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Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA report

Title	Olmesartan mono- and combination therapy in patients with essential hypertension
Author/Affiliation	Ingrid Rosian-Schikuta, Daniela Antony, Stefan Fischer, Astrid Füszl, Stefan Mathis-Edenhofer, Alexandra Posekany, 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 medoxomil (olmesartan for short)
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Executive summary

Background In the context of a Health Technology Assessment (HTA), the Federal Office of Public Health was tasked to re-evaluate public reimbursement of olmesartum medoxomilum (olmesartan for short). Olmesartan belongs to the family of angiotensin II receptor blockers (ARBs), one of the major classes of drugs recommended for essential hypertension treatment in adult patients. The efficacy, effectiveness and safety of olmesartan therapy in such patients have been questioned due to a suspected increased risk of adverse events and missing data on morbidity and mortality outcomes.

The central research questions for this report addressed the efficacy, effectiveness and safety of olmesartan in adult patients with essential hypertension compared with other sartans. A second focus covered their costs, cost effectiveness and the anticipated impact on the health insurance budget if olmesartan were delisted and substituted by other available sartans. In this context, issues were also examined as to whether legal, social, ethical or organisational aspects should be considered in the course of a potential delisting of olmesartan from the reimbursement list.

Method For all domains of the HTA, systematic literature searches were conducted. Seventy-two primary studies were analysed for effectiveness, efficacy and safety and – whenever possible – meta-analyses were conducted. For the economic domain, six relevant studies were identified; however, due to heterogenous study designs and outcomes, the results were not transferable to Switzerland. Therefore, the effects of the one retrospective cohort study identified with long-term outcomes were used to model the cost effectiveness of olmesartan, valsartan, losartan and irbesartan. Finally, to estimate the implications of a potential substitution of olmesartan for the health insurance budget, the allocation method was used, simulating three scenarios. In Scenario 1, the number of olmesartan preparations was allocated to the other sartans separately for mono- and combination

preparations (cost and volume for 2018). The market share of the different packs of alternative sartan preparations was used as the redistribution key. Scenario 2 considered the doses of alternative drugs equivalent to olmesartan (cost and volume for 2018) and Scenario 3 differed from Scenario 2 in that all reimbursed packs were valued with prices as of 1 August 2019.

Results Efficacy: 17 randomised controlled trials (RCTs, 4'036 participants) compared olmesartan with other sartans. Olmesartan lowered (systolic as well as diastolic) blood pressure more effectively compared with losartan and diastolic blood pressure more effectively compared with irbesartan. For olmesartan versus valsartan, azilsartan, candesartan and telmisartan as well as olmesartan/hydrochlorothiazide versus telmisartan/hydrochlorothiazide, the results did not differ significantly.

Effectiveness: Based on one study (Swindle et al.), in a limited subsample (108'567 participants), olmesartan reduced the risk of the composite outcome of cardiac events (particularly heart failure) more effectively than valsartan, losartan and irbesartan. We conducted independent statistical analyses of the available data and did not identify any significant differences between olmesartan, losartan, irbesartan and valsartan in any of the outcomes.

Safety: Regarding severe adverse events, we analysed five RCTs (1'721 participants) and 12 cohort studies (>8'250'000 participants). The comparisons indicated similar risk profiles for olmesartan and other sartans in the short-term follow-up (RCTs) and the long-term follow-up (cohort studies). The results were not consistent for enteritis. Two of the cohort studies suggested that olmesartan is associated with an increased risk of enteropathies compared with other ARBs while two other cohort studies found no significant difference.

Additionally, we evaluated data from 22 single-arm studies (67'922 participants) as well as the single-study arms of 11 RCTs (4'587 participants) and 8 cohort studies (125'669 participants). We identified no striking patterns regarding the occurrence of serious adverse events in olmesartan users.

Cost effectiveness: The calculated incremental cost effectiveness ratio (ICER) per patient for cardiac events was between CHF -20'000 and CHF -25'000 for olmesartan compared with valsartan, losartan and irbesartan (perspective: health insurance; time frame: 1 year). In other words, olmesartan was associated with higher effects and lower costs for cardiac events. However, the sensitivity analysis showed that the calculated cost-effectiveness results were not robust.

Budget impact: The total net budget impact (pharmaceutical expenditure and additional outpatient visits) for the potential substitution of olmesartan with other sartans in the three scenarios resulted in budget savings of CHF 4.8 million (Scenario 1), further expenses of CHF 1.3 million (Scenario 2)

and further expenses of CHF 2.6 million (Scenario 3) for the health insurance. In relation to pharmaceutical expenditures alone, there would be budget savings of CHF 7.4 million in Scenario 1, CHF 1.3 million in Scenario 2 and no savings in Scenario 3. The effects of a substitution of olmesartan depended strongly on the availability of alternative preparations within the equivalence groups (their specific prices and market shares) as well as on expenditure for additional visits to physicians in the course of changing medication.

Social/ethical issues: To avoid medication adherence problems, timely information for physicians about a potential disinvestment, the reasons for the decision and available equivalent doses of alternative sartans would be useful.

Organisational issues: It would be necessary to monitor if there were any problems with the delivery of valsartan products due to nitrosamine impurities and whether they could be provided in sufficient quantities (especially triple combinations) as this is the only alternative for olmesartan triple combinations.

In addition, patients could expect more frequent visits to their physician during the first year in the course of switching to another sartan.

Conclusions Olmesartan lowered systolic as well as diastolic blood pressure more effectively compared with losartan and diastolic blood pressure more effectively compared with irbesartan without showing a statistically significant effect compared with candesartan, telmisartan, telmisartan plus diuretics, azilsartan and valsartan. Evidence (of low quality) from one retrospective cohort study hinted at a potential advantage of olmesartan for long-term outcomes like certain cardiac events compared with losartan, irbesartan and valsartan.

The comparisons of harm indicated similar risk profiles for olmesartan and other sartans in the short-term follow-up (RCTs) and the long-term follow-up (cohort studies). Regarding enteritis, the results from four cohort studies (comparing olmesartan with other sartans) were inconsistent in terms of detecting a higher risk for olmesartan users. Despite occurring only rarely, clinicians should remain vigilant regarding this potential adverse event.

The cost-effectiveness calculations were not robust enough to draw any universal conclusions when using olmesartan compared with valsartan, losartan and irbesartan.

The budget impact of substituting olmesartan depended strongly on the prices and market shares of alternative preparations within the specific equivalence groups and the costs for additional medical consultations associated with the change in medication. Therefore, if physicians prescribing

equivalent doses of the alternative sartans to those of olmesartan, it is more likely that the substitution of olmesartan would result in increased healthcare expenditures.

To maintain blood pressure control after a potential disinvestment decision, physicians should receive timely information as well as guidance on prescribing equivalent doses of other sartans. To avoid access problems, the current market situation should be kept under observation, especially with regard to the availability of double and triple combinations and potential future recalls of some valsartan products.

Zusammenfassung

Hintergrund Im Rahmen eines Health Technology Assessment (HTA) überprüft das Bundesamt für Gesundheit die Vergütungspflicht für Olmesartanum medoxomilum (kurz: Olmesartan). Olmesartan gehört zur Gruppe der Angiotensin-II-Rezeptorblocker (ARB), einer der wichtigsten Arzneimittelklassen, die zur Behandlung von essentieller Hypertonie bei Erwachsenen empfohlen wird. Wegen des Verdachts auf ein erhöhtes Risiko für unerwünschte Ereignisse sowie fehlender Daten zu Morbidität und Mortalität wurden die Wirksamkeit – unter idealen Bedingungen sowie unter Alltagsbedingungen – und die Sicherheit der Olmesartan-Therapie für diese Patientinnen und Patienten in Frage gestellt.

Die zentralen Forschungsfragen für diesen Bericht befassten sich mit der Wirksamkeit unter idealen Bedingungen sowie unter Alltagsbedingungen und mit der Sicherheit von Olmesartan bei erwachsenen Patientinnen und Patienten mit essentieller Hypertonie im Vergleich zu anderen Sartanen. Ein zweiter Schwerpunkt lag auf deren Kosten, der Kosteneffektivität und der erwarteten budgetären Auswirkung für die Krankenversicherung, wenn Olmesartan aus dem Leistungskatalog entfernt und durch andere verfügbare Sartane ersetzt würde. In diesem Zusammenhang wurde auch geprüft, ob rechtliche, soziale, ethische oder organisatorische Aspekte bei einer allfälligen Entfernung von Olmesartan aus dem Leistungskatalog berücksichtigt werden müssten.

Methode Für alle Bereiche des HTA wurden systematische Literaturrecherchen durchgeführt. 72 Primärstudien wurden im Hinblick auf die Sicherheit und die Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen analysiert, und wo möglich wurden Metaanalysen durchgeführt. Zum Thema Wirtschaftlichkeit wurden sechs relevante Studien identifiziert; aufgrund der heterogenen Studiendesigns und -resultate waren die Ergebnisse allerdings nicht auf die Schweiz übertragbar. Aus diesem Grund wurde die Kosteneffektivität von Olmesartan, Valsartan, Losartan und Irbesartan anhand der Effekte modelliert, die sich in der einzigen identifizierten retrospektiven Kohortenstudie mit Langzeitergebnissen zeigten. Schliesslich wurden mittels Allokationsmethode drei Szenarien simu-

liert, um die budgetären Auswirkungen einer allfälligen Substitution von Olmesartan für die Krankenversicherung abzuschätzen. Im ersten Szenario wurden die Olmesartan-Präparate den anderen Sartanen gesondert nach Mono- und Kombinationspräparaten zugeordnet (Kosten und Mengen von 2018). Als Verteilschlüssel dienten dabei die Marktanteile der verschiedenen Packungen alternativer Sartan-Präparate. Das zweite Szenario berücksichtigte die zu Olmesartan äquivalenten Dosen von alternativen Arzneimitteln (Kosten und Mengen von 2018), ebenso das dritte Szenario mit dem Unterschied, dass für alle vergüteten Packungen die Preise gemäss Stichtag 1. August 2019 verwendet wurden.

Ergebnisse Wirksamkeit unter idealen Bedingungen: 17 randomisierte kontrollierte Studien (RCT, 4036 Teilnehmende) verglichen Olmesartan mit anderen Sartanen. Olmesartan senkte den (systolischen und diastolischen) Blutdruck wirksamer als Losartan und den diastolischen Blutdruck wirksamer als Irbesartan. Beim Vergleich zwischen Olmesartan und Valsartan, Azilsartan, Candesartan und Telmisartan sowie zwischen Olmesartan/Hydrochlorothiazid und Telmisartan/Hydrochlorothiazid zeigten sich keine signifikanten Unterschiede.

Wirksamkeit unter Alltagsbedingungen: Gemäss einer Studie (Swindle et al.) reduzierte Olmesartan in einer begrenzten Teilstichprobe (108 567 Teilnehmende) das Risiko eines kombinierten Outcomes aus kardialen Ereignissen (insbesondere Herzinsuffizienz) effektiver als Valsartan, Losartan und Irbesartan. Wir führten mit den verfügbaren Daten unabhängige statistische Analysen durch. Dabei fanden wir für keinen der Outcomes signifikante Unterschiede zwischen Olmesartan, Losartan, Irbesartan und Valsartan.

Sicherheit: Mit Blick auf schwere unerwünschte Ereignisse wurden 5 RCTs (1721 Teilnehmende) und 12 Kohortenstudien (> 8 250 000 Teilnehmende) analysiert. Die Vergleiche zeigten ähnliche Risikoprofile für Olmesartan und andere Sartane bei kurzfristigen (RCT) sowie langfristigen Nachbeobachtungszeiten (Kohortenstudien). Für Enteritis waren die Ergebnisse nicht konsistent. Zwei Kohortenstudien deuteten darauf hin, dass Olmesartan im Vergleich zu anderen ARBs mit einem erhöhten Risiko für Enteropathien assoziiert ist. Zwei weitere Kohortenstudien fanden jedoch keinen signifikanten Unterschied.

Zusätzlich evaluierten wir die Daten von 22 einarmigen Studien (67 922 Teilnehmende) sowie einzelnen Studienarmen von 11 RCTs (4587 Teilnehmende) und 8 Kohortenstudien (125 669 Teilnehmende), fanden jedoch keine auffälligen Muster in Bezug auf das Auftreten von schweren unerwünschten Ereignissen bei Olmesartan-Patientinnen und -Patienten.

Kosteneffektivität: Das berechnete inkrementelle Kosteneffektivitäts-Verhältnis (ICER) pro Patient/in für kardiale Ereignisse betrug zwischen CHF –20 000 und CHF –25 000 für Olmesartan im Vergleich mit Valsartan, Losartan und Irbesartan (Perspektive: Krankenversicherung; Zeitrahmen: 1 Jahr). Das

heisst, dass Olmesartan bezüglich kardialer Ereignisse mit höheren Effekten und tieferen Kosten assoziiert war. Allerdings zeigte die Sensitivitätsanalyse, dass die Ergebnisse der Kosteneffektivitätsberechnungen nicht solide waren.

Budgetäre Auswirkung: Insgesamt ergab die budgetäre Nettoauswirkung (Arzneimittelausgaben und zusätzliche ambulante Arztkontakte) eines möglichen Ersatzes von Olmesartan durch andere Sartane in den drei Szenarien für die Krankenversicherung Kosteneinsparungen von CHF 4,8 Millionen (Szenario 1), zusätzliche Kosten in Höhe von CHF 1,3 Millionen (Szenario 2) und zusätzliche Kosten von CHF 2,6 Millionen (Szenario 3). Betrachtet man nur die Arzneimittelausgaben, so resultieren Kosteneinsparungen in Höhe von CHF 7,4 Millionen in Szenario 1 bzw. CHF 1,3 Millionen in Szenario 2 sowie keine Einsparungen in Szenario 3. Die Auswirkungen einer Substitution von Olmesartan hingen stark von der Verfügbarkeit alternativer Präparate innerhalb der Äquivalenzgruppen (deren jeweiligen Preisen und Marktanteilen) sowie von den Ausgaben für zusätzliche Arztbesuche aufgrund der Medikationsumstellung ab.

Soziale/ethische Aspekte: Um Problemen mit der Medikationsadhärenz zuvorzukommen, wäre eine rechtzeitige Information der Ärzteschaft über eine mögliche Einschränkung der Vergütungspflicht («Disinvestment»), die Gründe für den Entscheid und erhältliche Äquivalenzdosen alternativer Sartane sinnvoll.

Organisatorische Aspekte: Es müsste beobachtet werden, ob es bei der Lieferung von Valsartan-Produkten aufgrund von Nitrosamin-Verunreinigungen zu Problemen kommen könnte und ob sie in ausreichenden Mengen lieferbar wären (insbesondere Dreifachkombinationen), da sie die einzige Alternative für Dreifachkombinationen mit Olmesartan sind.

Ausserdem ist zu erwarten, dass die Zahl der Arztkonsultationen für die Patientinnen und Patienten im ersten Jahr der Umstellung auf ein anderes Sartan zunehmen wird.

Schlussfolgerungen Olmesartan senkte den systolischen wie auch den diastolischen Blutdruck wirksamer als Losartan und den diastolischen Blutdruck wirksamer als Irbesartan. Im Vergleich mit Candesartan, Telmisartan, Telmisartan plus Diuretika, Azilsartan und Valsartan zeigte Olmesartan hingegen keinen statistisch signifikanten Effekt. Evidenz (von geringer Qualität) aus einer retrospektiven Kohortenstudie deutete auf einen möglichen Vorteil von Olmesartan bei Langzeit-Outcomes wie gewissen kardialen Ereignissen gegenüber Losartan, Irbesartan und Valsartan hin.

Bei Vergleichen der unerwünschten Wirkungen zeigten Olmesartan und andere Sartane sowohl bei kurzfristigen (RCT) als auch langfristigen Nachbeobachtungszeiten (Kohortenstudien) ähnliche Risikoprofile. Bezüglich der Frage, ob Olmesartan-Patientinnen und -Patienten ein höheres Risiko für Enteritis aufweisen, waren die Resultate von vier Kohortenstudien (die Olmesartan mit anderen

Sartanen verglichen) inkonsistent. Auch wenn dieses unerwünschte Ereignis nur selten eintritt, sollten Ärztinnen und Ärzte diesbezüglich wachsam bleiben.

Die Kosteneffektivitätsberechnungen waren nicht genügend solide und liessen deshalb keine allgemeingültigen Schlussfolgerungen zur Olmesartan-Therapie im Vergleich zu Valsartan, Losartan und Irbesartan zu.

Die budgetäre Auswirkung der Substitution von Olmesartan hing stark von den Preisen und Marktanteilen der alternativen Präparate innerhalb der spezifischen Äquivalenzgruppen und den Kosten für zusätzliche Arztkonsultationen in Zusammenhang mit der Medikationsumstellung ab. Es ist deshalb wahrscheinlicher, dass die Substitution von Olmesartan zu höheren Gesundheitsausgaben führen würde, wenn Ärztinnen und Ärzte zu Olmesartan äquivalente Dosen von alternativen Sartanen verschreiben.

Im Falle eines Disinvestment-Entscheids sollten die Ärztinnen und Ärzte rechtzeitig informiert werden und Hilfestellung zur Verschreibung von Äquivalenzdosen anderer Sartane erhalten. Um Versorgungsprobleme zu verhindern, sollte die aktuelle Marktsituation beobachtet werden, insbesondere im Hinblick auf die Verfügbarkeit von Zweifach- und Dreifachkombinationen und mögliche künftige Rückrufe gewisser Valsartan-Produkte.

Résumé

Contexte Dans le cadre des évaluations des technologies de la santé (HTA pour *Health Technology Assessment*), l'Office fédéral de la santé publique (OFSP) a été chargé de réévaluer le remboursement de l'olmesartum medoxomilum (ci-après olmésartan). L'olmésartan appartient à la famille des antagonistes des récepteurs de l'angiotensine II (ARB pour *Angiotensin II Receptor Blockers*), qui entrent dans la composition des principaux traitements recommandés pour l'hypertension essentielle chez les patients adultes. L'efficacité en conditions réelles et idéales et l'innocuité des traitements à l'olmésartan chez ces patients ont été remises en question en raison d'une suspicion de risque accru d'effets indésirables et d'un manque de données concernant la morbidité et le taux de mortalité.

Ce rapport s'est concentré sur l'efficacité en conditions réelles et idéales et l'innocuité de l'olmésartan chez des patients adultes atteints d'hypertension essentielle en comparaison avec d'autres sartans. Il a également abordé leurs coûts et leur rapport coût-efficacité, ainsi que l'impact prévu sur le budget de l'assurance maladie si l'olmésartan était retiré de la liste des spécialités et remplacé par d'autres

sartans. Dans ce contexte, le rapport a aussi examiné l'opportunité de considérer des aspects juridiques, sociaux, éthiques ou organisationnels dans le cadre d'un retrait de l'olmésartan de la liste des remboursements.

Méthode Des recherches bibliographiques systématiques ont été effectuées dans tous les domaines HTA. 72 études primaires ont été passées en revue pour observer l'efficacité en conditions réelles et idéales et l'innocuité ; des méta-analyses ont été effectuées lorsque cela était possible. 6 études ont été identifiées comme pertinentes pour le domaine économique ; cependant, leurs conceptions hétérogènes ont empêché de transposer les résultats à la Suisse. Pour modéliser le rapport coût-efficacité de l'olmésartan, du valsartan, du losartan et de l'irbésartan, nous avons donc utilisé les effets de la seule étude de cohorte rétrospective identifiée avec des résultats à long terme. Finalement, 3 scénarios ont été simulés avec la méthode de répartition pour estimer l'impact sur le budget de l'assurance maladie d'un éventuel remplacement de l'olmésartan. Dans le scénario 1, le nombre de préparations à l'olmésartan est réparti sur les autres sartans, de manière séparée pour les monopréparations et les préparations combinées (coût et volume de 2018). La clé de répartition est basée sur les parts de marché des différents emballages de préparations à base de sartans alternatifs. Le scénario 2 considère les doses de produits alternatifs équivalents à l'olmésartan (coût et volume de 2018). Le scénario 3 ne diffère du scénario 2 qu'en ce que les emballages remboursés sont évalués avec les prix en vigueur au 1er août 2019.

Résultats Efficacité en conditions idéales : 17 essais randomisés contrôlés (RCT pour *Randomised Controlled Trials*) comprenant 4036 participants ont comparé l'olmésartan à d'autres sartans. L'olmésartan a abaissé la pression sanguine (systolique et diastolique) plus efficacement que le losartan et la pression sanguine diastolique plus efficacement que l'irbésartan. Dans les comparaisons entre l'olmésartan et le valsartan, l'azilsartan, le candésartan et le telmisartan, ainsi qu'entre les combinaisons olmésartan/hydrochlorothiazide et telmisartan/hydrochlorothiazide, les résultats ne présentaient aucune différence significative.

Efficacité en conditions réelles : d'après une étude (Swindle et al.) et dans un sous-échantillon limité (108 567 participants), l'olmésartan a réduit le risque d'un résultat composite sous forme d'effets cardiaques (en particulier insuffisance cardiaque) plus efficacement que le valsartan, le losartan et l'irbésartan. Nous avons mené des analyses statistiques indépendantes avec les données disponibles et n'avons identifié aucune différence significative entre l'olmésartan, le losartan, l'irbésartan et le valsartan.

Innocuité : en ce qui concerne les effets indésirables graves, nous avons analysé 5 RCT (1721 participants) et 12 études de cohorte (> 8 250 000 participants). Les comparaisons ont indiqué des profils de risque similaires pour l'olmésartan et les autres sartans dans les suivis à court terme (RCT) et

les suivis à long terme (études de cohorte). Les résultats concernant l'entérite n'étaient pas constants. Deux des études de cohortes ont suggéré que l'olmésartan était associé à une augmentation du risque d'entéropathie par rapport à d'autres ARB, tandis que deux autres études de cohortes n'ont pas trouvé de différence significative.

De plus, nous avons évalué les données de 22 études à bras unique (67 922 participants), ainsi que les bras à étude unique de 11 RCT (4587 participants) et 8 études de cohorte (125 669 participants). Nous n'avons pas identifié de schémas marquants en ce qui concerne la présence d'effets indésirables graves chez les utilisateurs d'olmésartan.

Rapport coût-efficacité : le rapport coût-efficacité différentiel calculé par patient pour les problèmes cardiaques allait de - 20 000 francs à - 25 000 francs pour l'olmésartan comparé au valsartan, au losartan et à l'irbésartan (perspective de l'assurance maladie, période d'une année). Autrement dit, l'olmésartan était associé à des meilleurs effets et à des coûts moindres pour les problèmes cardiaques. Cependant, l'analyse de sensibilité a montré que les résultats calculés ne sont pas solides.

Impact budgétaire : le budget total net (dépenses pharmaceutiques et consultations ambulatoires) de l'éventuel remplacement de l'olmésartan par d'autres sartans dans les trois scénarios générerait, pour l'assurance maladie, des économies de l'ordre de 4,8 millions de francs dans le scénario 1 et des coûts supplémentaires de 1,3 million de francs dans le scénario 2 et de 2,6 millions dans le scénario 3. Les dépenses pharmaceutiques seules entraîneraient des économies de 7,4 millions dans le scénario 1 et de 1,3 million dans le scénario 2, tandis qu'aucune économie ne serait effectuée dans le scénario 3. Les effets d'un remplacement de l'olmésartan dépendaient fortement de la disponibilité de préparations alternatives au sein des groupes équivalents (prix spécifiques et parts de marchés), ainsi que des dépenses engendrées par les visites médicales supplémentaires au cours du changement de médication.

