ FP

3. Brunner & Arakawa, 2006

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding by Sankyo GmbH
- Double blinded, clinical trial, but nothing was mentioned about randomisation and allocation concealment
- General drop-out rate: 1.55 %
- Differential drop-out rate: 2.5 % in the intervention group and 0.62 % in the control group
- ITT analysis not based on number of patients randomised

* unclear because of missing information in the study.

Source: GÖ FP

4. Daikuhara et al., 2012

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?		X	
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)			X
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Open label randomised trial
- Antidiabetic drugs (including insulin) used at start of the study were continued without any change in type or dosage during the study
- ITT, results, drop-outs: no results for the whole randomised study population is presented, only results of patients who did not reach BP goals (BP ≥ 130/80 mmHg) and who were given CCB in addition to OLM or CAN are described. No drop-outs in these groups.
- General drop-out rate: no detailed information for whole study population given
- Differential drop-out rate: no detailed information for whole study population given
- No funding or sponsoring

* unclear because of missing information in the study.

Source: GÖ FP

5. De Luis et al., 2010

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)		X	
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)		X	
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Funding n.a.
- Open RCT
- No drop-outs of the study population

* unclear because of missing information in the study.

Source: GÖ FP

6. Destro et al., 2005

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)	X		
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Funding n.a
- Open-label RCT
- General drop-out rate: 6.14 %
- Differential drop-out rate not mentioned in the RCT and initial number of patients of the intervention and control group not stated.

* unclear because of missing information in the study.

Source: GÖ FP

7. Flack et al., 2012

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounder?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (OLM, OLM combined and LOS group)	X (Placebo/OLM)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
		X		

Comments

- ITT: only patients who received ≥ 1dose of study medication and had a baseline assessment and ≥ 1 post-baseline efficacy assessment were included in the EFF assessment
- Supported by Daiichi Sankyo, Inc.
- General drop-out rate: 13.1 %
- Differential drop-out rate: 11.9 % in the OLM Group, 28.8 % in the placebo/OLM group, 12.5 % in the combined OLM group and 12.4 % in the LOS group
- Differential drop-out rates for stage 1 and stage 2 hypertension are < 15 % except for Placebo/OLM group: 21.7 % for stage 1 hypertensive patients and 34.5 % for stage 2 hypertensive patients

* unclear because of missing information in the study.

Source: GÖ FP

8. Fogari et al., 2008

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)	X		
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?			
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)		X	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?	X		
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Randomised, open-label, blinded endpoint evaluation
- General drop-out rate: 19.8 %
- Differential drop-out rate: 19 % in intervention and control groups
- No information given on funding or sponsoring

* unclear because of missing information in the study.

Source: GÖ FP

9. Giles et al., 2007

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?			X
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)		X	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding by Daiichi Sankyo, Inc.
- Double blinded, clinical trial, but nothing was mentioned about randomisation and allocation concealment
- General drop-out rate: 12.86 %
- Differential drop-out rates mentioned in the study are based on the ITT population (696), not on the number of patients randomised (723); GOeG calculations of the differential drop-out rate: 9.6 % OLM, 13.04 % LOS, 10.84 % VAL and 17.92 % placebo
- ITT analysis not based on number of patients randomised

* unclear because of missing information in the study.

Source: GÖ FP

10. Jagodzinski et al., 2017

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (intervention group)	X (control group)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Double blinded randomised trial, but nothing was mentioned about randomisation and allocation concealment in detail
- ITT: number of patients included in analysis does not correspond to the number of patients randomised
- General drop-out rate: 16.6 %
- Differential drop-out rate: 3 drop-outs are not categorised to intervention or control group. 12.9 % in the intervention and 19.6 % in the control group
- Funding by Boehringer INgelheim Pharma GmbH. S. Blankenberg, Abbott, Abbott Diagnostics, Bayer, Boehringer Ingelheim, SIEMENS, Thermo Fisher

* unclear because of missing information in the study.

Source: GÖ FP

11. Kaiko et al., 2017

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)	X		
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?	X		
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Open label randomised trial
- General drop-out rate: 13.10 %
- Differential drop-out rate: 12.5 % in the intervention group and 13.6 % in the control group

* unclear because of missing information in the study.