Questions sociales et éthiques : pour éviter des problèmes d'adhésion aux médicaments, les médecins devraient être informés suffisamment tôt d'un éventuel désengagement, des raisons menant à cette décision et des doses équivalentes et disponibles de sartans alternatifs.

Questions organisationnelles : il serait nécessaire de surveiller qu'aucun problème ne puisse survenir dans l'approvisionnement en produits à base de valsartan à cause d'impuretés de nitrosamines, et si des quantités suffisantes seraient disponibles (particulièrement pour les combinaisons triples), étant donné qu'il s'agit de la seule alternative aux combinaisons triples d'olmésartan.

De plus, les patients pourraient s'attendre à devoir effectuer davantage de visites médicales pendant la première année suivant le changement de médication.

Conclusions L'olmésartan a abaissé la pression sanguine systolique et diastolique plus efficacement que le losartan et la pression sanguine diastolique plus efficacement que l'irbésartan, sans indiquer d'effet statistiquement significatif en comparaison avec le candésartan, le telmisartan, le telmisartan avec diurétiques, l'azilsartan et le valsartan. Les données (de faible qualité) d'une étude de cohorte rétrospective ont indiqué un éventuel avantage de l'olmésartan, par rapport au losartan, à l'irbésartan et au valsartan, pour les résultats à long terme tels que les problèmes cardiaques.

La comparaison des effets négatifs a indiqué des profils de risque similaires pour l'olmésartan et les autres sartans dans les suivis à court terme (RCT) et les suivis à long terme (études de cohorte). En ce qui concerne l'entérite, les résultats de quatre études de cohorte (comparaison entre l'olmésartan et d'autres sartans) étaient inconstants et ne permettaient donc pas de détecter un risque plus élevé pour les utilisateurs d'olmésartan. Bien qu'il s'agisse d'un phénomène rare, les médecins doivent rester vigilant à ce propos.

Les calculs du rapport coût-efficacité n'étaient pas assez solides pour tirer des conclusions universelles quant à l'utilisation de l'olmésartan par rapport à celle du valsartan, du losartan et de l'irbésartan.

L'impact budgétaire d'un remplacement de l'olmésartan dépendait fortement des prix et des parts de marché des préparations alternatives au sein du groupe spécifique d'équivalence, ainsi que des coûts des consultations médicales supplémentaires qu'un changement de médication entraînerait. En conséquence, si les médecins prescrivaient des doses de sartans alternatifs équivalentes à celles de l'olmésartan, il est probable que le remplacement de l'olmésartan entraînerait une hausse des coûts de la santé.

Afin de garder un contrôle sur la pression sanguine après une éventuelle décision de désengagement, les médecins devraient recevoir suffisamment tôt des informations à ce propos et sur la manière de prescrire des doses équivalentes d'autres sartans. Pour éviter des problèmes de disponibilité, la situation actuelle du marché devrait être surveillée, particulièrement en ce qui concerne l'approvisionnement en doubles et triples combinaisons, ainsi que pour d'éventuels rappels futurs de certains produits à base de valsartan.

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Abbreviations and acronyms

ACE inhibitors	Angiotensin-converting enzyme inhibitors
AHRQ	Agency for Healthcare Research and Quality
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
CI	Confidence interval
CHEC	Consensus Health Economic Criteria (CHEC) Checklist
DALYs	Disability adjusted life years
EMA	European Medicines Agency
EPR	Eprosartan
ERP	External reference price
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé
HCTZ	Hydrochlorothiazide (diuretics)
HMOD	Hypertension-mediated organ damage
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (The independent Institute for Quality and Efficiency in Health Care)

IRB	Irbesartan
ISPOR	The International Society for Pharmaeconomics and Outcome Research
KLV	Krankenpflege-Leistungsverordnung (Healthcare Benefits Ordinance)
LOS	Losartan
LS	List of specialities (Spezialitätenliste)
MeSH	Medical Subject Headings
MSAC	Medical Services Advisory Committee (Australian government)
MSD	Merck Sharp & Dohme
N.A.	Not applicable
NICE	National Institute for Health and Care Excellence (UK)
OLM	Olmesartan
PBAC	The Pharmaceutical Benefits Advisory Committee (Australia)
PICO	Population, Intervention, Comparator/Control, Outcome
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
TEL	Telmisartan
US/A	United States (of America)
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 report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytical methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost effectiveness and budget impact as well as legal, social, ethical and organisational issues. The purpose is to inform healthcare policy and decision making to promote an efficient, sustainable, equitable and high-quality healthcare system.

1 Policy question and context

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of olmesartum medoxomilum (OLM for short), a therapy for adult patients with essential hypertension, because its efficacy, effectiveness and safety have been questioned by the applicant santésuisse. One reason for the assessment comparing OLM with other sartans was the suggestion of the transparency committee of the Haute Autorité de Santé (HAS)[1] in France to exclude olmesartan (mono- and combination therapy) from its reimbursement list due to an increased risk of serious enteropathies (diseases of the intestinal tract), an increased risk of hospitalisation for intestinal malabsorption and OLM not demonstrating effects on morbidity and mortality (only on blood pressure reduction). The recommendation from April 2015 became effective on 31 December 2016.

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 HTA phase.

2 Research questions

The central research questions for this report are:

- What are the efficacy, effectiveness and safety of OLM mono- and combination therapy in adult patients with essential hypertension compared with mono- and combination therapy with other available sartans?
- What are the costs and cost effectiveness of OLM mono- and combination therapy in adult patients with essential hypertension compared with mono- and combination therapy with other available sartans? What is the budget impact for the health insurance under the assumption that OLM will be substituted by other available sartans?

3 Medical background

Essential – also called primary or idiopathic – arterial hypertension is defined 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 as well as metabolic risk factors such as obesity and 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 per cent of the world population.[3] Essential hypertension may be asymptomatic for many years and only a minority of affected patients complain about unspecific symptoms, such as morning headaches (cephalea), nausea, tinnitus, shortness of breath (dyspnoea), fatigue or nosebleeds (epistaxis). However, chronic arterial hypertension is associated with premature deaths, increased disability-adjusted life years (DALYs) and cardiovascular complications such as ischaemic heart disease and stroke as well as cognitive impairments.[4-6]

***Diagnosis**:* BP is measured in millimetres of mercury (mmHg) and is expressed as two numbers. 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.[2]

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 pauses in breathing while asleep (sleep apnoea), abnormal narrowing (stenosis) of the renal arteries, a tumour of the adrenal gland tissue and pregnancy- or drug-induced BP elevation, and
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 the European Society of Hypertension (ESH) recommend classifying BP as optimal, normal, high-normal or hypertension grades 1 to 3, see Table 1.[2]

Table 1: Classification of hypertension grades as recommended by the ESC/ESH guidelines

Blood pressure classification	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
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

Source: Williams et al.[2]

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 the disease. The ESC/ESH guidelines provide recommendations on when to initiate antihypertensive drug treatment based on the severity grade of the disease and cardiovascular risk stratification.[2] The Swiss Society of Hypertension[7] adheres to the recommendations published in the ESC/ESH guidelines.

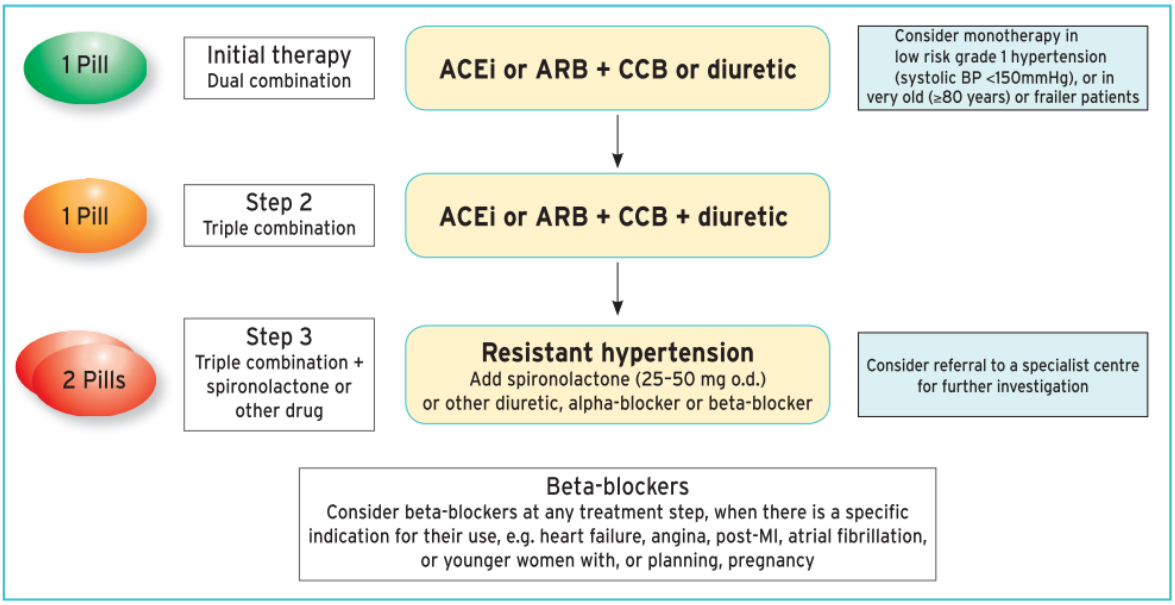
4 Technology

4.1 Technology description

There are five major classes of drugs recommended for antihypertensive pharmacotherapy, including angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE inhibitors), beta blockers, calcium channel blockers (CCBs) and diuretics (hydrochlorothiazide and thiazide-like diuretics, HCTZ).[8 9] ARBs and ACE inhibitors are amongst the most widely used antihypertensive substances worldwide. The core treatment algorithm for "uncomplicated" hypertension, focusing on the five major antihypertensive classes of drugs, is presented in Figure 1 and can be adapted for patients with concomitant coronary artery disease, chronic kidney disease, heart failure and atrial fibrillation.[2]

Combination therapy (two or more pharmaceutical agents in a single pill) is recommended in the current ESC/ESH guidelines for most hypertensive patients because the reduction in the number of pills taken on a daily basis improves adherence and increases the rate of BP control (this recommendation is supported by data from RCTs).[2]

Figure 1: Core drug treatment strategy for uncomplicated hypertension



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; MI = myocardial infarction; o.d. = omni die (every day)

Source: Williams et al.[2]

Sartans: Sartans are ARBs that selectively block the binding of angiotensin II to the AT1 subtype of angiotensin-II 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] Despite the fact that all ARBs share a common mechanism of action, they differ with respect to their pharmacological and dosing profiles.[13]

OLM was developed in 1995 and approved in Switzerland in 2005 as a mono- and combination therapy in patients with essential hypertension.[14] 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 2 weeks of the drug first being administered and reaches its maximum approximately 8 weeks after the start of therapy. Important contraindications for treatment with OLM include pregnancy and biliary obstruction.[15] The most frequently reported adverse events include headaches (cephalea, 7.7%), influenza-like symptoms (4.0%) and vertigo (3.7%). Rare adverse events include sprue-like enteropathy characterised by severe, chronic diarrhoea with significant weight loss, nausea, vomiting, abdominal pain and anaemia.[16]

The recommended starting dose of OLM is 10 mg once daily. In patients whose BP 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 BP is desired, the dose can be increased to a maximum of 40 mg daily or an additional therapy with hydrochlorothiazide (HCTZ) can be prescribed.[16]

4.2 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 HCTZ. Patients whose BP cannot be controlled effectively by first-line pharmaceutical therapy can be prescribed alpha-receptor blockers, spironolactone, centrally acting agents, mineral corticoid receptor antagonists or minoxidil (second-line pharmaceutical therapy).[2 17]

4.3 Regulatory status/provider

Olmetec™ (holder of marketing authorisation: Daiichi Sankyo AG) was approved in 2005. Generic drugs have been available for OLM since 2016.

In the group of sartans (ARBs), eight monoactive substances with 39 different brand names (without differentiation by dosage or package size) have been authorised by the Swiss Agency for Therapeutic Products (Swissmedic) and are reimbursable by the compulsory health insurance (as of 30 July 2019). Alternative sartans for OLM monotherapy are losartan (LOS), eprosartan (EPR), valsartan (VAL), irbesartan (IRB), candesartan (CAN), telmisartan (TEL) and azilsartan (AZI). For details, see Appendix A, Table 20.

In total 13 substances with 56 different brand names (without differentiation by dosage or package size) are available containing ARBs in combination with the diuretic hydrochlorothiazide (HCTZ) or calcium channel blockers (CCBs) in fixed doses.

For combination therapy with HCTZ, OLM, LOS, EPR, VAL, IRB, CAN, TEL and AZI are provided; for OLM combination therapy with CCBs, two substances – VAL with CCBs and TEL with CCBs – are provided. For the OLM triple combination with CCBs and HCTZ, only VAL with CCBs and HCTZ is available (See Appendix A, Table 21).

All pharmaceuticals approved by Swissmedic and listed in the so-called Spezialitätenliste (SL) are reimbursable. The cost share for patients is 10 per cent of the costs in excess of the annual deductible: If the SL contains more than one pharmaceutical with the same substance, co-payment for patients can be up to 20 per cent. The co-payments are normally limited to CHF 700 per year.

Table 2 presents the approved indications for sartans.

Table 2: Overview of the indications* for sartans in Switzerland approved by Swissmedic

ATC code	Substance	Essential hypertension	Heart failure	Diabetic nephropathy	Prevention of stroke	Cardiovascular risk reduction	Following myocardial infarction
C09CA01	LOS	Adults	Yes	Yes	Yes	No	No
C09CA02	EPR	Adults	No	No	No	No	No
C09CA03	VAL	Children, adults	Yes**	No	No	No	Yes
C09CA04	IRB	Adults	No	Yes***	No	No	No
C09CA06	CAN	Children, adults	Yes	No	No	No	No
C09CA07	TEL	Adults	No	No	No	Yes	No
C09CA08	OLM	Adults	No	No	No	No	No
C09CA09	AZI	Adults	No	No	No	No	No

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; EPR = eprosartan; IRB = irbesartan; LOS = losartan; TEL = telmisartan; VAL = valsartan
* According to information for medical professionals (“Fachbeilage”) of the first approved pharmaceutical
** For patients unable to take ACE inhibitors
*** For the treatment of renal disease in patients with hypertension and type II diabetes mellitus with elevated serum creatinine or micro-albuminuria or clinical albuminuria as part of antihypertensive treatment.
Note: Regarding combination preparations in general, the information for medical professionals states that combination preparations should be given if monotherapy is not sufficient.

Source: www.swissmedicinfo.ch as of 30 July 2019

A compilation of national coverage policy for OLM in selected European countries is provided in Table 3. The countries included are those named in Art. 34a KLV (Krankenpflege-Leistungsverordnung, Healthcare Benefits Ordinance) with whom an external reference price (ERP) is determined during the triennial review of all pharmaceuticals included in the Spezialitätenliste (SL) carried out by the Federal Office of Public Health (FOPH).

Table 3: Current national coverage policy for OLM (mono- and combination therapy) in selected European countries

ATC country/substance	C09CA08 OLM	C09DA08 OLM + HCTZ	C09DB02 OLM + CCBs	C09DX03 OLM + CCBs + HCTZ
Austria	Delisted*	Delisted*	Delisted*	Delisted*
Belgium	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Denmark	Reimbursed**	Reimbursed**	Not on market	Not on market
Finland	Reimbursed	Reimbursed	Reimbursed	(Reimbursed)****
France	Delisted***	Delisted***	Delisted***	Delisted***
Germany	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Netherlands	Reimbursed	Reimbursed	Reimbursed	Reimbursed*****
Sweden	Not on market	Not on market	Not on market	Not on market
United Kingdom	Reimbursed	Reimbursed*****	Reimbursed*****	Reimbursed*****

ATC = anatomic therapeutic classification; HCTZ = hydrochlorothiazide; CCBs = calcium channel blockers; OLM = olmesartan
* As of 1 January 2019
** Two manufacturers on the market
*** As of 31 December 2016
**** One manufacturer on the market, only one strength (20/5/12.5 mg) available
***** One manufacturer on the market

Source: Pharmaceutical Pricing Information (PPI) Service (2019), July 2019

5 PICO

Table 4 presents the adapted PICO scheme from the Scoping Report on Olmesartan[18] with specifications on the patient population, interventions and comparators as well as outcome parameters for the domains of efficacy, effectiveness, safety and costs/cost effectiveness.

Table 4: PICO for efficacy/effectiveness/safety/economic aspects

Population	Patients (≥18 years at start of study) with essential (primary) arterial hypertension that requires antihypertensive pharmacotherapy
Intervention	• OLM monotherapy • OLM combination therapy with HCTZ • OLM combination therapy with CCBs • OLM combination therapy with HCTZ and CCBs
Comparators	• All other sartans as monotherapy • All other sartans in combination with HCTZ • All other sartans in combination with CCBs • All other sartans in combination with HCTZ and CCBs
Outcomes	**Domain efficacy/effectiveness** **Surrogate endpoint:** • Reduction in blood pressure **Clinical endpoints:** • 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 • Health-related quality of life • All-cause mortality **Domain safety:** • Adverse events with a severity grade of at least 3 (following the definition of the EUnetHTA guidelines on safety*), including, for example, enteropathies, cardiovascular morbidity and cardiovascular mortality, cerebrovascular morbidity, cerebrovascular mortality • Withdrawals or discontinuations due to adverse events • All-cause mortality **Domain costs/cost effectiveness:** • For systematic literature search: all reported outcome measures (e.g. cost/QALY, cost/life year gained, costs/patient/treatment, costs/defined daily dose…) included.

CCBs = calcium channel blockers; HCTZ = hydrochlorothiazide; OLM = Olmesartan; QALY = quality-adjusted life year

* EUnetHTA guidelines (2015): endpoints used in Relative Effectiveness Assessment – Safety: Adverse Reaction Severity Grade 3: severe or medically significant but not immediately life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care, activities of daily living

Population

The target population consists of adult patients (≥18 years) of any gender and ethnicity with essential hypertension. In this population, co-morbidities such as cardiovascular disease (coronary and cerebrovascular disease, peripheral artery disease, diabetes, dyslipidaemia) or chronic kidney disease are common. Study populations with existing co-morbidities were not excluded from the analyses when the primary target of the study was the treatment of essential hypertension. In summary, co-morbities were not systematically excluded.

Intervention

The interventions under assessment are all OLM mono- and combination preparations (OLM with HCTZ, OLM with CCBs or OLM with HCTZ and CCBs).

Comparator

The above interventions are compared to all other sartans as monotherapy, all other sartans in double combination with HCTZ or CCBs and all other sartans in triple combination with HCTZ and CCBs.

Outcomes

Critical and important outcomes for the domains of efficacy and effectiveness include cardiovascular and cerebrovascular mortality, cardiovascular and cerebrovascular morbidity, health-related quality of life outcomes and all-cause mortality. BP reduction is also taken into account but being a surrogate outcome, it is considered an outcome of low importance.

Outcomes for safety are any adverse event with a severity grade of at least 3, withdrawals due to adverse events and all-cause mortality.

In general, critical and important outcomes for the costs/cost effectiveness domain include costs, cost per quality-adjusted life year (QALY), cost per life year gained, cost per event averted and budget impact.

For effectiveness/efficacy, evidence from direct comparisons (head to head) is included while for the safety domain, evidence from either RCTs (direct comparisons) or observational studies is incorporated. For the latter, prospective and retrospective cohort studies (direct comparisons) and case-control studies as well as single-arm studies or single OLM study arms from RCTs or cohort studies are included to assess the prevalence of adverse events (no comparison group).

6 HTA key questions

To evaluate the technology, the following key questions are addressed covering central HTA domains as designated by the EUnetHTA core model (clinical effectiveness, safety, costs, cost effectiveness, budget impact, legal, social, ethical and organisational aspects):

1. Is OLM effective/efficacious compared with other sartans?
2. Is OLM safe compared with other sartans?
3. What are the costs of OLM?
4. What would the budget impact be if OLM were to be substituted by other sartans?
5. How cost effective is OLM compared with other sartans?
6. Would there be any legal, social or ethical issues if OLM were to be delisted from the reimbursement list?
7. Would there be any organisational issues to consider if OLM were to be delisted from the reimbursement list?

7 Effectiveness, efficacy and safety

7.1 Methodology effectiveness, efficacy and safety

7.1.1 Databases and search strategy

We conducted a systematic literature search in the databases MEDLINE, EMBASE, Cochrane Systematic Reviews, Cochrane Central Register of Controlled Trials and the NHS Economic Evaluation databases from their inception up to June 2019 (including an update of the literature search for the scoping report). The (basic) search was performed for all domains. Search terms included a combination of keywords and medical subject headings (MeSH) relating to the intervention (OLM mono- and combination therapy), disease (essential hypertension) and study type (e.g. randomised controlled trials, cohort studies, case-control studies, economic evaluation, cost analysis). We conducted the search in English and set no time restrictions concerning the year of publication. Both German and English publications were eligible for inclusion. The detailed search strategies are outlined in Appendix B, Table 22 and Table 23.

Table 26 lists the study inclusion and exclusion criteria for each domain (efficacy, effectiveness, safety and the economic domain). For the efficacy domain, we included evidence from RCTs (direct comparisons) with a follow-up of at least 8 weeks (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”). For the effectiveness domain, we included evidence from RCTs as well as observational studies, specifically cohort studies (direct comparisons). For the safety domain, we included evidence from either RCTs (direct comparisons) or observational studies. For the latter, we included prospective and retrospective cohort studies (direct comparisons), case-control studies and single-arm studies or single OLM study arms from RCTs or cohort studies to assess the prevalence of adverse events (no comparison group). In order to identify potential safety concerns, we included studies with a duration of more than 8 weeks (harms that have been suspected of being associated with the use of OLM appear with a long latency period).

The search results were imported into Endnote X8. Two independent reviewers carried out the study selection. Both authors independently reviewed all the records by title and abstract and then by full text. Disagreements were resolved by discussion at each stage of the selection process. Studies were eligible for inclusion if they met the inclusion criteria listed in Appendix B, Table 26.

7.1.2 Other sources

The websites of international organisations including AHRQ, CADTH, EMA, EUnetHTA, FDA, HAS, HTAi, INAHTA, IQWIG, ISPOR, MSAC, NICE, PBAC, RePEc, WHO and ZIN were searched for additional relevant reports. We included information on ongoing clinical trials from the US National Library of Medicine (ClinicalTrials.gov) and EU clinical trial registries. The last search was done on 2 July 2019.

The search results were imported into Endnote X8. Two reviewers carried out the study selection for the domains of efficacy/effectiveness/safety and economy. For the other domains, one reviewer carried out the study selection. In cases of uncertainty, a second reviewer was consulted.