Source: GÖ FP

12. Kalikar, M. et al., 2017

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Randomised open-label-study
- General drop-out rate: 5 %
- Differential drop-out rate: 0 % in OLM, 5 % in TEL and 10 % in LOS
- No financial support

* unclear because of missing information in the study.

Source: GÖ FP

13. Khan et al., 2013

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?			X
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)	X		
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)		X	
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?	X		
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Open label randomised trial
- Funding by Daiichi Sankyo, Inc.
- General drop-out rate: 24.2 %; differential drop-out rate is not available and cannot be calculated because the number of drop-outs in the intervention and control group was not mentioned

* unclear because of missing information in the study.

Source: GÖ FP

14. Liau et al., 2005

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (Control)	X (Intervention)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
		X		

Comments

- Excluded patients after randomisation were not considered for EFF assessment
- Funding by Taiwan Sankyo Pharmaceutical Co. Ltd.
- General drop-out rate: 15.9 %
- Differential drop-out rate: 21 % in the intervention group and 11 % in the control group

* unclear because of missing information in the study.

Source: GÖ FP

15. Morii et al., 2012

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?		X	
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- ITT: number of patients included in analysis does not correspond to the number of patients randomised;
- General drop-out rate: 12.9 %
- Differential drop-out rate: 6.4 % in the intervention and control groups
- No information given on funding or sponsoring

* unclear because of missing information in the study.

Source: GÖ FP

16. Nakayama, S. et al, 2008

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?			X
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?	X		
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Open-label study
- Financial support not reported

* unclear because of missing information in the study.

Source: GÖ FP

17. Neutel et al., 2017

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)		X	
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)		X	
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)		X	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Funding by Takeda Development Center Americas, Inc.
- Open-label RCT; nothing was mentioned about randomisation
- General drop-out rate: 26.29 %; 31 % in the intervention group and 21 % in the control group
- nothing mentioned about an ITT analysis

* unclear because of missing information in the study.

Source: GÖ FP

18. Oparil et al., 2001

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)			X
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding n.a.
- Double blinded, clinical trial, but nothing was mentioned about randomisation and allocation concealment
- ITT: number of patients included in analysis does not correspond to the number of patients randomised; authors define the ITT population in the Methods section
- Drop-out rates of groups are mentioned in the study but there are several inconsistencies regarding the study population

* unclear because of missing information in the study.

Source: GÖ FP

19. Ohishi et al., 2010

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?		X	
Were the study participants blinded? (performance bias)			X
Were the persons who administered the intervention blinded? (performance bias)			X
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?		X	
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)			X
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding n.a.
- RCT but nothing was mentioned about randomisation, blinding and allocation concealment
- Drop-out rates and number of patients not reported in a sufficient manner
- Low drop-out rate: 7.8 % in the intervention group and 7.2 % in the control group

* unclear because of missing information in the study.

Source: GÖ FP

20. Perez et al., 2017 (a)

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X (all but four)		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (AZI, OLM)	X (Placebo)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
		X		

Comments

- ITT: 7 patients were excluded after randomisation and were not included in the EFF assessment; only patients who received ≥ 1dose of study medication were included in the EFF assessment
- Funded by Takeda Development Center Americas, Inc. and Absolute Healthcare Communications Ltd.
- General drop-out rate: 10 %
- Differential drop-out rates are < 15 % except for placebo group 18.8 %

* unclear because of missing information in the study.

Source: GÖ FP

21. Perez et al., 2017 (b)

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X (all but 19)		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
		X		

Comments

- ITT: 28 patients were excluded after randomisation and were not included in the EFF assessment; only patients who received ≥ 1dose of study medication were included in the EFF assessment
- Funded by Takeda Development Center Americas, Inc.
- General drop-out rate: 14 %
- Differential drop-out rate: no detailed information on drop-outs per group

* unclear because of missing information in the study.

Source: GÖ FP

22. Punzi et al., 2012

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?		X (not for all)	
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (OLM, OLM combined and LOS group)	X (Placebo/OLM)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- ITT: only patients who received ≥ 1dose of study medication and had a baseline assessment and ≥ 1 post-baseline efficacy assessment were included in the EFF assessment
- Supported by Daiichi Sankyo, Inc.
- General drop-out rate: 13.1 %
- Differential drop-out rate: 11.9 % in the OLM Group, 28.8 % in the placebo/OLM group, 12.5 % in the combined OLM group and 12.4 % in the LOS group
- Differential drop-out rates for treatment naïve subjects and previously treated patients are < 15 % except for placebo/OLM group: 35.7 % for treatment naïve subjects and 26.3 % for previously treated patients

* unclear because of missing information in the study.

Source: GÖ FP

23. Rump et al., 2006

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?		X (not for all)	
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X		
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- ITT: only patients who received ≥ 1dose of study medication and had both a baseline plus ≥ 1 postbaseline sitting DBP value were included in the EFF assessment
- General drop-out rate: 9,8 % (calculated from ITT population n=613, which is not corresponding to the number of patients randomized (n=629)).
- Differential drop-out rate: 10.7 % in the OLM/HCTZ group, 8,9 % in the LOS/HCTZ group.

* unclear because of missing information in the study.

Source: GÖ FP

24. Shiga et al., 2017

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?			X
Were the study participants blinded? (performance bias)			X
Were the persons who administered the intervention blinded? (performance bias)			X
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- ITT: number of patients included in analysis does not correspond to the number of patients randomised
- General drop-out rate: 12.5 %
- Differential drop-out rate: is not mentioned and cannot be calculated because the number of randomised patients per group is not described
- No information given on funding or sponsoring

* unclear because of missing information in the study.

Source: GÖ FP

25. Smith et al., 2005

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)			X
Was allocation concealment ensured? (allocation concealment, selection bias)			X
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)			X
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)		X	

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding by Sankyo Pharma Inc.
- Double blinded, clinical trial, but nothing was mentioned about randomisation and allocation concealment
- ITT: number of patients included in analysis does not correspond to the number of patients randomised; authors define the ITT population in methods section
- Due to inconsistencies in the study population, it was not possible to assess the general and differential drop-out rate

* unclear because of missing information in the study.

Source: GÖ FP

26. Tsutamoto et al., 2009

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?		X	
Were the study participants blinded? (performance bias)			X
Were the persons who administered the intervention blinded? (performance bias)			X
Were the persons who surveyed the endpoints blinded? (detection bias)	X with restrictions		
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)			X
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)			X
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
				X

Comments

- Funding n.a.
- Patients were randomised according to the envelope technique but there was no further description on blinding of patients or persons who administered the intervention
- Study population included 17 (out of 25) patients with chronic heart failure
- Physicians were blinded regarding neurohumoral data only
- No drop-outs and no final size of intervention and control group reported in the RCT
- Patients were allowed to continue with their usual medication besides CAN/OLM
- Endpoints: ANG 1-7 could not be measured

* unclear because of missing information in the study.

Source: GÖ FP

27. Ushijima et al., 2015

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)		X	
Was allocation concealment ensured? (allocation concealment, selection bias)		X	
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?			X
Were the study participants blinded? (performance bias)		X	
Were the persons who administered the intervention blinded? (performance bias)		X	
Were the persons who surveyed the endpoints blinded? (detection bias)		X	
Did all treatment groups receive identical treatments apart from the evaluated intervention?			X
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)		X	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?			X
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
			X	

Comments

- Funding by Japan Research Foundation for Clinical Pharmacology (KU) & Ministry of Education, Culture, Sports, Science and Technology of Japan
- Open-label RCT
- Patient population: 2 patients took additional medication (Azelnidipine and Amlodipine)
- Randomisation: patients were categorised in dippers and non-dippers; then non-dippers were divided in three treatment groups (VAL/OLM-M/OLM-E)
- General drop-out rate: 16.30 %;
- Differential drop-out rate 17.31 % VAL-M, 8.33 % VAL-E, 15.38 % OLM-M and 0.2 % OLM-E

* unclear because of missing information in the study.