7.1.3 Assessment of quality of evidence

The quality of the clinical studies was evaluated using the GRADE methodology as described in the Cochrane Manual (https://gdt.gradepro.org/app/handbook/handbook.htmlh.9rdbelsnu4iy).

We considered the relative importance of outcomes as follows:

Domain effectiveness/efficacy

- Reduction in BP: low importance
- Cardiovascular morbidity (e.g. myocardial infarction, heart failure, cardiac arrhythmia): critical/important
- Cardiovascular mortality (e.g. sudden heart death): critical/important
- Cerebrovascular morbidity (e.g. transient ischaemic attack, ischaemic stroke, haemorrhagic stroke, hypertensive dementia): critical/important
- Cerebrovascular mortality: critical/important
- Health-related quality of life: critical/important
- All-cause mortality: critical/important

Domain safety

- Adverse events with a severity grade of at least 3 (following the definition of the EUnetHTA guidelines on safety[19]), including, for example, enteropathies, cardiovascular morbidity and cardiovascular mortality, cerebrovascular morbidity, cerebrovascular mortality: critical/Important
- Withdrawals or discontinuations due to adverse events: low importance
- All-cause mortality: critical/important

For details, see Appendix C, Table 28 and Table 29.

7.1.4 Methodology data analysis effectiveness, efficacy and safety

To assess the efficacy/effectiveness of OLM, we focused on patient-relevant endpoints such as cerebro- and cardiovascular morbidity/mortality but also included the surrogate outcome blood pressure. The antihypertensive effect of OLM compared with other sartans is well documented in the literature.[20 21] To verify these findings, we performed our own (meta-)analyses to determine the effect of OLM on BP in comparison with other sartans. Meta-analyses were conducted whenever possible (at least two studies including the same comparator). In general, evidence is presented as the mean difference in BP reduction. Brunner et al.[22] assume a difference of 2 mmHg as a clinically relevant treatment difference. To obtain confidence intervals, we conducted pooled variances of two-sample Welch t-tests.

For the long-term outcomes (reduction in cardiovascular and cerebrovascular events), we calculated he absolute difference in the number of events per 1’000 participants per year comparing OLM with other sartans where available.

To assess the safety profile of OLM, we focused on serious adverse events. Regarding withdrawals, we identified only sparse data as well as inconsistencies in the reporting of this outcome in the studies included. For this reason, we could only perform a rudimentary analysis based on one RCT – Giles 2007[23] – with sufficient data.

For the safety outcomes, the data are presented as the absolute difference in the number of serious adverse events per 1'000 participants per year for direct comparisons (OLM versus another sartan). The results from RCTs were presented with meta-analyses whenever possible (data from at least two RCTs having the same comparator). Data from single-arm studies or single-study arms with OLM treatment were expressed as serious adverse events projected for one year per 1’000 participants. The analysis followed a step-wise approach, initially focusing on study designs yielding higher-quality evidence (lower risk of bias).

7.2 Results effectiveness, efficacy and safety

7.2.1 Evidence base pertaining to effectiveness, efficacy and safety

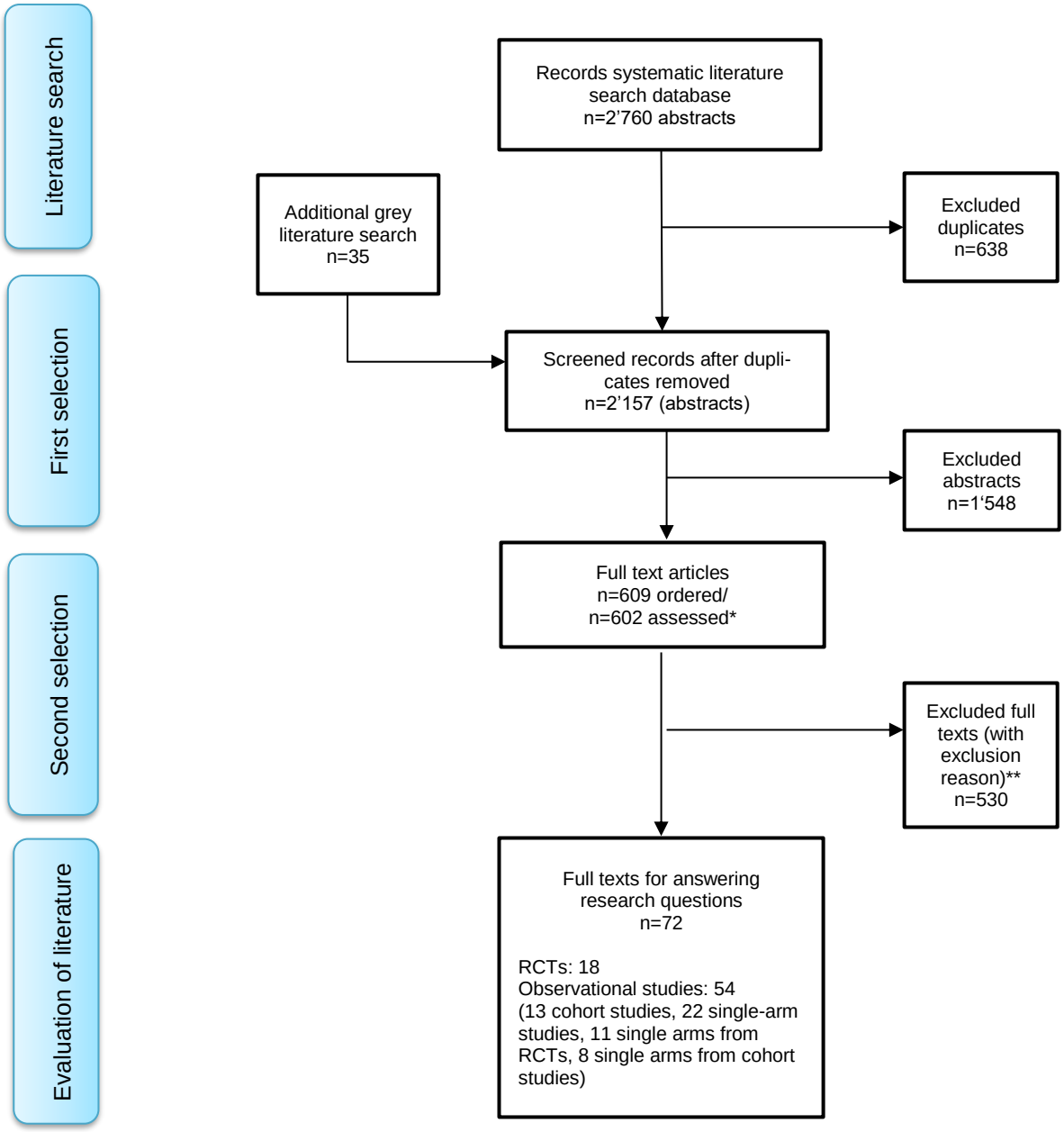
The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).

- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity when using the health technology. Relevant adverse events are those that result in death, are life threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious adverse events) and those that occur repeatedly and the most frequently (highest rate).

7.2.2 PRISMA flow diagram

Figure 2: PRISMA flow diagram for the domains EFF/SAF



EFF = efficacy/effectiveness; n = number; RCT = randomised controlled trial; SAF = safety

* Seven publications[24-30] were not obtainable

** Note: the authors also checked the reference lists of systematic reviews and meta-analyses which had been identified to verify that all relevant primary studies had been included in the current assessment; however, the systematic reviews and meta-analyses themselves were not included.

7.2.3 Evidence table

Overview

In total, we included 72 studies that reported on the effectiveness, efficacy or safety (or any combination of the three) of OLM compared with other sartans. The characteristics (including the references) of the studies included are listed in Table 5 and Table 6. **Seventeen RCTs**[22 23 31-45] (see Table 5) were analysed to assess the effect of OLM on BP compared with other sartans (efficacy). **One retrospective cohort study**[46] but no RCTs investigated the effect of OLM on cerebro- and cardiovascular outcomes compared with other ARBs (effectiveness) from routine data (see Table 5). Regarding comparative safety, we analysed five RCTs[23 38 39 40 47] (**one** RCT that only focused on the safety evaluation and four [23 39 38 40]that were also included in the analysis of BP reduction), **one prospective**[48] and **11 retrospective cohort studies**[49-59] (see Table 6) to assess the absolute risk of serious adverse events for OLM compared with other ARBs. We scanned **22 single-arm studies**[60-81] as well as the single arms (receiving OLM) of **eleven** RCTs[82 83-92] and **eight cohort studies**[93-100] (each with a comparator not defined by the PICO framework applied) for any striking patterns in the occurrence of serious adverse events in OLM users (non-comparative safety) (see Appendix C, Table 30). Due to the lack of (an appropriate) comparison group, the data can only yield descriptive evidence.

Table 5: Study characteristics of comparative effectiveness/efficacy studies

Study/Year	Study design	Country	Population	Sample size OLM vs. comparator(s)*	Intervention	Comparator(s)	Outcome	Statistical validation done by authors	Sponsor/COI
Ball et al. 2001[31]	RCT	Multicentre	HT	158 vs. 152	OLM	LOS	BP	MD	Daiichi Sankyo
Oparil et al. 2001[41]	RCT	USA	HT	145 vs. 433	OLM	IRB, LOS, VAL	BP	MD	NR
Brunner et al. 2003[22]	RCT	Multicentre	HT	312 vs. 323	OLM	CAN	BP	MD	Daiichi Sankyo
Destro et al. 2005[34]	RCT	Italy	HT	52 vs. 55	OLM	VAL	BP	MD	NR
Liau et al. 2005[39]	RCT	Taiwan	HT	49 vs. 57	OLM	LOS	BP	MD	Daiichi Sankyo
Giles et al. 2007[23]	RCT	USA	HT	199 vs. 380	OLM	LOS, VAL	BP	MD	Daiichi Sankyo
Fogari et al. 2008[36]	RCT	Italy	HT	63 vs. 63	OLM	TEL/HCTZ	BP	MD	NR
Tsutamoto et al. 2010[44]	RCT	Japan	HT	25 vs. 25	OLM	CAN	BP	MD	NR
De Luis et al. 2010a[32]	RCT	Spain	HT + obesity	17 vs. 17	OLM	IRB	BP	MD	NR
De Luis et al. 2010b[33]	RCT	Spain	HT + obesity	31 vs. 34	OLM	TEL	BP	MD	NR
CRUSH 2013[35]	RCT	USA	HT	290 vs. 300	OLM	LOS	BP	MD	Daiichi Sankyo
Morii et al. 2012[40]	RCT	Japan	HT	27 vs. 27	OLM	IRB	BP	MD	NR
Ushijima et al. 2015[45]	RCT	Multicentre	HT + DM	12 vs. 11	OLM	VAL	BP	MD	No COI
Kakio et al. 2017[37]	RCT	Japan	HT	40 vs. 44	OLM	AZI	BP	MD	NR
Kalikar et al. 2017[38]	RCT	India	HT	20 vs. 37	OLM	LOS, TEL	BP	MD	No COI
Shiga et al. 2017[43]	RCT	Japan	HT	28 vs. 28	OLM	AZI	BP	MD	Some COI

Study/Year	Study design	Country	Population	Sample size OLM vs. compara-tor(s)*	Interven-tion	Comparator(s)	Outcome	Statistical validation done by authors	Sponsor/COI
Ramesh et al. 2018[42]	RCT	India	HT	46 vs. 44	OLM	TEL/HCTZ	BP	MD	No COI
Swindle et al. 2011[46]	Retrosp. cohort study	USA	HT	21'494 vs. 44'085	OLM	IRB, LOS, VAL	Stroke, MI-IHD surg, MI, heart failure,cardiac event, acute IHD	AD	Daiichi Sankyo

AD = absolute difference; AZI = azilsartan; CAN = candesartan; COI = conflict of interest; BP = blood pressure; DM = diabetes mellitus; HCTZ = hydrochlorothiazide; HT = hypertension; IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MD = mean difference; MI = myocardial infarction; NR = not reported; OLM = olmesartan; RCT = randomised controlled trial; retrosp. = retrospective; surg = surgery; TEL = telmisartan; VAL = valsartan

* Sample size comparators: sum of all comparison groups; if the number of persons was not available, the number was downsampled from person years.

Table 6: Study characteristics of comparative safety studies

Study/Year	Study design	Country	Population	Sample size OLM vs. comparator(s)*	Intervention	Comparator(s)	Outcome	Statistical validation done by authors	Sponsor/COI
Liau et al. 2005[39]	RCT	Taiwan	HT	62 vs. 64	OLM	LOS	SAE	RR	Daiichi Sankyo
Rump et al. 2006[47]	RCT	Europe	HT	315 vs. 314	OLM/HCTZ	LOS/HCTZ	SAE	RR	NR
Giles et al. 2007[23]	RCT	USA	HT	414 vs. 410	OLM	LOS, VAL	SAE	RR	Daiichi Sankyo
Morii et al. 2012[40]	RCT	Japan	HT	31 vs. 31	OLM	IRB	SAE	RR	NR
Kalikar et al. 2017[38]	RCT	India	HT	40 vs. 40	OLM	LOS, TEL	SAE	RR	No COI
Graham et al. 2014[48]	Prosp. cohort study	USA	HT + DM	158'054 vs. 724'673	OLM	Other ARBs**	SAE	RR	No COI
Basson et al. 2015[49]	Retrosp. cohort study	France	HT	434'415 vs. 2'272'304	OLM	Other ARBs**	ENT	RR	French national
De Bortoli et al. 2017[50]	Retrosp. cohort study	Germany, Italy	HT	735'836 vs. 771'806	OLM	CAN, IRB, TEL, VAL	ENT	RR	A Menarini
Dong et al. 2018[51]	Retrosp. cohort study	USA	HT	350'430 vs. 1'504'562	OLM	Other ARBs**	ENT	RR	Some COI
Malfertheiner et al. 2018[54]	Retrosp. cohort study	Germany, Italy	HT	25'591 vs. 104'901	OLM	Other ARBs**	ENT	RR	A Menarini
You et al. 2019[58]	Retrosp. cohort study	Korea	HT	23'610 vs. 76'462	OLM	Other ARBs**	ENT	RR	No COI
Padwal et al. 2014[55]	Retrosp. cohort study	Canada	HT + DM	10'370 vs. 34'815	OLM	VAL, IRB	Mor	RR	No COI
Walker et al. 2014[57]	Retrosp. cohort study	USA	HT	38'750 vs. 72'326	OLM	Other ARBs**	Mor	RR	Daiichi Sankyo
Zhou et al. 2014[59]	Retrosp. cohort study	UK	HT	3'946 vs. 54'653	OLM	Other ARBs**	Mor, SAE	RR	No COI
Khurshid et al. 2012[52]	Retrosp. cohort study	India	HT	6 vs. 17	OLM	TEL	SAE	RR	No COI

Study/Year	Study design	Country	Population	Sample size OLM vs. comparator(s)*	Intervention	Comparator(s)	Outcome	Statistical validation done by authors	Sponsor/COI
Park et al. 2012[56]	Retrosp. cohort study	Korea	HT, hospitalised	397 vs. 1'421	OLM	TEL	SAE	RR	No COI
Lin et al. 2014[53]	Retrosp. cohort study	Taiwan	HT	177'230 vs. 655'017	OLM	CAN, IRB, LOS, TEL, VAL	SAE	RR	No COI

ARB = angiotensin II receptor blocker; COI = conflict of interest; CAN = candesartan; DM = diabetes melitus; ENT = severe enteropathy; HCTZ = hydrochlorothiazide; HT = hypertension; IRB = irbesartan; LOS = losartan; Mor = mortality; NR = not reported; OLM = olmesartan; Prosp. = prospective; RCT= randomised controlled trial; Retrosp. = retrospective; RR = risk ratio; SAE = severe adverse events; TEL = telmisartan; VAL = valsartan

* Sample size comparators: sum of all comparison groups; if the number of persons was not available, the number was downsampled from person years (divided by the average study length in years)

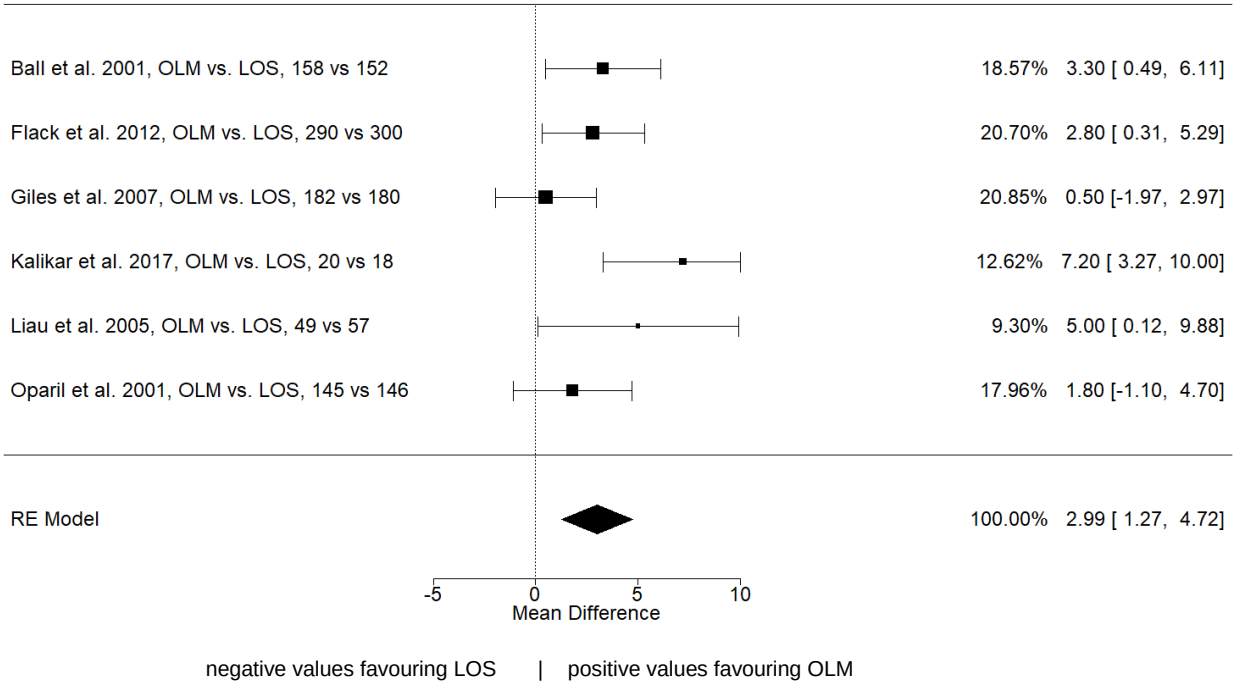
** Compared with other substances not specified, data only available as a group

7.2.4 Findings efficacy

Systolic blood pressure

We found evidence (of moderate quality) that OLM lowered systolic BP more effectively compared with LOS (six RCTs[23 31 35 38 39 41], 844 vs. 853 participants, mean difference 2.99 mmHg, 95% CI, 1.27, 4.72), see Figure 3 and Table 7.

Figure 3: Meta-analysis of systolic blood pressure OLM versus LOS



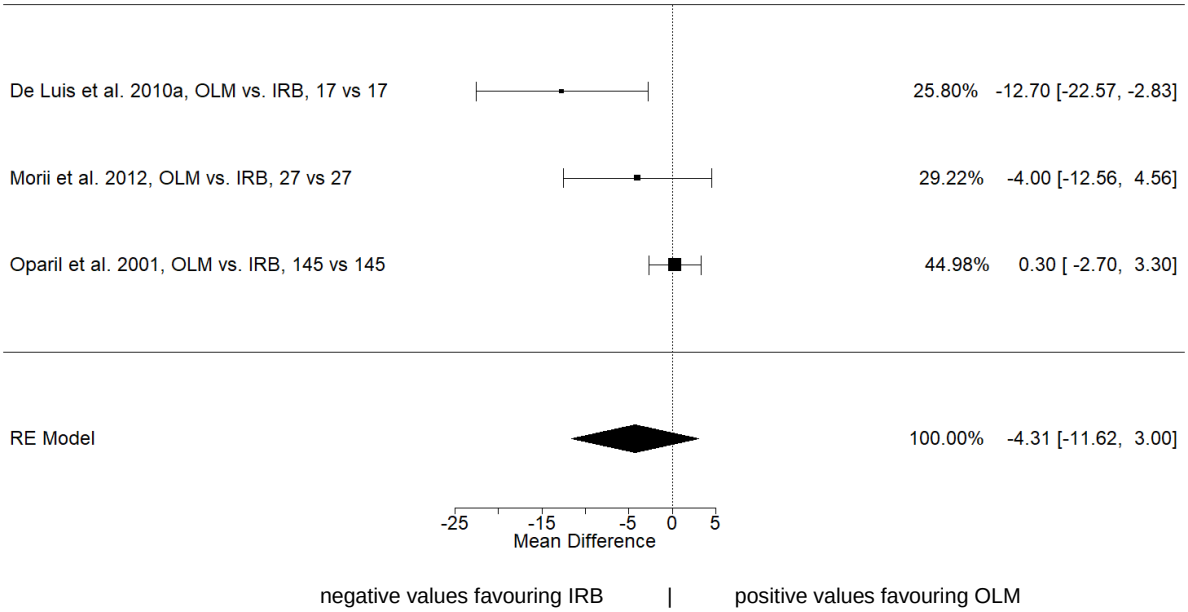
LOS = losartan; OLM = olmesartan
Test for heterogeneity:
Q(df = 5) = 9.4846, p-val = 0.0912

Source: authors' own calculations

In contrast, there was no statistically significant difference between OLM versus CAN,[22 44] OLM versus TEL, [33 38] OLM and HCTZ versus TEL and HCTZ[36 42] or OLM versus AZI[37 43] in terms of systolic BP reduction (OLM vs. CAN: 337 vs. 348 participants in two RCTs, mean difference 0.12 mmHg, 95% CI, -1.76, 2.01; OLM vs. TEL: 51 vs. 53 participants in two RCTs, mean difference 1.05 mmHg, 95% CI, - 7.35, 9.45; OLM and HCTZ vs. TEL and HCTZ: 109 vs. 107 participants in two RCTs, mean difference -2.35 mmHg, 95% CI, -5.98, 10.00; OLM vs. AZI: 68 vs. 72 participants in two RCTs, mean difference - 1.99 mmHg, 95% CI, -6.27, 2.30; see Table 7).

Our meta-analysis found no significant difference (evidence of moderate quality) between OLM versus IRB (three RCTs,[32 40 41] 189 vs. 189 participants, mean difference -4.31 mmHg, 95% CI, -11.62, 3.00, see Figure 4 and Table 7), or OLM versus VAL (four RCTs,[23 34 41 45] 391 vs. 389 participants, mean difference -0.55 mmHg, 95% CI, -3.42, 2.31, see Figure 5 and Table 7) in terms of systolic blood pressure reduction.

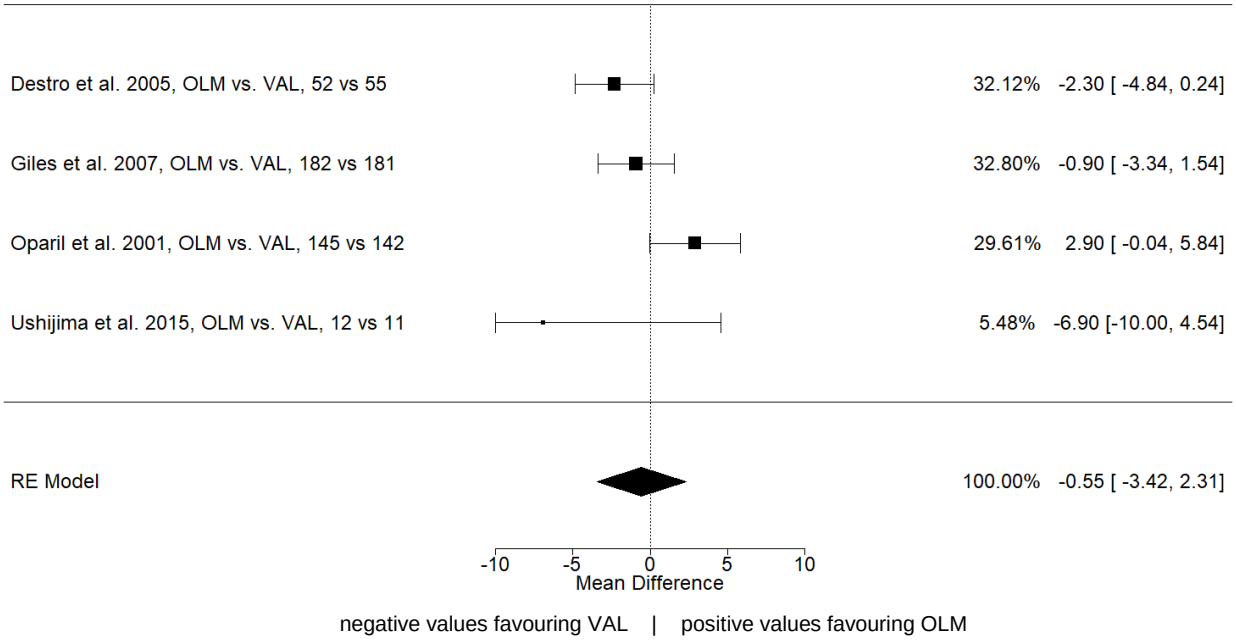
Figure 4: Meta-analysis of systolic blood pressure OLM versus IRB



IRB = irbesartan; OLM = olmesartan
Test for heterogeneity:
Q(df = 2) = 6.5771, p-val = 0.0373

Source: authors' own calculations

Figure 5: Meta-analysis of systolic blood pressure OLM versus VAL



OLM = olmesartan; VAL = valsartan
Test for heterogeneity:
Q(df = 3) = 8.3628, p-val = 0.0391

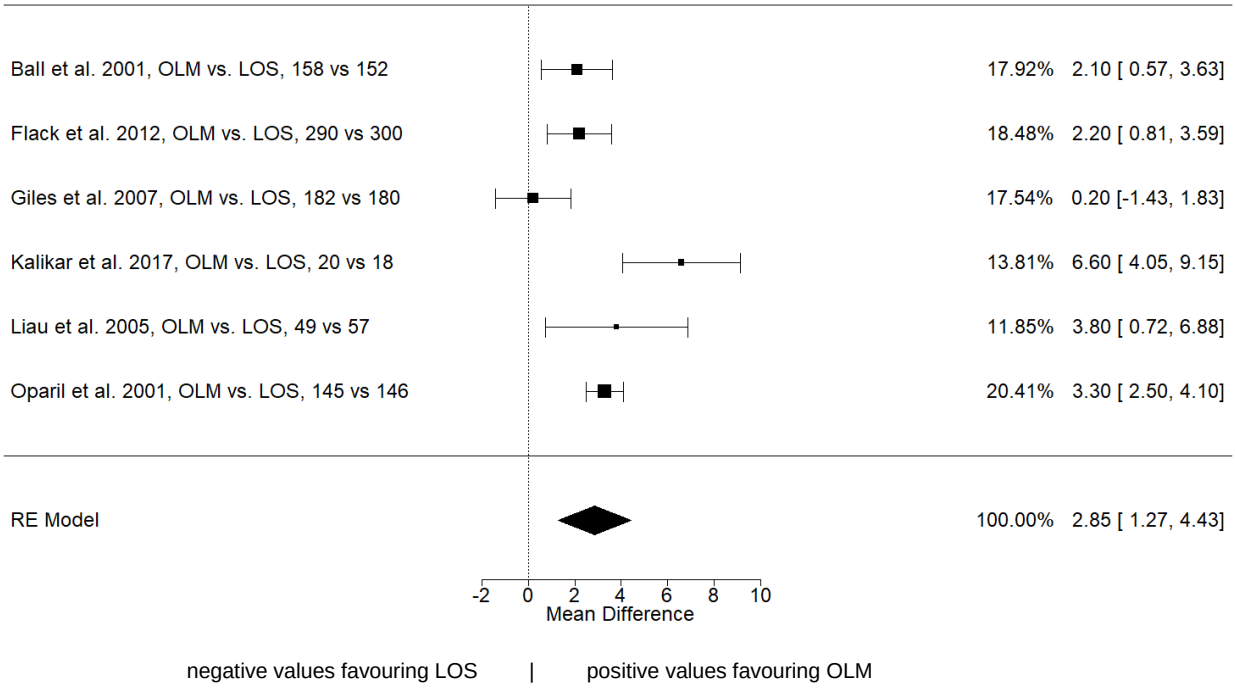
Source: authors' own calculations

The potential risk of bias introduced by limitations like an open-label design in many of the included trials was deemed important enough to downgrade the overall quality of evidence. A detailed assessment of the limitations of each individual study (risk of bias) can be found in Appendix C, Table 28.

Diastolic blood pressure

We found evidence (of moderate quality) that OLM lowered diastolic BP more effectively compared with LOS (six RCTs,[23 31 35 38 39 41] 844 vs. 853 participants, mean difference 2.85 mmHg, 95% CI, 1.27, 4.43, see Figure 6 and Table 7).

Figure 6: Meta-analysis of diastolic blood pressure OLM versus LOS

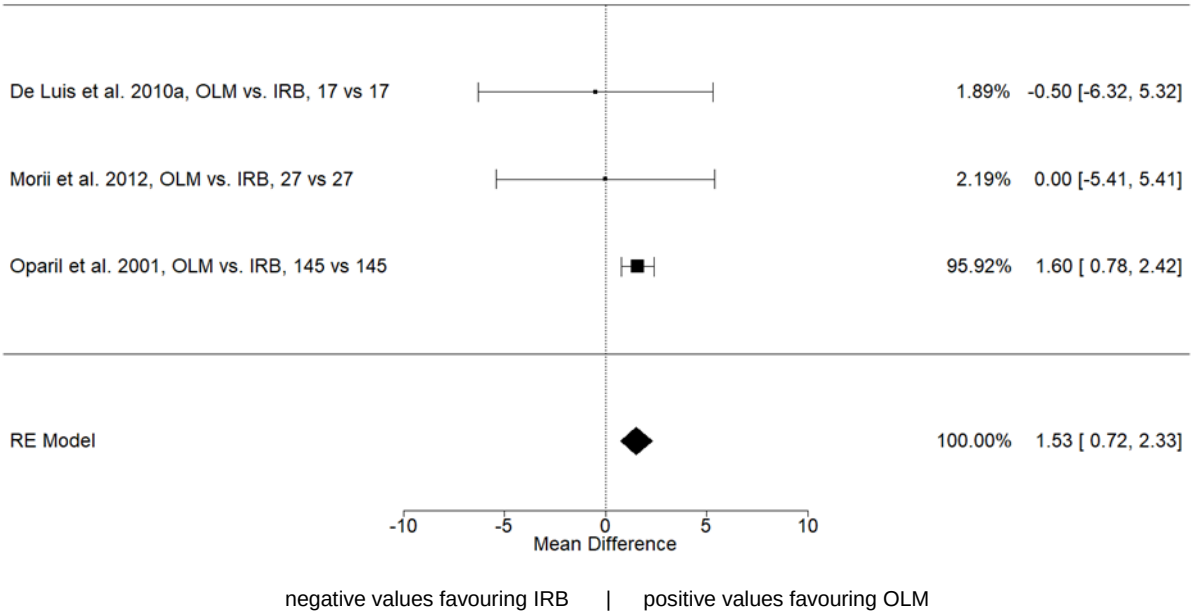


LOS = losartan; OLM = olmesartan
Test for heterogeneity:
Q(df = 5) = 21.7419, p-val = 0.0006

Source: authors' own calculations

Similarly, we found evidence (of moderate quality) that OLM lowered diastolic BP more effectively than IRB (see Figure 7 and Table 7; 189 vs. 189 participants in three RCTs[32 40 41], mean difference 1.53 mmHg, 95% CI, 0.72, 2.33).

Figure 7: Meta-analysis of diastolic blood pressure OLM versus IRB



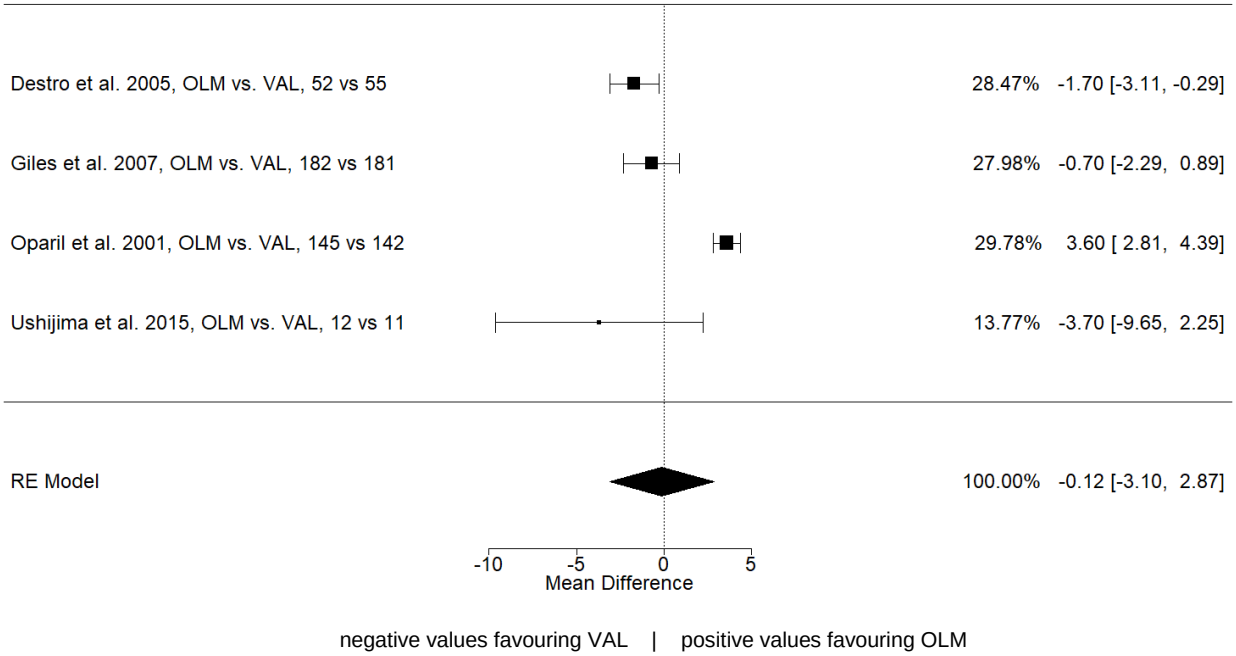
IRB = irbesartan; OLM = olmesartan
Test for heterogeneity:
Q(df = 2) = 0.8035, p-val = 0.6691

Source: authors' own calculations

By contrast, there was no statistically significant difference between OLM versus AZI[37 43] (68 vs. 72 participants in two RCTs, mean difference 0.09 mmHg, 95% CI, -3.01, 3.20), OLM versus TEL[33 38] (51 vs. 53 participants in two RCTs, mean difference -1.04 mmHg, 95% CI, -6.61, 4.53), OLM and HCTZ versus TEL and HCTZ[36 42] (109 vs. 107 participants in two RCTs, mean difference 1.99 mmHg, 95% CI, -2.81, 6.79) and OLM versus CAN[22 44] (337 vs. 348 participants in two RCTs, mean difference 1.19 mmHg, 95% CI, -1.11, 3.49) in terms of diastolic BP reduction (see Table 7).

Our meta-analysis found no significant difference (evidence of moderate quality) between OLM versus VAL in terms of diastolic BP reduction (four RCTs,[23 34 41 45] 391 vs. 389 participants, mean difference -0.12 mmHg, 95% CI, -3.10, 2.86; see Figure 8 and Table 7).

Figure 8: Meta-analysis of diastolic blood pressure OLM versus VAL



OLM = olmesartan; VAL = valsartan
Test for heterogeneity:
Q(df = 3) = 56.4724, p-val <0.0001

Source: authors' own calculations

The potential risk of bias introduced by limitations like an open-label design in many of the included trials was deemed important enough to downgrade the overall quality of evidence. A detailed assessment of the limitations of each individual study (risk of bias) can be found in Appendix C, Table 28.

We identified no RCTs (typically representing studies with preferable analytical conclusiveness) for important or even critical outcomes of OLM versus other ARBs.

Table 7: Synthesis of evidence of comparative efficacy/effectiveness based on randomised controlled trials (GRADE assessment)

Outcome	Comparators	Number of studies	Total number of patients (OLM vs. comparators)	OLM: BP reduction (mean; mmHg)	Comparators: BP reduction (mean; mmHg)	Mean difference [CI lower; CI upper] from meta-analysis*	Quality of evidence (see Table 28)	Importance
Systolic BP	AZI	2 RCTs[37 43]	68 vs. 72	7.5	9.5	-1.99 [-6.27, 2.30]	Moderate	Low importance of outcome BP because BP is known as surrogate parameter**
	CAN	2 RCTs[22 44]	337 vs. 348	11.9	11.6	0.12 [-1.76, 2.01]	Moderate	
	IRB	3 RCTs[32 40 41]	189 vs. 189	11.1	16.6	-4.31 [-11.62, 3.00]	Moderate	
	LOS	6 RCTs[23 31 35 38 39 41]	844 vs. 853	15.1	11.7	2.99 [1.27, 4.72]	Moderate	
	TEL	2 RCTs[33 38]	51 vs. 53	19.4	18.7	1.05 [-7.35, 9.45]	Moderate	
	TEL/HCTZ	2 RCTs[36 42]	109 vs. 107	17.5	15.3	2.35 [-5.98, 10.00]	Moderate	
	VAL	4 RCTs[23 34 41 45]	391 vs. 389	10.8	12.6	-0.55 [-3.42, 2.31]	Moderate	
Diastolic BP	AZI	2 RCTs[37 43]	68 vs. 72	5.0	5.0	0.09 [-3.01, 3.20]	Moderate	Low importance of outcome BP because BP is known as surrogate parameter**
	CAN	2 RCTs[22 44]	337 vs. 348	5.7	2.9	1.19 [-1.11, 3.49]	Moderate	
	IRB	3 RCTs[32 40 41]	189 vs. 189	7.1	6.8	1.53 [0.72, 2.33]	Moderate	
	LOS	6 RCTs[23 31 35 38 39 41]	844 vs. 853	12.1	9.1	2.85 [1.27, 4.43]	Moderate	
	TEL	2 RCTs[33 38]	51 vs. 53	9.6	10.9	-1.04 [-6.61, 4.53]	Moderate	
	TEL/HCTZ	2 RCTs[36 42]	109 vs. 107	9.4	7.5	1.99 [-2.81, 6.79]	Moderate	

Outcome	Comparators	Number of studies	Total number of patients (OLM vs. comparators)	OLM: BP reduction (mean; mmHg)	Comparators: BP reduction (mean; mmHg)	Mean difference [CI lower; CI upper] from meta-analysis*	Quality of evidence (see Table 28)	Importance
	VAL	4 RCTs[23 34 41 45]	391 vs. 389	8.8	10.1	-0.12 [-3.10, 2.86]	Moderate	
Long-term outcomes (see PICO Table 4)	No evidence							

AZI = azilsartan; BP = blood pressure; CI = confidence interval; CAN = candesartan; IRB = irbesartan; LOS = losartan; LOS/HCTZ = losartan/hydrochlorothiazide; N.A. = not applicable; OLM = olmesartan; RCT = randomised controlled trial; TEL = telmisartan; TEL/HCTZ = telmisartan and hydrochlorothiazide; VAL = valsartan

* Pooled variance of two-sample Welch t-test

** GRADE handbook[101]

Source: authors' own calculations

7.2.5 Findings effectiveness

For the long-term outcomes of OLM versus other ARBs, we identified one study[46] applying a retrospective cohort study design with data from US medical and pharmacy claims with a mean follow-up of 2.5 years. No other study evaluated comparable long-term outcomes. Due to the observational study design, we rated the overall quality of evidence as low.

This subsection describes the results from Swindle et al.[46] relating to the absolute difference in the number of events per 1'000 participants per year (Table 8). The largest absolute difference can be observed for cardiac events (a composite measure consisting of heart failure, stroke, myocardial infarction, acute ischemic heart disease diagnosis [other than myocardial infarction] and surgery related to myocardial infarction/ischemic heart disease) and heart failure, meaning a lower event rate for OLM.

The study authors used different analytical strategies. In a limited subsample excluding cases with relevant comorbidities, OLM reduced the risk of the composite outcome of cardiac events (particularly heart failure) more effectively than LOS and IRB in a multivariate analysis. There were no statistically significant differences in the risk of stroke, myocardial infarction or myocardial infarction/ischemic heart disease-related surgery between OLM and other ARBs. However, VAL was associated with a higher adjusted risk of an acute ischemic heart disease event compared with OLM. We used this study as a base for the cost-effectiveness analysis evaluation (Subsection 8) and calculated confidence intervals for the differences in the aforementioned outcomes between the study groups. Using our own statistical analyses, we found no significant differences between OLM, LOS, IRB and VAL in any of the outcomes.

Table 8: Synthesis of evidence of comparative long-term outcomes on efficacy/effectiveness based on one study

Outcome	Compara-tors	Number of studies	Total number of pa-tients (OLM vs. compara-tor)	Events OLM	Events com-parator	Absolute difference (events per 1'000 patients per year)***	Quality of evidence (see Table 29)	Importance of outcome
Acute IHD	IRB	1*	21'494 vs. 5'847	131 / 21'494	49 / 5'847	0.9 (2.4 vs. 3.4)	Low	High
	LOS	1*	21'494 vs. 10'874	131 / 21'494	90 / 10'874	0.9 (2.4 vs. 3.3)		High
	VAL	1*	21'494 vs. 27'364	131 / 21'494	217 / 27'364	0.7 (2.4 vs. 3.2)		High
Cardiac event**	IRB	1*	21'494 vs. 5'847	736 / 21'494	302 / 5'847	7.0 (13.7 vs. 20.7)		High
	LOS	1*	21'494 vs. 10'874	736 / 21'494	603 / 10'874	8.5 (13.7 vs. 22.2)		High
	VAL	1*	21'494 vs. 27'364	736 / 21'494	1'315 / 27'364	5.5 (13.7 vs. 19.2)		High
Heart failure	IRB	1*	21'494 vs. 5'847	373 / 21'494	171 / 5'847	4.8 (6.9 vs. 11.7)		High
	LOS	1*	21'494 vs. 10'874	373 / 21'494	352 / 10'874	6.0 (6.9 vs. 12.9)		High
	VAL	1*	21'494 vs. 27'364	373 / 21'494	741 / 27'364	3.9 (6.9 vs. 10.8)		High
MI	IRB	1*	21'494 vs. 5'847	145 / 21'494	36 / 5'847	-0.2 (2.7 vs. 2.5)		High
	LOS	1*	21'494 vs. 10'874	145 / 21'494	86 / 10'874	0.5 (2.7 vs. 3.2)		High
	VAL	1*	21'494 vs. 27'364	145 / 21'494	204 / 27'364	0.3 (2.7 vs. 3.0)		High
MI-IHD surg	IRB	1*	21'494 vs. 5'847	226 / 21'494	74 / 5'847	0.9 (4.2 vs. 5.1)		High
	LOS	1*	21'494 vs. 10'874	226 / 21'494	123 / 10'874	0.3 (4.2 vs. 4.5)		High
	VAL	1*	21'494 vs. 27'364	226 / 21'494	341 / 27'364	0.8 (4.2 vs. 5.0)		High
Stroke	IRB	1*	21'494 vs. 5'847	172 / 21'494	74 / 5'847	1.9 (3.2 vs. 5.1)		High
	LOS	1*	21'494 vs. 10'874	172 / 21'494	148 / 10'874	2.2 (3.2 vs. 5.4)		High
	VAL	1*	21'494 vs. 27'364	172 / 21'494	308 / 27'364	1.3 (3.2 vs. 4.5)		High

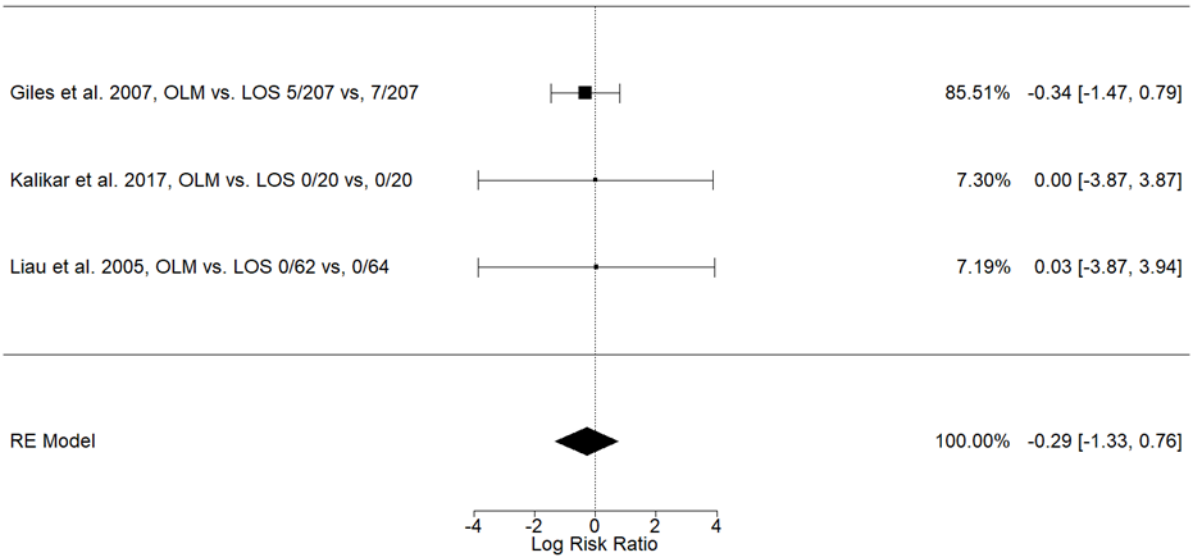
IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; OLM = olmesartan; MI = myocardial infarction; surg = surgery; VAL = valsartan
* Swindle et al.[46] duration of study: 130 weeks
** Composite measure
*** Every single number was rounded separately; deviations may result from internal roundings. For a statistical evaluation of the differences, see economic domain.
Source: authors' own calculations

7.2.6 Findings safety

Evidence of comparative outcomes on safety based on RCTs and cohort studies is summarised in Table 9.