Source: GÖ FP

28. Weir et al., 2011

Criteria to assess the risk of bias of RCTs	Yes	No	Unclear
SELECTION			
Was an adequate randomising method applied in order to assign participants in the study to different treatment groups? (random sequence generation, selection bias)	X		
Was allocation concealment ensured? (allocation concealment, selection bias)	X		
COMPARABILITY			
Were the treatment groups after randomisation similar with respect to essential prognostic characteristics or confounders?	X		
Were the study participants blinded? (performance bias)	X		
Were the persons who administered the intervention blinded? (performance bias)	X		
Were the persons who surveyed the endpoints blinded? (detection bias)			X
Did all treatment groups receive identical treatments apart from the evaluated intervention?	X		
ENDPOINTS			
Were the endpoints in all treatment groups evaluated at the same point in time?	X		
Was the general drop-out rate lower than 20 %? (attrition bias)	X		
Was the differential drop-out rate between treatment groups lower than 15 percentage points? (attrition bias)	X (OLM, OLM combined and LOS group)	X (placebo/OLM)	
Was an intention-to-treat (ITT) analysis conducted and was it carried out correctly?		X	
Is it reasonable to assume that all gathered endpoints have been reported? (reporting bias)	X		

Assessment of the risk of bias	Low	Moderate	High	Unclear
		X		

Comments

- ITT: only patients who received ≥ 1dose of study medication and had a baseline assessment and ≥ 1 post-baseline efficacy assessment were included in the EFF assessment
- 4 out of 7 authors are employees of Daiichi Sankyo, Inc.
- General drop-out rate: 13.1 %
- Differential drop-out rate: 11.9 % in the OLM Group, 28.8 % in the placebo/OLM group, 12.5 % in the combined OLM group and 12.4 % in the LOS group

* unclear because of missing information in the study.

Source: GÖ FP

9.5 Appendix V: Assessment of Quality for Economic Evaluations

1. Belsey, J. D. 2001

CHEC-Checkliste

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X	□	□
2.	Are competing alternatives clearly described?	X	□	□
3.	Is a well-defined research question posed in answerable form?	X	□	□
4.	Is the economic study design appropriate to the stated objective?	X	□	□
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	X	□	□
6.	Is the actual perspective chosen appropriate?	X	□	□
7.	Are all important and relevant costs for each alternative identified?	□	□	X
8.	Are all costs measured appropriately in physical units?	□	X	□
9.	Are costs valued appropriately?	□	□	X
10.	Are all important and relevant outcomes for each alternative identified?	□	X	□
11.	Are all outcomes measured appropriately?	□	X	□
12.	Are outcomes valued appropriately?	□	□	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	□	X	□
14.	Are all future costs and outcomes discounted appropriately?	X	□	□
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	□	X	□
16.	Do the conclusions follow from the data reported?	X	□	□
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?	X	□	□
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	□	□
19.	Are ethical and distributional issues discussed appropriately?	□	X	□
	Comments: Without costs for adverse events and costs for general physician visits Effects based on indirect comparison studies			

Source: [21 22]

2. Boersma, C. et al., 2010

CHEC-Checkliste

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	□	X	□
2.	Are competing alternatives clearly described?	X	□	□
3.	Is a well-defined research question posed in answerable form?	X	□	□
4.	Is the economic study design appropriate to the stated objective?	X	□	□
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	□	□	X
6.	Is the actual perspective chosen appropriate?	X	□	□
7.	Are all important and relevant costs for each alternative identified?	□	X	□
8.	Are all costs measured appropriately in physical units?	□	X	□
9.	Are costs valued appropriately?	□	□	X
10.	Are all important and relevant outcomes for each alternative identified?	□	X	□
11.	Are all outcomes measured appropriately?	X	□	□
12.	Are outcomes valued appropriately?	□	□	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	□	□	X
14.	Are all future costs and outcomes discounted appropriately?	X	□	□
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	□	□	X
16.	Do the conclusions follow from the data reported?	X	□	□
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	□	X	□
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	□	X	□
19.	Are ethical and distributional issues discussed appropriately?	□	X	□
	Comments: Cardiovascular endpoints were extrapolated on BP decrease no adverse effects included adherence data not available low number of patients who received OLM			

Source: [21 22]