In three RCTs, we found consistent evidence (of low quality) that there was no statistically significant difference in the occurrence of serious adverse events when comparing OLM with LOS[23 38 39] (289 vs. 291 participants, mean study duration 12 weeks, absolute difference in events per 1'000 participants per year -0.29, 95% CI, -1.33, 0.76, Figure 9). The evidence base from RCTs (of moderate quality) to assess the difference in serious adverse events between OLM and IRB,[40] LOS and HTCZ[47] and VAL[23] is scant; however, the absolute event rates are very similar between the groups and so do not hint at safety concerns with OLM.

Figure 9: Comparative safety of OLM versus LOS



LOS = losartan; OLM = olmesartan
Test for heterogeneity:
Q(df = 2) = 0.0546, p-val = 0.9731

Source: authors' own calculations

Similarly, for serious adverse events in cohort studies (with very low quality evidence), we found no striking differences in event rates between OLM and CAN,[53] IRB,[48] LOS,[53] ARBs (not differentiated),[48 59] TEL[52 53 56] and VAL.[53]

Regarding all-cause mortality, we found evidence from three cohort studies[55 57 59] (of very low quality) that show similar mortality rates.

One cohort study[49] (of very low quality) found a significant association for the occurrence of enteropathies when using OLM versus other ARBs. The association became more apparent the longer participants were exposed to OLM. Additionally, Dong et al.[51] (of moderate quality) observed a significantly

higher rate of concomitant diagnoses of diarrhoea and weight loss (hazard ratio 1.22; 95% CI, 1.10-1.36) but not for non-infectious enteropathy (hazard ratio 1.05; 95% CI, 0.99-1.11) for OLM compared with other ARBs (not further distinguished). With regard to the prevention of severe enteritis with weight loss, an important result from this study is that not only OLM but also other ARBs (cited in Dong et al.:[51] "candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, azilsartan, including single and combination products") are associated with adverse events like coeliac disease, concomitant diagnoses of diarrhoea and weight loss or non-infectious enteropathy. In contrast to the higher risk of OLM, two cohort studies[54 58] (of very low quality) report no significant association. Overall, enteropathies were a rare event in all these studies. For the study limitations (risk of bias) of the cohort studies included, see Appendix C, Table 29.

Data from 22 single-arm studies (n=67'922), the single-study arms of 11 RCTs (n=4'587) and 8 cohort studies (n=125'669) show heterogeneous results in terms of the occurrence of serious adverse events in OLM users (see Appendix C, Table 30). Due to differences in study populations and their individual risk profiles, we could not apply a combined assessment across the studies. Even more heterogeneity is present in the included case-control studies (see Appendix C, Table 31). Therefore, and because of the limitations of the study design itself, the results were not used for an interpretation of the safety profile of OLM.

Regarding withdrawals, Giles et al.[23] report that 9 out of 207 participants in the OLM group withdrew from the study, while 4 from the LOS group (207 participants) and 5 from the VAL group (203 participants) withdrew in a 12-week follow-up period.

Table 9: Synthesis of evidence of comparative long-term outcomes on safety based on RCTs/cohort studies

Outcome	Comparators	Number of studies/design/mean duration	Total number of patients (OLM vs. comparator)	Events OLM	Events comparator	Absolute difference (events per 1'000 participants per year)* rounding method*****	Quality of evidence (see Table 28 and Table 29)	Importance of outcome
SAE short term	IRB	1 RCT / 12 weeks[40]	31 vs. 31	0 / 31	0 / 31	0.0 (0.1 vs. 0.1)	Moderate	High
SAE long term	IRB	1 CohSt / 146 weeks[48]	35'446 vs. 120'372	253 / 35'446	1'470 / 120'372	1.8 (2.5 vs. 4.4)	Very low**	High
SAE short term	LOS	3 RCTs / 12 weeks[23 38 39]	289 vs. 291	5 / 289	7 / 291	38.6 (96.9 vs. 135.6)	Low****	High
SAE short term	LOS/HCTZ	1 RCT / 12 weeks[47]	315 vs. 314	8 / 315	8 / 314	0.3 (103.2 vs. 103.5)	Moderate	High
SAE long term	LOS	1 CohSt / 146 weeks[53]	35'446 vs. 175'668	253 / 35'446	1'809 / 175'668	1.1 (2.5 vs. 3.7)	Very low**	High
SAE short term	VAL	1 RCT / 13 weeks[23]	207 vs. 203	5 / 207	7 / 203	41.3 (96.6 vs. 137.9)	Moderate	High
Withdrawals short term	LOS, VAL	1 RCT / 13 weeks[23]	207 vs. 207/203	9/207	4/207, 5/203	79/75 (174 vs. 77, 174 vs. 99)	Moderate	Low
SAE long term	VAL	1 CohSt / 146 weeks[53]	35'446 vs. 255'012	253 / 35'446	3'397 / 255'012	2.2 (2.5 vs. 4.8)	Very low**	High
Mor long term	VAL/IRB/TEL/LOS	1 CohSt / 120 weeks[55]	10'370 vs. 34'815	0 / 10'370	0 / 34'815	0.0 (0.0 vs. 0.0)	Very low**	High
Mor long term	Other ARBs	2 CohSt / 47 weeks[57 59]	42'696 vs. 126'979	85 / 42'696	809 / 126'979	3.8 (10.1 vs. 13.8)	very low**	High
SAE long term	CAN	1 CohSt / 146 weeks[53]	35'446 vs. 54'226	253 / 35'446	392 / 54'226	0.0 (2.5 vs. 2.6)	Very low**	High
SAE long term	Other ARBs	2 CohSt / 103 weeks[48 59]	162'000 vs. 779'326	33'573 / 162'000	182'427 / 779'326	19.1 (89.7 vs. 108.7)	Very low**	High
SAE long term	TEL	3 CohSt / 157 weeks[52 53 56]	35'849 vs. 51'177	256 / 35'849	433 / 51'177	-0.6 (4.3 vs. 3.7)	Very low**	High

Outcome	Comparators	Number of studies/design/mean duration	Total number of patients (OLM vs. comparator)	Events OLM	Events comparator	Absolute difference (events per 1'000 participants per year)* rounding method*****	Quality of evidence (see Table 28 and Table 29)	Importance of outcome
ENT long term	CAN	1 CohSt / 52 weeks[50]	183'959 vs. 214'690	22 / 183'959	33 / 214'690	0.034 (0.120 vs. 0.154)	Very low**	High
ENT long term	IRB	1 CohSt / 52 weeks[50]	183'959 vs. 142'420	22 / 183'959	10 / 142'420	-0.049 (0.120 vs. 0.070)	Very low**	High
ENT long term	Other ARBs	4 CohSt / 72 weeks[49 51 54 58]	834'046 vs. 3'958'229	509 / 834'046	2'011 / 3'958'229	-0.031 (1.987 vs. 1.956)	low***	High
ENT long term	TEL	1 CohSt / 52 weeks[50]	183'959 vs. 131'188	22 / 183'959	16 / 131'188	0.002 (0.120 vs. 0.122)	Very low**	High
ENT long term	VAL	1 CohSt / 52 weeks[50]	183'959 vs. 283'508	22 / 183'959	30 / 283'508	-0.014 (0.120 vs. 0.106)	Very low**	High

ARB = angiotensin II receptor blockers; CAN = candesartan; CohSt = cohort study; ENT = severe enteritis; HCTZ = hydrochlorthiazide; IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; OLM = olmesartan; Mor = mortality; MI = myocardial infarction; surg = surgery; SAE = severe adverse events; TEL = telmisartan; VAL = valsartan

** Only one study, multiple measures including combined measures, retrospective design, possible reporting bias, possible unbalanced study groups

*** One study with moderate quality supports preferable evidence,[51] the others have very low quality of evidence. Across all studies we rate the overall evidence as low

**** Remarkable inconsistency: no events in two studies, few events

***** Every single number was rounded separately; deviations may result from internal roundings.

Source: authors' own calculations

Summary statement on efficacy, effectiveness and safety

Seventeen RCTs evaluated the efficacy of OLM at lowering BP versus other ARBs. OLM lowered (systolic and diastolic) BP more effectively compared with LOS, and diastolic BP more effectively compared with IRB. For OLM versus VAL, AZI, CAN and TEL as well as OLM and HCTZ versus TEL and HCTZ, the results did not differ significantly. Overall, the differences in the effect on BP between different ARBs were small (usually below 2 mmHg). No RCTs assessed critical/important outcomes such as cardiovascular and cerebrovascular morbidity and mortality.

Based on one study of routine (real world) data, the differences in effectiveness in terms of absolute numbers between OLM and other ARBs (VAL, LOS and IRB) were most striking for cardiac events (composite outcome) and heart failure, showing a beneficial effect for OLM. In terms of the relative risk, we could not confirm the findings of Swindle et al.,[46] who reported that OLM use lowered the risk of cardiac events (composite outcome) more effectively compared with other sartans (see Subsection 8.1.)

The comparisons regarding severe adverse events indicate similar risk profiles for OLM compared with other sartans in short-term follow-up (based on the RCTs) and in the long-term follow-up (based on the cohort studies).

In terms of safety, the data from two cohort studies suggest that OLM is associated with a (more or less clearly defined) increased risk of enteropathies compared with other ARBs (but also indicate that not only OLM is associated with a risk of enteropathies) while two other cohort studies found no significant difference. The absolute risk (by different manifestations) is very small (between 0.05 and 2 events per 1'000 participants per year).

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8 Costs, cost effectiveness and budget impact

8.1 Methodology costs, cost effectiveness and budget impact

8.1.1 Databases and search strategy

We conducted a systematic literature search (see Subsection 7.1.1) to retrieve relevant economic studies. The results are presented in Subsection 8.2.2 and Appendix D, Table 32.

8.1.2 Other sources

See Subsection 7.1.2. In addition, to identify cost and quantity data relevant for the calculation for Switzerland, a manual literature search was done. Furthermore, the FOPH was consulted and provided relevant information and data.

8.1.3 Assessment of quality of evidence

The quality of the economic studies retrieved from the systematic literature search was evaluated by applying the Consensus Health Economic Criteria (CHEC) Checklist.[102] For details on quality assessment, see Appendix E, Subsection 14.5.

8.1.4 Methodology costs, cost efffectiveness and budget impact

Cost effectiveness

Estimating the effects

Based on the studies we identified in the literature search (see also Subsection 8.2.2), we did not find a robust and reliable economic model to evaluate the cost effectiveness of OLM. There was a lack of prospective comparative studies analysing adequate efficacy outcomes (that is, outcomes other than surrogate parameters, like a reduction of BP). Therefore, the retrospective observational study by Swindle et al.[46] was used to estimate the clinical effects of OLM, meaning that the evidence base for estimating the clinical effects is low (for further details, see also Subsection 7.2).

The effects we used from Swindle et al.[46] are the effects of OLM on cardiac events compared with treatment using VAL, LOS and IRB. Cardiac events is a composite of different components including myocardial infarction, stroke, heart failure and ischemic heart disease. These individual cardiac events were also used for our effect estimation.

The effects in Swindle et al.[46] are given as the number and proportion of patients with at least one event (meaning that the composite outcome “cardiac event” is not the sum of its components). However, the study by Swindle et al.[46] only presented the numbers of cardiac events for each treatment group (OLM,

VAL, LOS, and IRB) at the end of follow-up (meaning that there was no before and after comparison). Furthermore, the results of Swindle et al.[46] did not show confidence intervals for the limited study sample (=population without pre-existing conditions or risk factors); neither is the original study sample available. Therefore, to increase the comparability between the event rates of the treatment groups and to estimate their variation (by gaining confidence intervals), the results of the limited study sample were bootstrapped in combination with the empirical Bayes methodology.[a]

Estimating the costs

The costs considered in the economic model cover direct treatment costs for the composite measure of cardiac events including all its components (myocardial infarction, stroke, heart failure and ischemic heart disease) and the costs for treatment with the individual sartan for one year (OLM, VAL, LOS and IRB).

The costs for cardiac events and their related components (see "*Estimating the effects*" above) were taken from Brändle et al.[103] and converted into Swiss Francs (CHF) for the year 2018. For the cost conversion, the online tool of the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) was used (implied inflation factor: 1.0337).[104] The event costs included the costs for fatal events (considering, for instance, emergency physicians, ambulance transport and hospitalisation) and non-fatal events (considering, for instance, inpatient treatment, rehabilitation and outpatient treatment), as well as for maintenance (considering, for instance, phsyician visits). Brändle et al.[103] was identified as the only comprehensive data source that considered comparable treatment costs for the outpatient and inpatient sector due to cardiac events.[b]

The costs per year for treatment with each individual sartan were based on data from Swiss healthcare insurances and the Spezialiltätenliste (SL).[105,106]

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[a] Bootstrapping is a computing method intended to simulate virtual data when too few observations or repetitions of an experiment are available for the law of large numbers to apply. The original method draws repetitively from the original sample and data, creating new virtual samples in the process. Bootstrapping with the empirical Bayes methodology introduces a virtual prior distribution to the model which is derived from the observed proportions reported in the paper by Swindle et al. This allows the number of events occurring per 100'000 patients to be simulated for 50'000 virtual studies. In this way, we obtained an approximation for the differences in the number of events between the different drugs and also for the variation in these observations. This corrects for the different sizes of patient populations in the original studies as well as for the lack of other studies to combine information with.

[b] Even though we could have used more recent data (e.g. Swiss DRG data), the use of the data from Brändle et al. was considered a pragmatic approach to obtaining comprehensive treatment costs that occur in the outpatient and inpatient sector.

Calculating cost effectiveness

Cost effectiveness was calculated in two ways:

- *Costs per one more event averted* by OLM, compared with VAL, LOS and IRB (comprising cardiac events in general, myocardial infarction, stroke, heart failure and ischemic heart disease),
- A crude *incremental cost-effectiveness ratio* of the cardiac events difference after treatment with OLM compared with VAL, LOS and IRB.[c]

Cost perspective, time frame and discounting

The cost calculations (in CHF 2018) were performed from the perspective of the public health insurance (public healthcare payer) and covered only direct treatment costs for the pharmaceutical and for cardiac events (as stated above). Thus, potential co-payments by patients, which might reduce the costs for the healthcare payer, were not considered.

The calculations were performed for a time frame of 1 year (and per patient).[d] Thus, discounting of the costs was not applied. In Swindle et al. the patients in the limited study sample were followed up for at least 1 year (mean 2.5 years).[46]

Sensitivity analysis

To control for the uncertainty of the calculated results, we applied two univariate sensitivity analyses for an optimistic and pessimistic scenario respectively. However, the sensitivity analysis was applied exclusively to the ICER results (an interpretation of the sensitivity analysis of the costs per event averted would not be useful because the costs of harming patients or “negative” costs would occur due to the above-mentioned issue of the wide confidence intervals). An overview of the scenarios of the sensitivity analysis is shown in Table 10.

[c] Instead of QALYs, the rate of cardiac events and the corresponding components were used for estimating the incremental effects.

[d] Due to the restricted clinical data from Swindle et al. which the calculations were based on, it was considered prudent to choose the short time frame of 1 year.

Scenario A: To this end, the lower and upper confidence intervals of the bootstrapping results of the effect differences between OLM and VAL/LOS/IRB were considered for the calculations. It was assumed that variations in the clinical effects would have the greatest impact on the results.[e]

Scenario B: Additionally, to analyse a potential effect of the costs on the results, the event costs associated were varied. Therefore, these costs - including the costs for fatal and non-fatal events as well as for maintenance - were varied (the costs for the treatment by the individual sartans was kept constant). It was assumed that the event costs could vary by 25 per cent in each direction. To picture an optimistic scenario, 25 per cent lower event costs of OLM were contrasted to 25 per cent higher event costs of VAL/LOS/IRB. To picture a pessimistic scenario, 25 per cent higher event costs of OLM were contrasted to 25 per cent lower event costs of VAL/LOS/IRB.

Table 10: Scenarios for sensitivity analysis

	Scenario A	Scenario B
Optimistic	High effect OLM, low effect VAL/LOS/IRB	25% lower event costs OLM, 25% higher event costs VAL/LOS/IRB
Pessimistic	Low effect OLM, high effect VAL/LOS/IRB	25% higher event costs OLM, 25% lower event costs VAL/LOS/IRB

IRB = irbesartan; LOS = losartan; OLM = olmesartan; VAL = valsartan

Source: authors' own calculations

Budget impact analysis

Assuming that OLM would be substituted by other pharmaceuticals in the sartan group, we estimated the likely effects on the Swiss healthcare budget.

The FOPH provided data on the number of pharmaceutical packs, the cost per pack and the associated health insurance expenditure within the sartan group at individual product level (Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]). The last available year with complete data is 2018. The SL (Source: www.spezialitätenliste.ch as of 30 July 2019) was consulted for current prices. The number of and costs for additional outpatient visits due to a change in therapy were taken from the literature (Matter-Walstra et al.[107] and Signorovitch et al.[108]).

The costs per pack were calculated on the basis of data on pharmaceutical expenditure and the number of packs reimbursed in 2018, the available pharmaceutical data base covers both the out- and inpatient sector.[105] The average costs thus determined were compared with prices in the SL; there were only

[e] When comparing the upper and lower bounds of the confidence intervals of the effects on the event rate for OLM and VAL/LOS/IRB, OLM no long shows any superiority (e.g. the rate of cardiac events with OLM is higher than with VAL/LOS/IRB). This fact was considered sufficient to demonstrate the uncertainty of the results of the economic analysis.

minor differences between costs per pack and price per speciality in the SL due to possible discounts in the inpatient sector. In addition to pharmaceutical expenditures, the costs for additional visits in the course of switching from OLM to other sartans were included in the budget impact analysis.

The three scenarios mentioned below represent a range of possible budget impacts.

To estimate the implications of a potential substitution of OLM on the Swiss healthcare budget, the allocation method was used. Three scenarios were simulated.

Scenario 1: OLM mono-preparations substituted by mono-preparations of alternative sartans, OLM combination preparations substituted by combination preparations of alternative sartans, number of packages prescribed in 2018 valued with costs per pack in 2018

In Scenario 1, the number of OLM preparations to be substituted was allocated to the other sartans separately for mono- and combination preparations. The market share of packs of alternative sartan preparations was used as the redistribution key. The assumption of redistribution according to the corresponding market share of the alternative preparations was made on the basis of experiences in Austria (for details, see Appendix B, Table 27), where, after delisting OLM from the reimbursement list, it became apparent that the prescriptions were not distributed equally amongst the alternative sartans. Instead, those preparations with a previously higher market share recorded a higher increase in prescriptions than those with a lower market share (i.e. a trend towards the market leaders). The calculation base for determining the new market share of the alternative sartans was the total number of packs of mono- (2018: 1’155’282 packs) and combination preparations (2018: 221’001 packs) which were reimbursed in Switzerland in 2018 (see Appendix D, Table 34).

Table 11 illustrates the allocation method performed using a fictitious example.

Table 11: Fictitious example of the allocation method with a distribution key: market share

	Before allocation				After allocation				
Product	**Packs**	**Pharm. expenditure**	**Cost/ pack Ø**	**Market share packs**	**New market share packs***	**Increase packs****	**Packs total*****	**Pharm. expenditure********	**Budget impact*********
	No.	**in CHF**	**in CHF**	**in %**	**in %**	**No.**	**No.**	**in CHF**	**in CHF**
A	58	6'146.00	105.97	16.16	21.64	19.69	77.69	8'232.81	2'086.81
B	26	2'495.00	95.96	7.24	9.70	8.83	34.83	3'342.28	847.28
C	91	6'584.00	72.35	25.35	0%	0	0	0	-6'584.00
E	184	9'616.00	52.26	51.25	68.66	62.48	246.48	12'881.04	3'265,04
Total	359	24'841.00	-	100.00	100.00	91.00	359.00	24'456.13	-384.87

pharm. = pharmaceutical
* New market share base: total packs – packs C (to be allocated) = 359 – 91 = 268 packs
New market share after allocation: packs/268 = 58/268; for A = 21.64%
** Increase in packs after allocation: packs C × new market share = 91 × 21.64% = 19.69 packs more for A
*** Total packs after allocation: packs before allocation + increase in packs: 58 + 19.69 = 77.69 packs for A
**** Pharm. expenditure after allocation: total packs after allocation × Ø cost/pack = 77.69 × 105.97 = 8'232.81 for A
*****Budget impact: pharm. expenditure after allocation – pharm. expenditure before allocation; 8'232.81 – 6'146 CHF = 2'086.81 CHF increase for A

Source: authors' own calculations

The costs for additional physician visits which would result from switching from OLM to another sartan were also taken into account. The assumption and data for additional visits was based on the study by Signorovitch et al. 2010. The authors assessed the effects of switching from valsartan to any other ARB (mainly generics) in the United States and concluded that 19.1 additional outpatient visits per 100 patients were recorded (=0.191 per patient). Furthermore the ESC/ESH Guidelines[2] state that "after initiation of antihypertensive drug therapy, it is important to review the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects until BP is under control, the frequency of review will depend on the severity of hypertension". The additional visits only relate to the year in which the medication was changed.

The budget impact results from the comparison of health insurance expenditure for pharmaceuticals in the group of sartans in 2018 with new pharmaceutical expenditure after the re-allocation of OLM and costs for additional physician visits for patients in the year of change.

Scenario 2: OLM mono-preparation substituted by equivalent doses of mono-preparations of alternative sartans, OLM combination preparations substituted by equivalent doses of combination preparations of alternative sartans, number of packages prescribed in 2018 valued with costs per pack in 2018

Scenario 2 considers the doses of alternative drugs equivalent to OLM. An equivalent dose is defined as the dose at which a mean reduction in diastolic BP of 8-16 mmHg (in sitting position) is achieved in

patients with stages I to II of hypertension.[109] Physicians should consider equivalent doses when switching from OLM to other sartans.

Firstly, the sartan preparations were grouped with regard to their equivalent dose for OLM. For example 20 mg OLM are equivalent to 80 mg VAL, 40 mg AZI, 8 mg CAN, 600 mg EPR, 150 mg IRB, 50 mg LOS or 40 mg TEL. These alternative ARB doses form the equivalence group for OLM 20 mg. For details on the equivalence groups, see the compilation published in the German Apothekerzeitung[110] (Appendix D, Table 32).

Within the equivalence groups, the OLM preparations were allocated to the equivalent alternative sartans according to their market share (measured in packs) as in Scenario 1. However, in contrast to Scenario 1, the basis for determining the new market share of packs was the total number of packs in the specific equivalence group and not the total number of reimbursed packs of mono- or combination preparations as in Scenario 1. The market shares and costs of the alternative sartans within the narrowly defined equivalence groups used in Scenario 2 might differ from those assumed in Scenario 1. Therefore, Scenario 2 might result in a different budget impact estimate than Scenario 1.

The new number of packs of alternative sartarns after re-allocation of OLM were also valued with the costs per pack in 2018 as in Scenario 1. The costs for additional physician visits were the same as in Scenario 1. Scenario 2 represents a more appropriate prescribing procedure from a medical point of view.

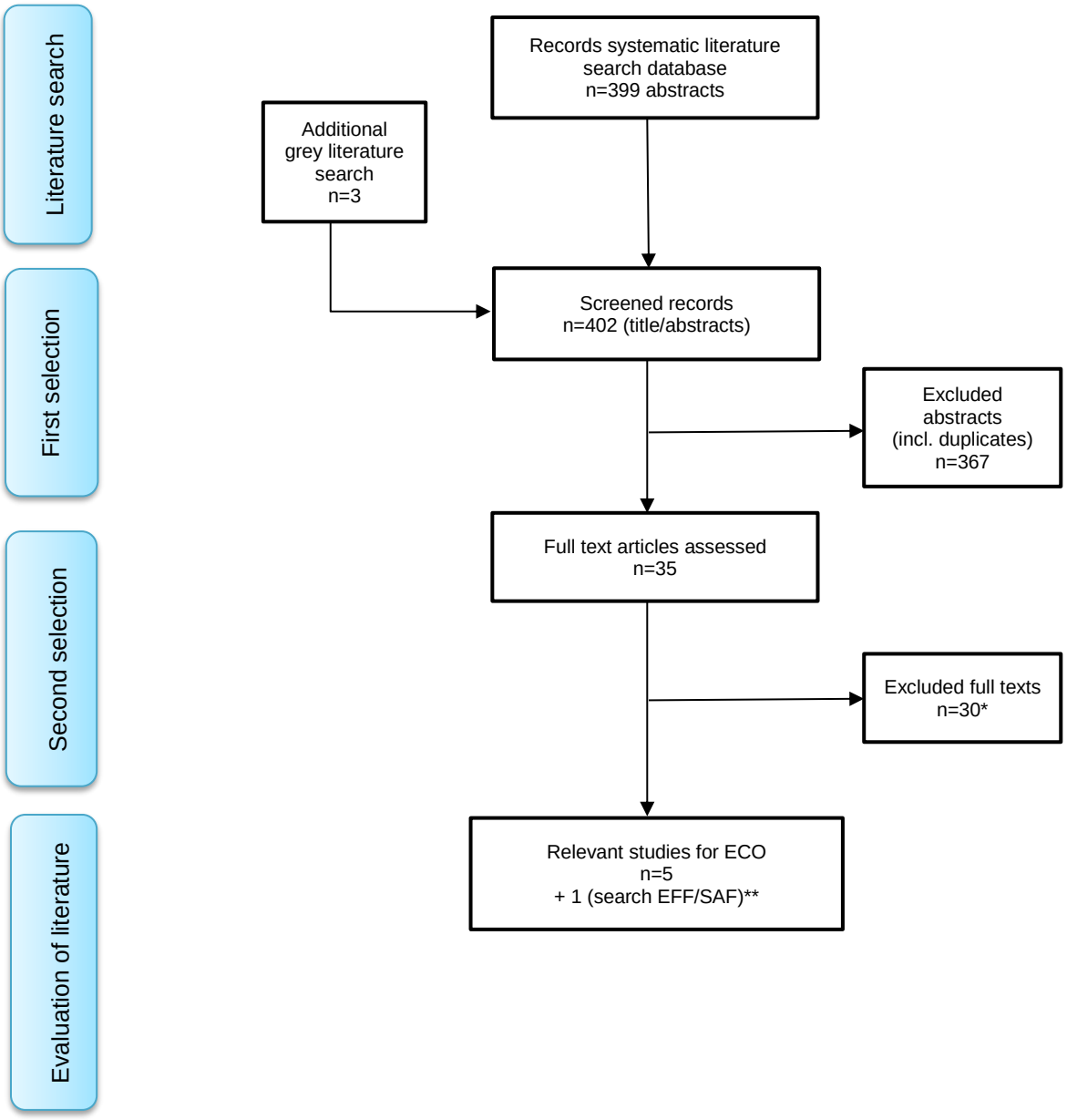
Scenario 3: OLM mono-preparation substituted by equivalent doses of mono-preparations of alternative sartans, OLM combination preparations substituted by equivalent doses of combination preparations of alternative sartans, number of packages prescribed in 2018 valued with prices as of 1 August 2019.

Scenario 3 is like Scenario 2 except that the number of packs from 2018 are valued with the current prices according to the SL[106] as of 1 August 2019. The scenario is intended to illustrate the effects of any price changes that may have taken place in 2019.

8.2 Results costs, cost effectiveness and budget impact

8.2.1 PRISMA flow diagram

Figure 10: PRISMA flow diagram for the domain ECO



ECO = costs/cost effectiveness; EFF = efficacy/effectiveness; SAF = safety; n = number
* With exclusion reason
** One additional study (Swindle et al.)[46] which is also relevant for ECO and was already included in EFF/SAF

8.2.2 Evidence table

The systematic literature search for the ECO domain retrieved five relevant studies[111-115] and one additional study[46] which had already been included in the EFF/SAF domain. The characteristics and results of the six studies are presented in Appendix D, Table 33. Two studies (Boersma et al.[112] and Simons[115]) assessed the cost effectiveness of OLM, LOS, VAL and IRB (monotherapy) for the treatment of hypertension using clinical trial data on their BP lowering effects taken from Oparil et al.[41] and the authors stated that they extrapolated cardiovascular events based on the results of the Framingham Heart Study.

Belsey et al.[116] conducted a cost-effectiveness model using either OLM or CAN (monotherapy) for a cohort of patients with moderate hypertension; effect data were taken from the clinical trial data (indirect comparisons). Miller et al.[117] compared OLM, LOS, VAL and IRB (mono- and combination therapy with HCTZ) in 1'600 randomly selected patients. The effectiveness was assessed by medical chart data and costs were based on administrative claims data (real world).

Mazza et al.[113] compared OLM, CAN, IRB, LOS, TEL and VAL (mono- and fixed-dose combinations with HCTZ). The data on effectiveness were based on a retrospective cross-sectional study with 114 patients (small sample size).

Based on a large retrospective observational study (65'579 patients with hypertension), long-term clinical outcomes (e.g. heart failure, stroke) and healthcare costs for OLM, LOS, VAL and IRB (mono- and HCTZ combination) are reported by Swindle et al.[46]

Three out of the six studies were conducted in the USA and the other three in the Netherlands, the United Kingdom and Italy.

The outcomes of the six studies cannot be compared with each other due to the different outcome parameters presented (cost per patient reaching BP goal, healthcare costs, net costs per cardiovascular complication, treatment costs per patients, etc.). However, in five out of the six economic studies, OLM performed better than the comparators. Just one study[113] concluded that the "treatment of BP with CAN appeared to be the most favourable option". Of note: The other five studies were sponsored by the marketing authorisation holder of OLM.

The body of evidence presented in the six studies is moderate and of low to moderate quality due to heterogeneity in terms of study designs, outcomes, transparency and individual study quality.

After reviewing the studies described above, a further analysis of the results was not deemed appropriate, firstly because the outcomes and study designs presented are too heterogeneous and secondly because the cost data used are already outdated and, moreover, not applicable to Switzerland.

8.2.3 Findings costs

In 2018 the health insurances reimbursed a total of 2.4 million packs of ARBs resulting in expenditures of around CHF 173 million. The average cost per pack (aggregated by substance class) was CHF 56.8 for mono-preparations and CHF 85.7 for combination preparations. Within the group of mono-preparations, EPR followed by AZI and then OLM had the highest average cost per pack in 2018. Within the sartan-HCTZ combination preparations, EPR followed by TEL and AZI combination preparations showed the highest costs per pack. Within the sartan-CCB combination preparations, the average costs per pack for VAL and TEL combination preparations were higher than for OLM combination preparations. In the group of triple combinations with a sartan, HCTZ and CCBs, only VAL and OLM combination preparations are available, the average cost per pack for the triple combination being slightly lower for the OLM combination preparation. For details, see Appendix D, Table 34.

8.2.4 Findings cost effectiveness

The calculations in this section are based on limited clinical evidence from one single retrospective observational study by Swindle et al.[46] and are therefore purely explorative. Moreover, the costs considered in the economic model cover direct treatment costs for the composite measure of cardiac events (including all its components) extracted from Brändle et al.[103] and the costs for treatment with the individual sartan for one year (based on data from Swiss healthcare insurances and the Spezialiltätenliste SL[105,106]). Furthermore, in this section the results are rounded to two decimal places, whereas for the calculations in the model no rounding was applied.

Please note that "cardiac event" is a composite outcome measure comprising the following components: myocardial infarction *(MI), stroke, heart failure and* ischemic heart disease (*IHD). Since a cardiac event can comprise one or all of these components, the numbers, probabilities or costs of a cardiac event are not necessarily the sum of these components (for further explanations, see Subsection 8.1.4.).*

Cost supplemental data can be found in Appendix D, Table 35, Table 36, Table 37.

Effect estimation

The calculations to estimate the effects were based on the probability of the occurrence of cardiac events, including MI, stroke, heart failure and IHD (see Table 12). For example, within a time frame of at least one year, an MI occurred in 0.6 per cent of the patients and a cardiac event (composite outcome) occurred in 3.25 per cent of the patients treated with OLM.

Table 12: Probability of a cardiac event per patient (within at least one year)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM	0.60%	0.73%	1.64%	0.54%	**3.25%**
VAL	0.68%	1.05%	2.58%	0.72%	**4.54%**
LOS	0.72%	1.28%	3.08%	0.76%	**5.20%**
IRB	0.55%	1.19%	2.77%	0.77%	**4.85%**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan

Source: authors' own bootstrapping results based on Swindle et al.[46] (limited study sample)

The estimation of the incremental effect of OLM versus VAL, LOS and IRB was performed separately using the above-mentioned bootstrapping method (see Table 13).[f] The data for the confidence intervals can be found in Table 36 and Table 37 in Appendix D. In general, the rate of a cardiac event was mainly lower for OLM compared with VAL, LOS and IRB.

Table 13: Incremental effect (difference in probability of a cardiac event per patient)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM vs. VAL	0.08%	0.31%	0.91%	0.16%	**1.27%**
OLM vs. LOS	0.11%	0.53%	1.42%	0.21%	**1.93%**
OLM vs. IRB	-0.04%	0.45%	1.11%	0.22%	**1.60%**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan; VAL = valsartan

* A negative number means that the effect of OLM was lower, compared with the comparator.

Source: authors' own bootstrapping, effects based on Swindle et al.[46] (limited study sample)

Cost estimation

The cost calculations were based on the utilisation data of the individual pharmaceuticals to gain the pharmaceutical treatment costs per patient for the individual sartans (see Table 14). Overall, the highest turnover per year was for VAL as the greatest number of patients was treated with VAL. The second highest turnover per year occured for OLM, which also had the highest costs per patient. The lowest costs per patient occurred with LOS (mainly because larger packages were sold).

[f] Please note that the differences were calculated separately and are therefore not quite the same as the stated probabilities in Table 12.

Table 14: Utilisation data on the use and costs per pharmaceutical and patient (in CHF 2018)

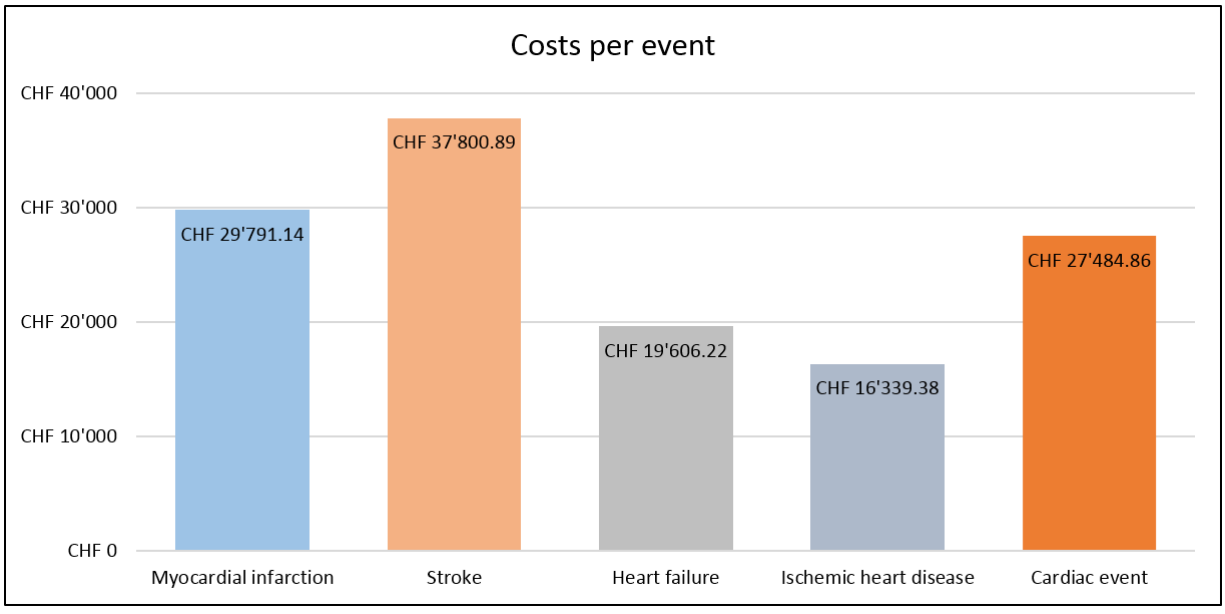
Drug*	Turnover p.a.	Patients treated p.a.**	Costs per patient p.a.
OLM	CHF 32'242'858.40	82'669	**CHF 390.02**
VAL	CHF 52'214'745.08	150'223	**CHF 347.58**
LOS	CHF 16'339'614.56	64'316	**CHF 254.05**
IRB	CHF 22'587'169.48	76'514	**CHF 295.20**

CHF = Swiss Francs; IRB = irbesartan; LOS = losartan; OLM = olmesartan; p.a. = per annum; VAL = valsartan
* Includes mono-preparations and fixed-dose combinations
** Rounded (for further calculations, non-rounded values were used)

Sources: authors' own calculations based on Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft[106]

The cost calculations were also based on the treatment costs of a cardiac event. A cardiac event can involve any one or a combination of the following: MI, stroke, heart failure or IHD. The event of a stroke is associated with the highest costs (CHF 37'801), followed by MI (CHF 29'791), heart failure (CHF 19'606) and IHD (CHF 16'339).[103] The total costs of a cardiac event are around CHF 27'485 (see Figure 11). These treatment costs comprise the costs for both fatal and non-fatal events as well as costs for maintenance and were calculated using the weighted average costs of the individual components of a cardiac event. Further information can be found in Table 35 in Appendix D.

Figure 11: Costs per event (in CHF 2018)



Source: Brändle et al.;[103] including costs for fatal and non-fatal events and for maintenance

In a next step, the treatment costs per patient were calculated. These costs include the costs for the pharmaceutical treatment with the sartan concerned, plus the proportionate costs for a cardiac event. For example, in 2018 treatment with OLM cost CHF 390 (see Table 14), plus approx. CHF 29'791 for MI in 0.6 per cent of the patients (see Figure 11), adding up to around CHF 569 (see Table 15).

Table 15: Treatment costs per patient (in CHF 2018)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM	CHF 569.07	CHF 665.21	CHF 712.15	CHF 478.75	**CHF 1'282.73**
VAL	CHF 550.46	CHF 745.25	CHF 852.64	CHF 465.55	**CHF 1'594.16**
LOS	CHF 469.44	CHF 736.39	CHF 858.32	CHF 378.23	**CHF 1'682.99**
IRB	CHF 459.35	CHF 746.17	CHF 838.49	CHF 421.18	**CHF 1'628.49**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; OLM = olmesartan; MI = myocardial infarction; VAL = valsartan

Source: authors' own calculations

The estimation of the incremental costs of OLM versus VAL, LOS and IRB in Table 16 is based on the costs from Table 15 above. Positive costs mean that the average treatment costs are higher for OLM than the average treatment costs of the compared sartan (e.g. per patient, the treatment costs of OLM are approx. CHF 19 higher compared with the treatment costs of VAL in the case of MI). Negative costs mean that the average treatment costs are lower for OLM than with the compared sartan (e.g. per patient, the costs of OLM are around CHF 400 lower compared with LOS in the case of a cardiac event).

Table 16: Incremental costs per patient (difference in treatment costs, in CHF 2018)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM vs. VAL	CHF 18.61	-CHF 80.03	-CHF 140.48	CHF 13.20	**-CHF 311.42**
OLM vs. LOS	CHF 99.63	-CHF 71.18	-CHF 146.16	CHF 100.52	**-CHF 400.26**
OLM vs. IRB	CHF 109.72	-CHF 80.95	-CHF 126.34	CHF 57.57	**-CHF 345.76**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan; VAL = valsartan

* A negative number means that the costs of OLM were lower.

Source: authors' own calculations from bootstrapping results based on Swindle et al.[46] (limited study sample)

Costs per event averted

To estimate the costs per event averted, the number needed to treat (NNT) was calculated in a first step. The NNT gives the number of patients that has to be treated with OLM to avert one additional cardiac event compared with VAL, LOS and IRB. In this case, a positive NNT indicates a better effect of OLM on events compared with VAL, LOS and IRB. The smaller this positive NNT, the higher the effect of OLM.

Since the original study by Swindle et al.[46] did not provide data on before and after comparisons, it was not possible to calculate the NNT individually for the sartans.

For instance, compared with OLM there is an additional probability of 0.08 per cent for MI in patients treated with VAL (see also Table 13). Consequently, a total of 1'266 patients have to be treated with OLM to avert one additional MI than with VAL while 110 patients have to be treated with OLM to avert

one more heart failure than with VAL. To avert a cardiac event in general, 81, 76 and 75 patients have to be treated with OLM compared with VAL, LOS and IRB respectively (see Table 17).

The calculated NNTs are based on the study by Swindle et al.[46] The NNTs in Table 16 are mainly positive, indicating a superiority of OLM compared with the other sartans. However, since the effect of OLM on MI compared with IRB was worse (negative), this NNT is negative. In fact, this number represents the number needed to *harm*, meaning that 2'439 patients have to be treated with OLM to *harm* one additional patient with MI.

Table 17: Number needed to treat per additional event averted (rounded)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM vs. VAL	1'266	319	110	613	**79**
OLM vs. LOS	917	187	71	488	**52**
OLM vs. IRB	-2'439	223	90	460	**63**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan; VAL = valsartan

Source: authors' own calculations from bootstrapping results based on Swindle et al.[46] (limited study sample)

In a second step, the NNTs were multiplied by the treatment costs of OLM from Table 15. The results are the costs of a treatment with OLM to avert one additional event (see Table 18).[g]

Overall, the data can be interpreted as follows: the lower the costs per event averted, the better the "cost effectiveness" of OLM compared with the other sartans. For example, averting one additional cardiac event with OLM costs around CHF 66'000 compared with LOS, CHF 80'000 compared with IRB and CHF 101'000 compared with VAL. This indicates that OLM is more cost effective at averting cardiac events compared with LOS and less cost effective compared with VAL.

However, the clinical data in the study by Swindle et al.[46] indicated that IRB might be more effective at averting MI than OLM. Thus, averting an additional MI with IRB compared with treatment with OLM would cost nearly CHF 1.4 million (CHF 569 from Table 14 multiplied by 2'439). Consequently, the relevant cell in the table below is declared as 'n/a'.

[g] Please note that to estimate the costs per event averted, the exact NNT was used while the NNT presented in the report was rounded.

Table 18: Costs of OLM per event averted per year and patient (comp. to VAL, LOS and IRB)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM vs. VAL	CHF 720'339.37	CHF 212'528.38	CHF 78'517.49	CHF 293'709.30	**CHF 101'321.60**
OLM vs. LOS	CHF 522'080.83	CHF 124'571.88	CHF 50'293.33	CHF 233'534.72	**CHF 66'325.31**
OLM vs. IRB	n/a	CHF 148'485.23	CHF 64'331.85	CHF 220'113.18	**CHF 80'321.32**

IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan; VAL = valsartan

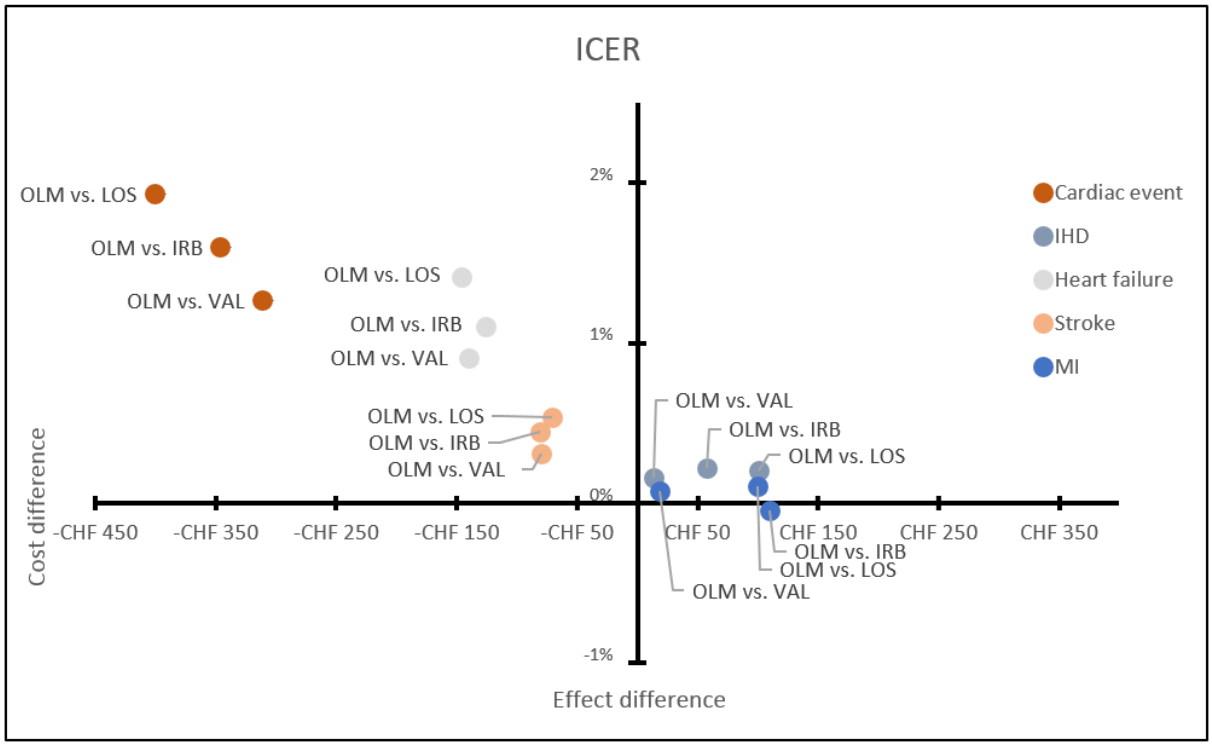
Sources: authors' own calculations based on Brändle et al.;[103] Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft;[106] authors' own bootstrapping results, effects based on Swindle et al.[46] (limited study sample)

Incremental cost-effectiveness ratio (ICER)

To estimate the cost effectiveness per patient for the difference in rates of cardiac events (which is a composite outcome measure comprising MI, stroke, heart failure and IHD) for treatment with OLM compared with VAL, LOS and IRB, the results from Table 13 and Table 16 were considered. These results are visualised in Figure 12 and can be summarised as follows:

- OLM is associated with *higher effects* and *lower costs* for cardiac events in general compared with the other three sartans (VAL, LOS and IRB).
- In addition, OLM is associated with *higher effects* and *lower costs* for heart failure and stroke compared with VAL, LOS and IRB (northwest quadrant).
- OLM is associated with *higher effects* but also *higher costs* for IHD compared with VAL, LOS and IRB as well as for MI compared with VAL and LOS
- Conversely, OLM is associated with *lower effects* and *higher costs* for MI compared with IRB.