3. Miller L. et al., 2010

CHEC-Checkliste

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X	□	□
2.	Are competing alternatives clearly described?	X	□	□
3.	Is a well-defined research question posed in answerable form?	X	□	□
4.	Is the economic study design appropriate to the stated objective?	X	□	□
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	□	□	X
6.	Is the actual perspective chosen appropriate?	X	□	□
7.	Are all important and relevant costs for each alternative identified?	□	□	X
8.	Are all costs measured appropriately in physical units?	□	□	X
9.	Are costs valued appropriately?	□	□	X
10.	Are all important and relevant outcomes for each alternative identified?	□	□	X
11.	Are all outcomes measured appropriately?	□	□	X
12.	Are outcomes valued appropriately?	□	□	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X	□	□
14.	Are all future costs and outcomes discounted appropriately?	X	□	□
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	X	□	□
16.	Do the conclusions follow from the data reported?	X	□	□
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	□	X	□
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	□	□
19.	Are ethical and distributional issues discussed appropriately?	□	X	□
	Comments: Olmesartan group was younger and healthier Proportion of diabetes patients was lower in Olmesartan group No detailed cost data shown No adverse events calculated No results for combination products shown			

Source: [21 22]

4. Mazza, A. et al., 2017

CHEC-Checkliste

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	□	□	X
2.	Are competing alternatives clearly described?	□	X	□
3.	Is a well-defined research question posed in answerable form?	□	□	X
4.	Is the economic study design appropriate to the stated objective?	□	□	X
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	□	X	□
6.	Is the actual perspective chosen appropriate?	□	□	X
7.	Are all important and relevant costs for each alternative identified?	□	□	X
8.	Are all costs measured appropriately in physical units?	□	X	□
9.	Are costs valued appropriately?	□	□	X
10.	Are all important and relevant outcomes for each alternative identified?	□	X	□
11.	Are all outcomes measured appropriately?	□	□	X
12.	Are outcomes valued appropriately?	□	□	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	□	X	□
14.	Are all future costs and outcomes discounted appropriately?	□	X	□
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	□	X	□
16.	Do the conclusions follow from the data reported?	□	□	X
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	□	X	□
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	□	X	□
19.	Are ethical and distributional issues discussed appropriately?	□	X	□
	Comments: Conclusion unclear (Cost/Effect not shown) Small population group No adverse events Non transparent description regarding effect data and cost data No year of cost data, adherence? Study design poorly described			

Source: [21 22]

5. Simons, W. R., 2003

CHEC-Checkliste

	Item	Yes	No	Unclear
1.	Is the study population clearly described?	X	□	□
2.	Are competing alternatives clearly described?	X	□	□
3.	Is a well-defined research question posed in answerable form?	X	□	□
4.	Is the economic study design appropriate to the stated objective?	X	□	□
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	□	□	X
6.	Is the actual perspective chosen appropriate?	X	□	□
7.	Are all important and relevant costs for each alternative identified?	□	X	□
8.	Are all costs measured appropriately in physical units?	□	X	□
9.	Are costs valued appropriately?	□	□	X
10.	Are all important and relevant outcomes for each alternative identified?	□	□	X
11.	Are all outcomes measured appropriately?	□	□	X
12.	Are outcomes valued appropriately?	□	□	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X	□	□
14.	Are all future costs and outcomes discounted appropriately?	□	X	□
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	□	x	□
16.	Do the conclusions follow from the data reported?	X	□	□
17.	Does the study discuss the generalizability of the results to other settings and patient/client groups?	□	X	□
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	□	□
19.	Are ethical and distributional issues discussed appropriately?	□	X	□
	Comments: No prices stated, assumption price of Olmesartan is the same as all others (at that time Olmesartan had no price in USA), however price was lower later on No adverse events included Dosage like clinical trial, no real world data			

Source: [21 22]

9.6 Appendix VI: Market Data Sartans

Table 6: Mono-preparations: turnover and packages sold at pharmacy retail prices in Switzerland, 2014 – 2018