Figure 12: Cost-effectiveness ratio of OLM (compared with VAL, LOS and IRB)



ICER = incremential cost-effectiveness ratio; IRB = irbesartan; LOS = losartan; VAL = valsartan

Sources: authors' own calculations based on Brändle et al.;[103] Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft;[106] authors' own bootstrapping results, effects based on Swindle et al.[46] (limited study sample)

The ICER in this report was calculated by dividing the cost difference (incremental costs) by the effect difference (incremental effects) between OLM and the other sartans (VAL, LOS and IRB). The effect difference is measured as the difference in the occurrence of events per patients (cardiac events, including the components MI, stroke, heart failure and IHD). Thus, the ICER is not given in units (e.g. CHF per QALY).[h]

Overall, the calculated ICER per patient for cardiac events was between -20'000 and -25'000 for OLM compared with VAL, LOS and IRB. The incremental cost-effectiveness ratios (ICER) per patient are summarised in Table 19 (results from Table 13 divided by results from Table 16).

[h] The ICER in this report would be CHF per occurence in cardiac events (or its composite).

Table 19: ICER (incremental costs per incremental effect)

Drug	MI	Stroke	Heart failure	IHD	Cardiac event
OLM vs. VAL	23'556.72	-25'569.38	-15'488.79	8'095.23	**-24'599.12**
OLM vs. LOS	91'400.32	-13'329.09	-10'322.18	49'031.75	**-20'695.86**
OLM vs. IRB	-267'601.57	-18'069.88	-11'412.57	26'467.71	**-21'650.67**

ICER = incremental cost-effectiveness ratio; IHD = ischemic heart disease; IRB = irbesartan; LOS = losartan; MI = myocardial infarction; OLM = olmesartan; VAL = valsartan

Sources: authors' own calculations based on Brändle et al.;[103] Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft;[106] authors' own bootstrapping results, effects based on Swindle et al.[46] (limited study sample)

Sensitivity analysis

The sensitivity analysis was calculated for four different scenarios and only for the costs and effects on cardiac events (basic scenario are the above calculated results):

- Scenario A:
    - Optimistic: OLM has a high effect while VAL, LOS and IRB have a relatively low effect.
    - Pessimistic: OLM has a low effect while VAL, LOS and IRB have a relatively high effect.
- Scenario B:
    - Optimistic: OLM is associated with 25 per cent lower event costs while VAL, LOS and IRB are associated with 25 per cent higher event costs (compared with the basic scenario).
    - Pessimistic: OLM is associated with 25 per cent higher event costs while VAL, LOS and IRB are associated with 25 per cent lower event costs (compared with the basic scenario).

To assume a low effect of OLM, the lower bounds of the confidence intervals from the bootstrapping results were applied to the economic model. To assume a high effect of OLM, the upper bounds of the conficdence intervals were applied (see also Table 38 and Table 39 in Appendix D).

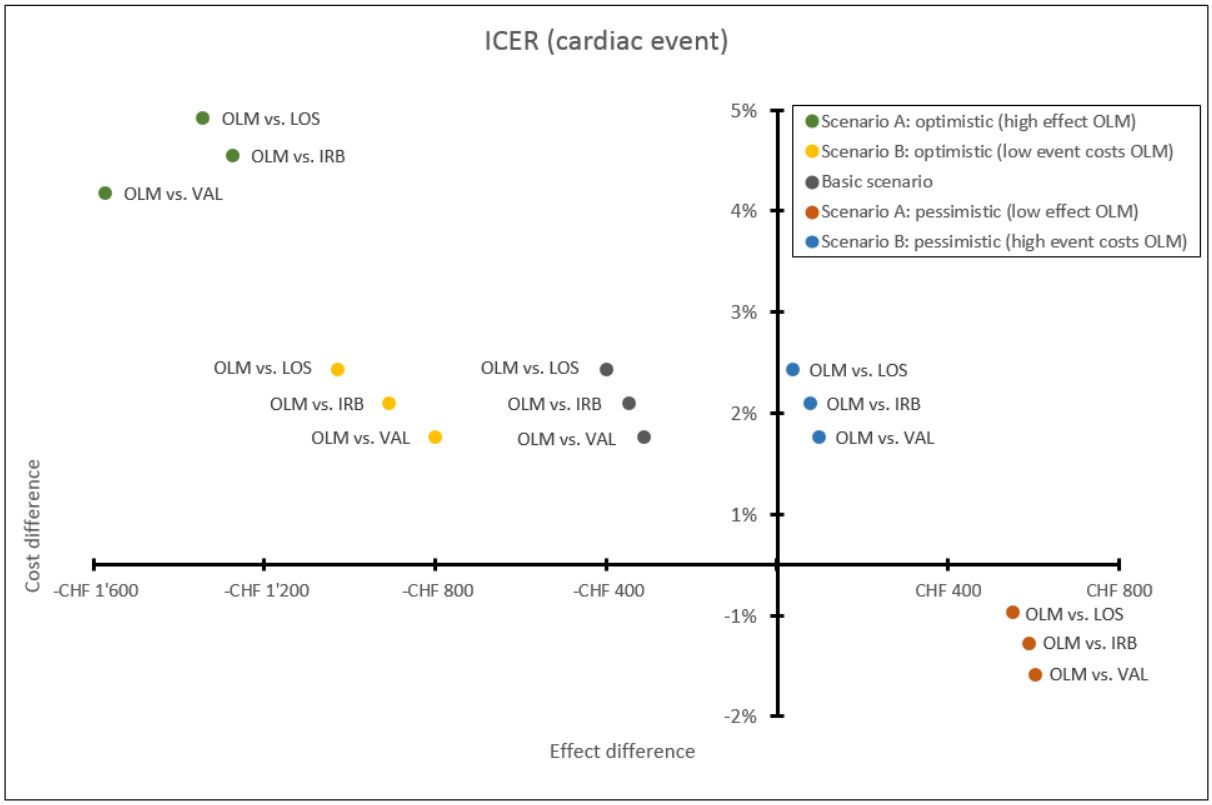
When assuming a high effect of OLM (Scenario A: optimistic), treatment with OLM is highly cost effective for all considered events in the applied model (cardiac events in general, plus MI, stroke, heart failure and IHD). When assuming a low effect of OLM (Scenario A: pessimistic), treatment with OLM is not cost effective (higher costs and higher rates of events). Since the costs in our model depend on the event rate, variation in the events (Scenario A) has an effect on the costs.

When assuming 25 per cent lower event costs for OLM and 25 per cent higher event costs for VAL, LOS and IRB (Scenario B: optimistic), OLM is also cost effective for nearly all considered event models (cardiac events in general, plus MI, stroke, heart failure and IHD). However, when assuming 25 per cent higher event costs for OLM and 25 per cent lower event costs for VAL, LOS and IRB (Scenario B: pessimistic), treatment with OLM can still be considered cost effective in the majority of the considered events but at higher costs than for VAL, LOS and IRB.

The results of the sensitivity analysis of the costs and effects for all cardiac events are visualised in Figure 13 (including the basic scenario calculated above). The numeric results of the sensitivity analysis for the individual events are shown in Table 38 and Table 39 in Appendix D.

Nevertheless, the sensitivity analysis shows that the calculated cost-effectiveness results are not robust. This is mainly due to the study results in Swindle et al.[46] that did not show a statistically significant difference in the occurrence of events and due to the wide confidence intervals from the bootstrapping results.

Figure 13: Results of the sensitivity analysis



Sources: authors' own calculations based on Brändle et al.;[103] Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft;[106] authors' own bootstrapping results, effects based on Swindle et al.[46] (limited study sample)

8.2.5 Findings budget impact

In Scenario 1, the re-allocation of 111'470 packs of OLM mono- and 221'000 packs of combination preparations to alternative sartans (allocated by individual market share, base: market share for mono- or combination preparations) results in a total savings effect on pharmaceutical expenditure of around CHF 7.4 million (CHF 2.9 million on mono- and CHF 4.5 million on combination preparations). Additional physician visits account for around CHF 2.6 million so that the total net budget savings are around CHF 4.8 million. For details, see Appendix D, Table 42.

Additional physician visits due to a potential delisting of OLM will only occur for OLM patients and just during the time after switching to an alternative ARB. Additional physician visits for patients starting a new antihypertensive therapy after the delisting of OLM will not be necessary.

Scenario 2 (allocated to equivalent groups) indicates a different picture. In the case of mono-preparations, there is a saving potential of around CHF 2.0 million and additional pharmaceutical expenditure of CHF 0.7 million for combination preparations. The budget impact on pharmaceutical expenditure thus amounts to a saving potential of CHF 1.3 million. Including additional visits to physicians (CHF 2.6 million), the total net budget impact in Scenario 2 results in additional expenses of around CHF 1.3 million (Appendix D, Table 43).

The differences in the results of scenarios 1 and 2 are mainly for the following reasons:

Mono-preparations: In Scenario 2, for OLM 10 mg with pack sizes of 98 and 100 units, only two equivalent alternative products were available in 2018: Edarbi™ 20 mg (AZI) and Actavis™ 25 mg (LOS). The cost per pack for Edarbi™ (CHF 90.6) was significantly higher than for OLM preparations (the average costs per pack for OLM products ranged between CHF 63.0 and CHF 81.4). Although the cost per pack for Actavis™, a generic, was considerably lower (CHF 37.8) than the cost of OLM products, this did not have an impact on the budget because the market share of the LOS product was negligible in 2018. Therefore, almost all OLM preparations (33'272 OLM packs in total) were allocated to the more expensive AZI product, achieving a market share on packs of 99.8 per cent after re-allocation. This resulted in additional expense of just under CHF 0.5 million for this group. However, if the market share of LOS (Actavis™) increased in the future, this would reduce the additional expense.

In all other equivalence groups within the mono-preparations, budget savings were achieved but not to the same extent as in Scenario 1.

Combination preparations: In Scenario 2 the equivalence group "sartans and HCTZ" resulted in budget savings of about CHF 1.2 million while Scenario 1 for this subgroup showed a budget increase of CHF

5.5 million. This is due to the fact that Scenario 1 did not take into account whether combinations contained two or three active substances; only the market share within the whole group of combination products determined the distribution key.

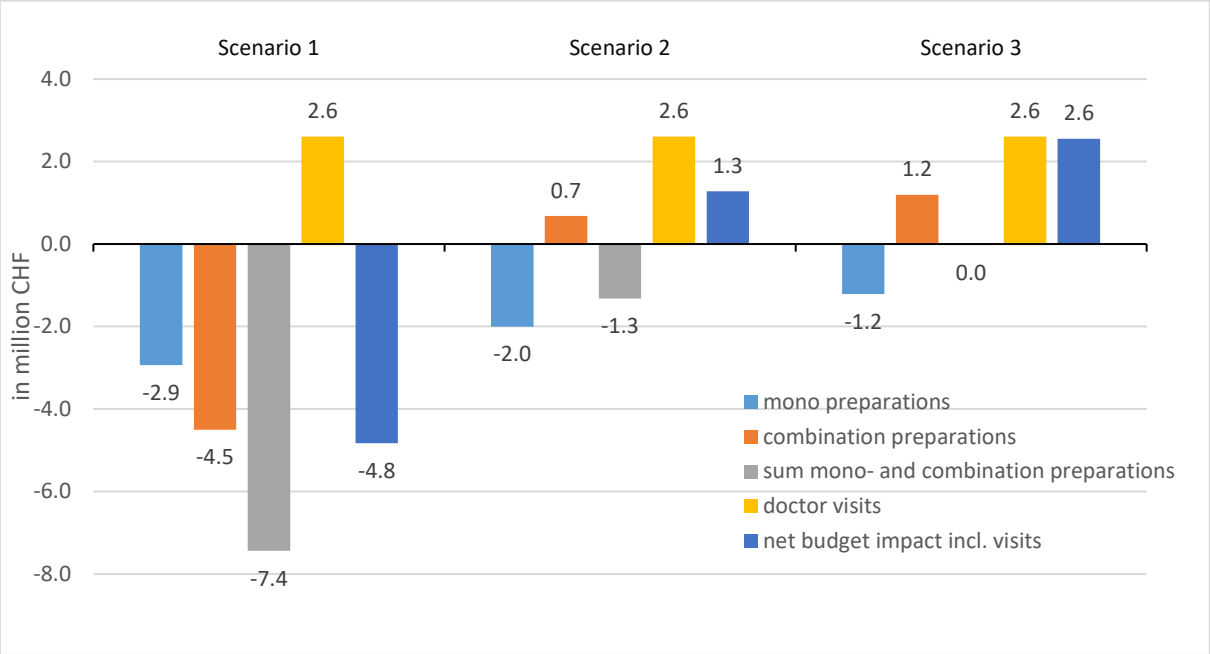
In contrast, Scenario 1 showed budget savings of CHF 4.4 million for combination products with CCB and CHF 5.6 million for triple combinations with CCB and HCTZ. In comparison, Scenario 2 resulted in a budget increase of CHF 1.8 million for combination preparations with CCB. The increase in expenditure is explained by the fact that the cost per pack for many combination preparations with the two available comparator substances (VAL and CCBs as well as TEL and CCBs), especially those which an already had a high market share (Exforge™), were significantly higher than those of the combination preparations of OLM and CCBs. In the equivalence group of triple combinations with CCBs and HCTZ there was a small budget increase of CHF 0.04 million.

In the equivalence group for OLM and CCBs (ATC code CDB01-04), the only available alternatives are VAL and CCBs or TEL and CCBs. Before the re-allocation of OLM, VAL and CCBs already had a market share of around 58 per cent, with OLM and CCBs at around 38 per cent and TEL and CCBs at 4 per cent. The original preparations of VAL and CCBs (Exforge™) with the highest market share in this group showed a higher cost per pack than the original comparator of OLM and CCBs (Sevikar™), which resulted in additional expenditure of around CHF 1.8 million after re-allocation in this group.

Scenario 3 differs from Scenario 2 in that the number of reimbursed packs from 2018 were valued with current prices (Spezialitätenliste as of 1 August 2019). For many preparations, the prices increased compared with 2018, with the effect that a budget saving of about CHF 1.2 million for mono-preparations and additional pharmaceutical expenditures of about CHF 1.2 million for combination preparations occurred. Including additional doctor visits, the net budget impact for the health insurance results in an increase of CHF 2.6 million. For details, see Appendix D, Table 44.

Figure 14 presents a comparison of the results of the three scenarios.

Figure 14: Overview of budget impact scenarios 1-3, in million CHF*



* Valid in the first year of switching

Sources: authors' own calculations based on data from Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste, Schweizerische Eidgenossenschaft[106]

Summary statement on costs, cost effectiveness and budget impact

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Costs

In 2018, 2.4 million packs of sartans were sold, amounting to pharmaceutical expenditures of CHF 173 million overall for the health insurance. The average costs per pack for mono-preparations for OLM were the third highest (CHF 80.61) while EPR showed the highest costs per pack at CHF 95.68 followed by AZI at CHF 92.24 (for details, see Appendix D, Table 28). There are no generic drugs available for EPR and AZI. Within the group of combination preparations with HCTZ, the average costs per pack of EPR and HCTZ, TEL and HCTZ as well as AZI and HCTZ were higher than that of OLM and HCTZ. Likewise the average costs per pack for the comparator substance VAL and CCBs were higher than that of OLM and CCBs. For the triple combination with HCTZ and CCBs, the average costs per pack for the VAL triple combination were slightly higher than those for the OLM triple combination. For details, see Appendix D,Table 34.

Cost effectiveness

In general, our calculations suggest that OLM is associated with higher effects and lower costs for cardiac events compared with VAL, LOS and IRB. The calculated ICER per patient for cardiac events was between -20’000 and -25’000 for OLM compared with VAL, LOS and IRB. Nevertheless, the sensitivity analysis has shown that in a pessimistic scenario, OLM is no longer cost effective. Thus, the results of the cost-effectiveness calculations in the present report are not robust enough to draw any conclusion.

Budget impact

Considering only pharmaceutical expenditures, there would be budget savings for the health insurance of CHF 7.4 million in Scenario 1, CHF 1.3 million in Scenario 2 and no savings in Scenario 3.

However, taking into account the additional outpatient visits, the net budget impact ranges between CHF savings of 4.8 million (Scenario 1), further expenses of CHF 1.3 million (Scenario 2) and further expenses of CHF 2.6 million (Scenario 3).

The budgetary effects of a substitution of OLM depend strongly on the alternative preparations available within the equivalence group – their specific prices and market shares – as well as the expenditure for additional visits to physicians in the course of changing medication. Therefore, if the physicians prescribe equivalent doses for OLM, it is more likely that additional expenses will occur overall (Scenarios 2 and 3).

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9 Legal, social and ethical issues

9.1 Methodology legal, social and ethical issues

9.1.1 Databases and search strategy

In the scoping report, no studies were identified that directly address legal, social or ethical issues related to OLM therapy in hypertensive patients in Switzerland. Therefore, a systematic and widened literature search on legal, social and ethical issues was conducted for the HTA in MEDLINE and EMBASE. The search terms included a combination of keywords and medical subject headings (MeSH) relating to ethical and social issues (e.g. health service accessibility, physician-patient communication, patient attitude) and organisational issues (e.g. medication switch, drug substitution). The search was conducted in English and no time restrictions were set concerning the year of publication. The detailed search strategies are outlined in Appendix B, Table 24.

9.1.2 Assessment of the quality of evidence

All potentially relevant studies and articles were included; no quality assessment was carried out.

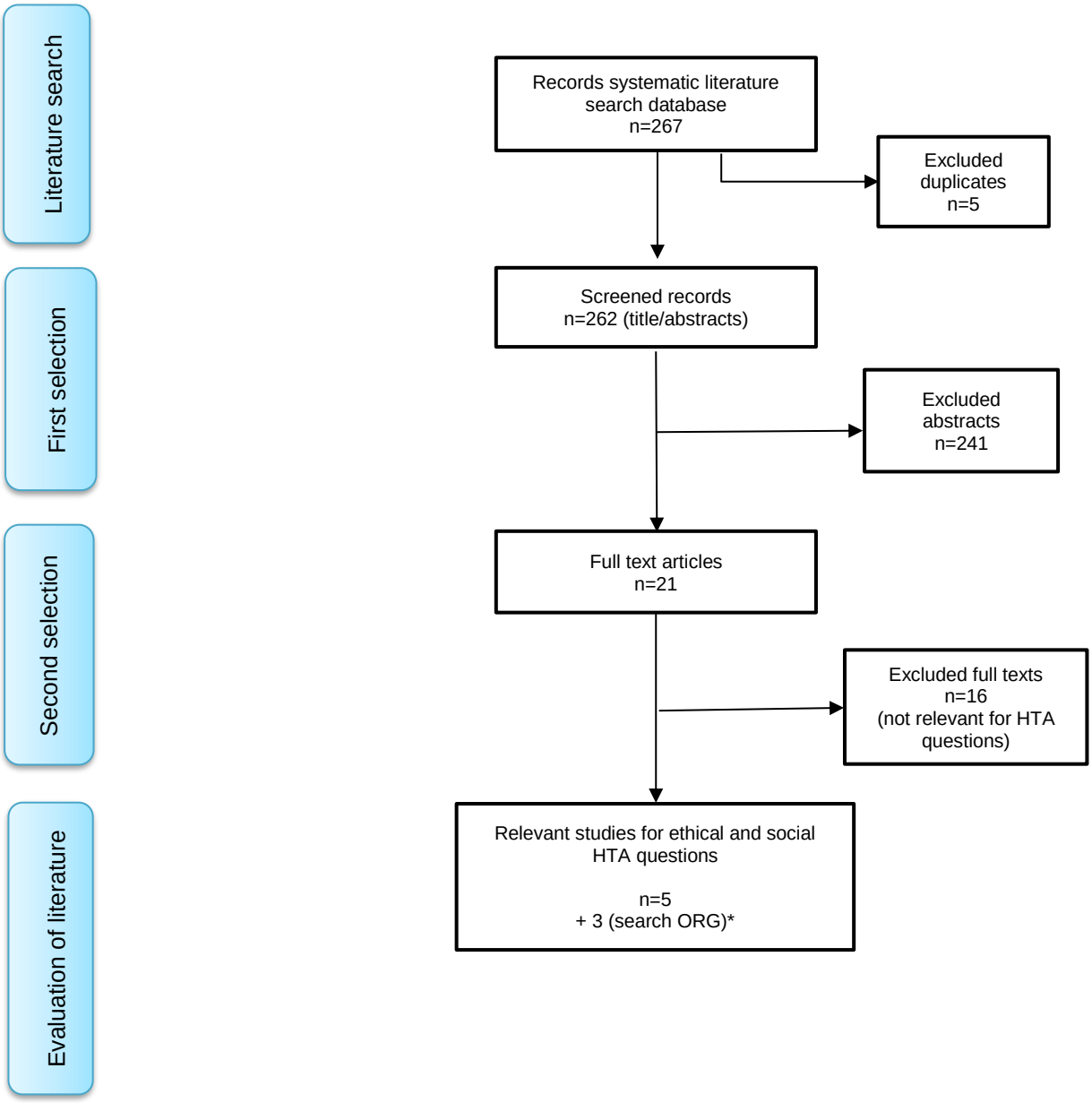
9.1.3 Methodology data analysis legal, social and ethical issues

In order to identify and describe relevant legal, social and ethical issues, assessment elements from the EUnetHTA core model[118] were checked. Additionally, the four principles described by Beauchamp[119] (as guiding principles for ethical aspects) and the “Morally Relevant Questions with Respect to Assessing Health Technology” by Hofmann[120] were checked and additional ethical issues were added if they did not overlap with the EUnetHTA checklist. These steps were done in an iterative process. The results of the potentially relevant full texts identified in the systematic literature search are described narratively to the extent that they are relevant to the questions.

9.2 Results legal, social and ethical issues

9.2.1 PRISMA flow diagram

Figure 15: PRISMA flow diagram for the domains LEG/SOC/ETH



SOC/ETH = social/ethical; ORG = organisational; n = number

* Plus three studies[121-123] from the literature search in the ORG domain

9.2.2 Findings legal issues

Regarding legal aspects, the literature search revealed no specific sources besides the general legal framework laid down in the health insurance law, article 32 ("WZW criteria" – clinical effectiveness, appropriateness and economic efficiency). EUnetHTA assessment elements did not reveal any further relevant aspects either.