	2014		2015		2016		2017		2018[1]	
ATC Code/Substance	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Number Packages**	**Turnover in CHF**	**Number Packages**
	in CHF	***Number***	***in CHF***	***Number***	***in CHF***	***Number***	***in CHF***	***Number***		***Number***
C09CA01 Losartan	7,500,307	149,140	8,373,576	194,933	8,358,506	160,070	8,305,919	154,116	6,005,061	110,509
C09CA02 Eprosartan	555,635	6,055	498,783	5,230	433,071	4,756	391,920	3,965	258,680	2,735
C09CA03 Valsartan	8,997,022	147,431	9,522,832	158,460	10,070,134	171,720	10,535,826	177,903	7,771,118	137,775
C09CA04 Irbesartan	11,521,780	144,782	10,910,589	147,649	10,733,602	144,250	10,600,674	143,696	7,651,599	105,369
C09CA06 Candesartan	20,560,763	400,693	20,880,204	424,173	21,796,523	450,191	22,623,776	481,777	16,799,552	371,872
C09CA07 Telmisartan	4,812,909	51,917	4,446,776	52,531	4,279,367	51,412	4,048,912	50,782	2,903,160	37,362
C09CA08 Olmesartan medoxomil	8,878,009	88,624	8,337,585	97,402	9,007,041	104,205	9,089,776	106,506	6,689,308	82,524
C09CA09 Azilsartan medoxomil	597,527	7,325	726,838	8,293	959,271	10,770	1,076,976	11,940	832,947	9,003
Total	**63,423,952**	**995,967**	**63,697,182**	**1,088,671**	**65,637,515**	**1,097,373**	**66,673,778**	**1,130,684**	**48,911,425**	**857,148**

[1] as of 1.1.2018 – 30.9.2018

Source: Tarifpool: © SASIS AG, 2018, 10.12.2018

Table 7: Fixed dose combinations: Turnover and sold packages at pharmacy retail prices in Switzerland, 2014 – 2018

	2014		2015		2016		2017		2018 [1]	
ATC Code/Substance	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**	**Turnover**	**Packages**
	in CHF	***Number***	***in CHF***	***Number***	***in CHF***	***Number***	***in CHF***	***Number***	***In CHF***	***Number***
C09DA01 Losartan and diuretics	7,716,863	95,602	8,869,196	114,831	8,898,841	114,641	8,622,229	113,808	6,028,077	78,457
C09DA02 Eprosartan and diuretics	713,972	6,967	651,080	6,327	581,684	5,635	521,638	5,122	349,187	3,377
C09DA03 Valsartan and diuretics	10,132,849	162,202	10,025,491	164,906	9,796,422	159,667	9,588,930	157,080	6,822,160	112,192
C09DA04 Irbesartan and diuretics	19,124,220	194,528	15,724,262	186,796	14,292,571	177,509	13,127,543	166,724	8,923,314	117,407
C09DA06 Candesartan and diuretics	20,516,967	303,387	19,404,839	302,173	18,919,292	299,118	18,423,472	298,646	12,986,125	217,104
C09DA07 Telmisartan and diuretics	5,513,168	42,908	4,272,186	39,597	3,977,807	37,771	3,554,119	35,450	2,438,674	24,852
C09DA08 Olmesartan medoxomil and diuretics	6,596,133	61,044	5,841,872	62,659	6,005,911	64,223	5,877,447	63,106	4,172,614	47,547
C09DA09 Azilsartan medoxomil and Diuretika			225,348	3,001	875,296	10,844	1,199,433	13,622	977,626	10,627
C09DB01 Valsartan and Amlodipin	13,742,376	106,782	14,062,183	108,895	14,610,727	112,282	14,807,492	119,260	10,513,950	90,473
C09DB02 Olmesartan medoxomil and Amlodipin	6,216,092	62,924	6,824,898	68,957	7,432,317	75,157	7,763,338	78,124	5,655,048	59,865
C09DB04 Telmisartan and Amlodipin	836,497	8,133	865,610	8,607	880,958	8,680	904,378	9,009	646,838	6,502
C09DX01 Valsartan, Amlodipin and Hydrochlorothiazid	16,007,119	122,922	16,787,958	128,597	17,833,595	134,802	18,163,320	141,025	13,095,899	106,514
C09DX03 Olmesartan medoxomil, Amlodipin and Hydrochlorothiazid	6,932,164	54,191	7,683,031	61,797	8,756,346	71,071	9,320,581	77,034	7,038,337	56,704
Total	114,048,420	1,221,589	111,237,957	1,257,142	112,861,767	1,271,400	111,873,921	1,278,010	79,647,849	931,621

[1] as of 1.1.2018 – 30.9.2018

Source: Tarifpool: © SASIS AG, 2018, 10.12.2018