In total eight studies[121-128] addressed some aspects of social or ethical issues:

9.2.3 Findings social issues

Checking the social domain in the EUnetHTA core model for relevant social aspects, we deemed questions relating to communication with patients to be most relevant. Drug adherence has an important effect on treatment outcomes. Hence, ensuring that patients continue to take an antihypertensive agent after a potential disinvestment decision is paramount. The literature search revealed information on factors influencing drug adherence and the impact of drug switching on treatment outcomes. However, we identified no studies that focused specifically on communication aspects to ensure adherence when switching from OLM to another, broadly therapeutically equivalent hypertensive agent.

Amongst other factors, adherence to medication is influenced by patients' expectations and views. Switching may cause anxiety and confusion, especially in the elderly, or result in a "nocebo effect", where patients' negative expectations lead to adherence problems and, subsequently, worse clinical outcomes.[121 123] This problem might be addressed by providing adequate patient education: A Greek observational study found counselling to be effective in improving treatment adherence.[123]

In general, the patient-physician relationship is frequently cited as an important factor influencing adherence to treatment. Specifically, communication skills, trust in the physician and overall patient satisfaction have been found to be associated with greater adherence.[127] Other factors that are believed to have a positive effect on adherence include confidence in the health system, routine visits to the same service or doctor and the number of visits.[124] These findings should be taken into account to mitigate the potential negative consequences of delisting OLM from reimbursement.

The end of OLM reimbursement in France in 2017 was accompanied by decreased BP control in those patients who were switched to an alternative ARB. However, it is worth noting that these results are based on only two home BP monitorings on OLM and a single home BP monitoring 4 weeks after the therapy switch.[122] In contrast, a retrospective cohort study[128] investigating compliance, persistence and switching patterns did not detect any significant variations between different ARBs. In general, major adherence problems are not anticipated in the case of drug substitution due to the variety of other available sartans and their favourable tolerability profile compared with other antihypertensive drugs such as diuretics and beta blockers.[125 126]

In order to ensure the maintenance of BP control following drug substitution, physicians also need to receive appropriate guidance and information on equivalent doses of drugs within the same therapeutic class, which is currently not always the case.[123]

9.2.4 Findings ethical issues

The EUnetHTA checklists for relevant ethical aspects revealed that several questions – in principle – are relevant, comprising issues regarding the benefit-harm balance (an issue overlapping with the EFF and SAF domains), justice and equity (partly overlapping with the ECO domain) as well as potential ethical consequences with regard to the chosen methodological approach (e.g. choice of endpoints, cut-off values or assumptions in the economic evaluation). With regard to justice and equity, ethical considerations include the question as to how access to OLM would be affected by a disinvestment decision.

In general, major access problems upon OLM disinvestment are not expected due to the variety of other sartans available. They provide the same flexibility in terms of dose titration and therefore equivalent dosage can be achieved. Regarding fixed-dose combinations, all sartans offer combination therapies (for example, in combination with HCTZ, CCBs or both). However, the only other 3-drug fixed-dose combination therapy currently available in Switzerland is for VAL, which might have a negative impact on access for patients on multidrug regimes in case OLM reimbursement was ceased. Compared with extemporaneous combinations, fixed-dose combinations are associated with improved adherence because they reduce the complexity of the therapeutic scheme.[121]

In terms of the methodological approach, it must be noted that studies evaluating OLM's efficacy compared with other sartans focus on BP, a surrogate outcome. The benefit for relevant clinical endpoints such as cerebrovascular or cardiovascular events has not yet been firmly established. Hence, caution is warranted when interpreting the results of OLM's relative effectiveness.

Summary statement on legal, social and ethical issues

Patients' adherence to BP medication may be negatively influenced by medication switching, which could cause insufficient BP control and potentially poor clinical outcomes. Hence, adequate communication about the importance of adherence is a key factor influencing treatment success. The evidence base for assessing communication aspects when switching from OLM to another compound appears to be scant. In general, patients' negative expectations towards a new drug might be managed by education and motivation as well as a high-quality doctor-patient relationship built on trust. Overall, major adherence problems are not expected as a result of a potential disinvestment decision because a variety of other sartans is available in Switzerland; however for triple combinations and some double combinations, the choice of comparator products may be somewhat limited. Apart from ensuring patients' adherence, physicians should prescribe equivalent doses to ensure BP control after drug substitution.

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10 Organisational issues

10.1 Methodology organisational issues

10.1.1 Databases and search strategy

In the scoping report no studies were identified that directly addressed organisational issues in Switzerland. Therefore a systematic and widened literature search was conducted for the HTA in MEDLINE and EMBASE. The search terms included a combination of keywords and medical subject headings (MeSH) relating to organisational issues (e.g. medication switch, drug substitution). The search was conducted in English and no time restrictions were set concerning the year of publication. The detailed search strategies are outlined in Appendix B, Table 25.

10.1.2 Other sources

In addition to the systematic literature search, inquiries were made to various stakeholders regarding their experiences with the withdrawal of OLM in Austria and France (for documentation, see Appendix B, Table 27).

10.1.3 Assessment of quality of evidence

All potentially relevant studies and articles were included; no quality assessment was carried out.

10.1.4 Methodology data analysis organisation issues

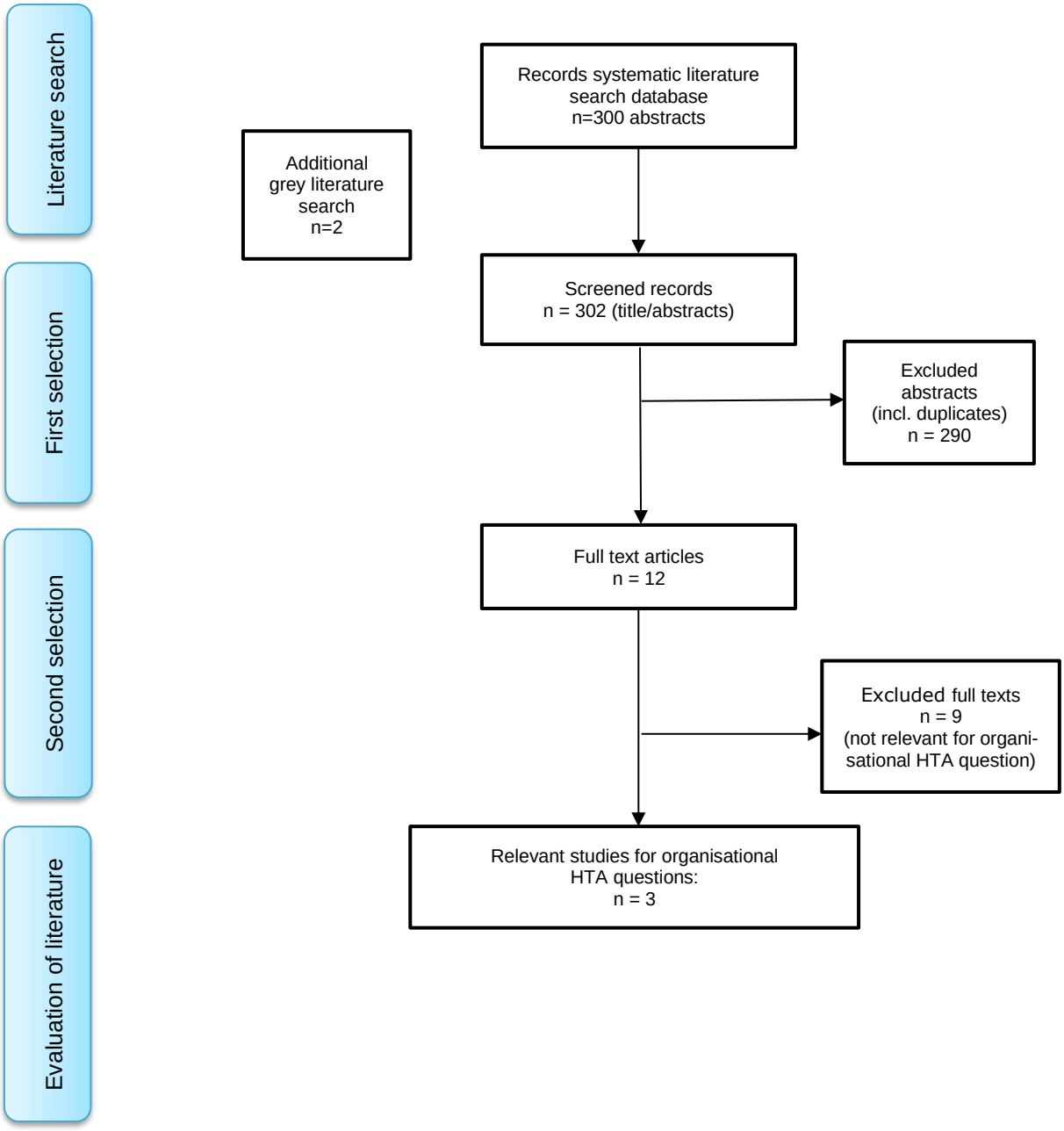
The results are based on the widened literature search as well as on responses gathered from the inquiries in Austria. Unfortunately we got no reply to our questions from France.

The studies identified in the systematic literature search are described narratively to the extent that they are relevant to the question.

10.2 Results organisational issues

10.2.1 PRISMA flow diagram

Figure 16: PRISMA flow diagram for the domain ORG



n = number; ORG = organisational

10.2.2 Findings organisational issues

From the systematic search, three studies[2 108 129] addressed aspects of organisational issues to some extent. Farrukh et al.[129] reported on the recall of VAL due to contamination with N-nitrosodimethylamin (NDMA), a potential human carcinogen, in medicines manufactured by Zhejiang Huahai Pharmaceutical Co Ltd., Linhai, China, which was reviewed by the European Medicines Agency (EMA). Later on, NDMA

impurity was also detected in a product from a second manufacturer (Zhejiang Tianyu, Taizhou, China). After the EMA review, 24 European countries (Switzerland was not mentioned) recalled 2'300 batches of VAL products. In September 2018, the EMA reported another impurity, N-Nitrosodiethylamin (NDEA), also in a product manufactured by Zhejiang Huahai. On 31 January 2019, EMA recommended that companies producing sartan BP medicines have to review their manufacturing processes so that they do not produce nitrosamine impurities. Companies have a transition period of 2 years to make any necessary changes, during which strict temporary limits on the levels of these impurities will apply. After this period, companies have to demonstrate that their sartan products have no quantifiable levels of these impurities before they can be used in the EU.[130]

These findings could affect a possible substitution of OLM insofar as VAL is an important alternative ARB in Switzerland. However, so far no preparations containing VAL have been recalled by Swissmedic.[131]

Furthermore, if the triple combination OLM with HCTZ and CBBs was removed from the reimbursement list, only VAL with HCTZ and CBBs would be available as a substitute. If there were future problems with possible nitrosamine impurities in VAL products in Switzerland, no substitute would be available.Therefore, it is recommended to monitor recalls of VAL products and whether there are any delivery problems with this preparation.

Signorovitch et al.[108] investigated the economic impact of switching from VAL (without medical reason) to an alternative ARB by analysing claims data in the USA. "Switchers" were found to have higher healthcare costs. However the study authors could not identify specific reasons for this association due to a lack of information. The authors concluded that it is likely because of an increase in outpatient visits, partly due to follow-up visits for dose titration and tolerability assessments. The study documented 19.1 additional outpatient visits per 100 patients. The ESC/ESH guidelines also state that "after initiation of antihypertensive drug therapy, it is important to review the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects until BP is under control, the frequency of review will depend on the severity of hypertension".[2]

According to information from the Main Association of Austrian Social Security Institutions (Appendix D, Table 27), patients asked why OLM had been delisted (as of 1 January 2019) and what the alternative drugs were. A complaint by the manufacturing company to the Federal Administrative Court was dismissed. The doctors were informed that OLM was no longer reimbursed and alternative preparations and the equivalent doses to OLM were pointed out.

Summary statement on organisational issues

Relevant organisational issues are timely information for physicians about a possible delisting of OLM from the Spezialitätenliste, the reasons for the delisting and a list of alternative ARBs and equivalent doses.

Furthermore, it should be monitored whether there are any problems with the delivery of VAL products due to nitrosamine impurities and whether they can be provided in sufficient quantities (especially triple combinations).

In addition, patients can expect more frequent visits to their physician during the first year after switching from OLM to an alternative sartan.

11 Discussion

Numerous studies have compared the effect of OLM on BP compared with other sartans. However, the assessment of health benefits should primarily consider clinically meaningful endpoints such as mortality, morbidity and quality of life (see the EUnetHTA guidelines on endpoints used in the relative effectiveness assessments (REA) of pharmaceuticals – clinical endpoints[132]). To date, only one retrospective study has compared OLM's performance with regard to long-term outcomes versus other sartans.[46] This low-quality evidence hints at a superiority of OLM in averting certain cardiac events compared with other sartans. By contrast, for some other sartans, including LOS and TEL, more evidence is available from randomised controlled trials reporting on critical endpoints.[133-135]

Apart from investigating the effects of OLM on BP and long-term outcomes, we also examined its safety profile in comparison with other sartans, using data from RCTs as well as observational studies and country registries. Due to short trial durations and inconsistent reporting of adverse events amongst the RCTs included, we could not obtain a complete estimate of the incidence of harms associated with OLM versus other ARBs. Additional data from observational studies/country registries provided evidence on rare adverse events that arise with a long latency period such as enteropathies. Due to the lack of randomisation, the degree of certainty of these results is limited. Overall, the quality of evidence assessing the risk of enteropathies associated with OLM use was low due to concerns regarding the methods used in most of the studies to make adequate statistical adjustment for confounding and selection bias. Additionally, relatively short follow-up periods as well as low event rates hampered efforts to identify differences that might not just be due to random variations. Furthermore, the studies yielded inconsistent results, with some suggesting an increased risk for enteropathies in OLM users compared with other ARBs while others did not find a significant difference. Certain subanalyses indicate that OLM might be associated with a comparatively higher risk for enteropathies. However, future studies might solidify or change the effect estimate.

Observational studies only including patients using OLM were analysed for an explorative investigatation of any striking patterns regarding unexpected serious adverse events and all-cause mortality (compared with baseline epidemiological rates). The results of the individual studies were heterogeneous, with some studies finding a high incidence of serious adverse events in OLM users and others reporting none at all. These differences might be predominately explained by heterogeneous study populations (multimorbid patients versus patients with primary hypertension only) and are likely to be due to their different risk profiles rather than attributable to the use of OLM itself.

In 2013, the FDA approved the addition of a warning about the risk of sprue-like enteropathy to OLM labelling based on an evaluation of data from the Centers for Medicare and Medicaid Services (CMS), the FDA Adverse Event Reporting System (FAERS) and a case series by Rubio-Tapia et al.[136]

In 2015, the French National Authority for Health (HAS)[1] recommended discontinuation of the reimbursement of OLM due to a lack of evidence regarding its beneficial effect on outcomes other than BP such as morbidity and mortality as well as evidence showing an increased risk of sprue-like enteropathies for OLM, although the overall observed risk was small. Their findings regarding the safety profile of OLM were based on case series and French pharmacovigilance data that showed the resolution or improvement of sprue-like enteropathy symptoms as well as intestinal changes once OLM was discontinued.[137] [136] Their evidence base also included an analysis of the French National Health Insurance claim database (Basson et al. 2015)[49] showing an increased risk of hospitalisation due to intestinal malabsorption with OLM but not other sartans compared with ACE inhibitors. However, more recent long-term studies could not clearly confirm an increased risk of enteropathies associated with OLM versus other sartans.[51] [54] [58]

In contrast, in 2019 the FDA[138] denied a petition for the removal of drug products containing OLM from the market for safety reasons, arguing that more recent evidence using the same core evidence base (as used in this HTA report) from studies with long-term outcomes (Basson et al., Dong et al.)[49] [51] as well as case series/case reports[139] and one additional systematic review[140] did not indicate a new, worsened or more prevalent enteropathy-related risk than already described in the OLM labelling.[138] The FDA argued that due to the very low incidence of sprue-like enteropathy in OLM users described in the literature and the reversibility of symptoms upon medication cessation, disrupting BP therapy for a vast number of OLM users by removing this drug from the market was not warranted.[138]

In summary, by analysing a broad range of studies, we ensured that no significant new evidence regarding critical and important outcomes as well as potential harms associated with OLM versus other sartans has been overlooked. Definite conclusions about the balance of benefits and harms associated with OLM cannot be drawn due to the lack of high-quality evidence for important endpoints. Future studies should try to fill this evidence gap by providing high-quality data on critical and important outcomes and harms to enable a valid risk/benefit assessment of OLM compared with other sartans. We did not identify any ongoing studies addressing these issues in our search of clinical trial registries.

Due to the lack of adequate comparative studies, cost effectiveness was estimated by calculating costs per one additional event averted by OLM compared with VAL, LOS and IRB and by a crude incremental cost-effectiveness ratio estimation of the event difference for treatment with OLM compared with VAL,

LOS and IRB.[i] The only comparative study analysing the effect of OLM on outcomes other than hypertension was Swindle et al.[46] Therefore, the results of the economic evaluation were mainly determined by the effects based on Swindle et al.[46] To correct for the different sizes of the patient populations in Swindle et al.,[46] empirical Bayesian bootstrapping was applied and confidence intervals were calculated. However, the calculated confidence intervals were wide and when considering the lower bounds, the cardiac event rates (including myocardial infarction, stroke, heart failure and ischemic heart disease) were higher with OLM compared with VAL, LOS and IRB. Another disadvantage of the original study by Swindle et al.[46] was that it was a retrospective analysis conducted in the USA with a short follow-up time and OLM was compared exclusively with VAL, LOS and IRB (i.e. there was no comparison with CAN, EPR, TEL or AZI).

Under the assumption that OLM would be substituted by other sartans, three scenarios were calculated for the possible budget impact on the health insurance.

In Scenario 1, OLM products were allocated to other sartans according to the market share of the different packs of the relevant alternatives separated into mono- and combination preparations. Scenario 2 bundled OLM and alternative preparations into equivalence groups and distributed them according to their market share. Scenario 3 differs from Scenario 2 insofar as the number of reimbursed packs in 2018 were valued at prices as of 1 August 2019. In addition to the effects on pharmaceutical expenditure, patients' visits to physicians due to the medication switch were taken into account. A potential weakness of these calculations is that the prices of the individual pharmaceuticals in Scenario 3 were taken from the Spezialitätenliste of August 2019 for Switzerland and combined with the number of packages sold in 2018. This was done to take into account the actual list prices of reimbursed pharmaceuticals for our calculations. However, the number of listed and reimbursed sartans was higher in 2018 than in August 2019. Nevertheless, the turnover of the delisted pharmaceuticals was low and, therefore, the impact on our results is negligible.

Considering just pharmaceutical expenditures, there would be budget savings of CHF 7.4 million in Scenario 1, CHF 1.3 million in Scenario 2 and no savings in Scenario 3. However, taking the additional outpatient visits into account, the net budget impact ranged between savings of CHF 4.8 million (Scenario 1), additional expenses of CHF 1.3 million (Scenario 2) and additional expenses of CHF 2.6 million (Scenario 3).

Scenario 2 and Scenario 3 probably present a more realistic picture as they take the specific market situation in the equivalence groups into account. Since prices and volumes are not constant, the results

[i] This comparison applies exclusively to the cost-effectiveness calculation.

of the budget impact analysis are only valid for a limited period of time (first year after medication switch). Further developments depend on the prescribing behaviour of physicians (e.g. prescribing more generics or originals) and future developments on the supplier side (e.g. changes in prices). For example, after completion of this HTA report, a major price revision for all sartans took place in December 2019. The price reductions for OLM preparations have been stronger than for the other sartans. Valued with current prices as of April 1, 2020[106] the pharmaceutical expenditures for OLM preparations would be reduced by around 5.2 Mio. CHF and for the other sartans by around 6.3 Mio. CHF (assuming constant prescription volume of 2018). For the scenarios presented in chapter 8.2.5, a valuation with the most current prices of the Spezialitätenliste of April 1, 2020 would have the consequence that the savings potential of the health insurance for pharmaceutical expenditures due to a potential substitution of OLM would be somewhat lower.

Some evidence indicates that adherence to medication might be negatively influenced by drug substitution, resulting in worse BP control. To mitigate the potentially negative effects of drug switching, patients' negative expectations towards a new drug might be managed by education and motivation as well as a high-quality doctor-patient relationships built on trust.

Relevant organisational issues are timely information for physicians about a possible disinvestment of OLM, the reasons for this decision and information about equivalent doses of alternative ARBs.

It should also be clarified whether the manufacturers of VAL in Switzerland are affected by nitrosamine impurities and whether they can provide sufficient quantities (especially triple combinations) as VAL is the only alternative sartan available in the triple combination with HCTZ and CCBs. However until now there have been no recalls of VAL in Switzerland.

Additional doctor visits due to a potential delisting of OLM will occur only for OLM patients and only in the first year after switching medication. Additional doctor visits for patients starting a new antihypertensive therapy after the delisting of OLM will not be necessary.

12 Conclusions

The available evidence is insufficient to clearly demonstrate a higher risk of the occurrence of sprue-like enteropathies for OLM users compared with users of other sartans. However, safety concerns cannot be ruled out. Although enteropathies are rare, clinicians should remain vigilant to this potential adverse event even years after initiating medication.

Based on the data from Swindle et al.,[46] our own calculations (bootstrapping) demonstrated non-statistical differences between OLM and three other sartans in relation to the cardiac event rate. Thus, the calculations are not robust enough to draw any conclusions regarding the cost effectiveness of OLM compared with VAL, LOS and IRB.

Taking the costs for additional visits to physicians into account, a substitution of OLM with equivalent alternatives would lead to additional expenses for the health insurance. Disregarding equivalent doses, the substitution would result in budget savings.

To avoid medication adherence problems, timely information for physicians about the planned disinvestment, the reasons for the decision and available equivalent doses of alternative sartans would be useful, as would appropriate education of the patients by the doctors. Furthermore, as the availability of alternative double and triple combinations is limited and as some VAL products have been recalled in some countries, the current market situation should be kept under observation.

13 References

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14 Appendices

14.1 Appendix A: Regulatory status

Table 20: Sartans: reimbursed mono-preparations in Switzerland and authorisation status

ATC code	Substance	Brand name	Dosage mg*	Package size*	Marketing authorisation holder	Date of first approval	Approval valid until
C09CA01	LOS	Cosaar 50	50/100	28/98	MSD Merck Sharp & Dohme AG	21.12.1994	13.01.2024
C09CA01	LOS	Losaratan Axapharm	50/100	28/98	Axapharm AG	06.10.2009	05.10.2019
C09CA01	LOS	Losaratan Helvepharm	50/100	28/98	Helvepharm AG	14.01.2011	13.01.2021
C09CA01	LOS	Losartan Mepha Lactabs	50/100	28/98	Mepha Pharma AG	09.09.2009	08.09.2019
C09CA01	LOS	Losartan Sandoz	50/100	28/98	Sandoz Pharmaceuticals AG	14.07.2009	13.07.2019
C09CA01	LOS	Losartan Spirig HC	50/100	28/98	Spirig HealthCare AG	07.07.2009	06.07.2019
C09CA02	EPR	Eprotan Mepha Lactabs 600	600	28/98	Mepha Pharma AG	19.03.2007	18.03.2022
C09CA02	EPR	Teveten	600	28/98	BGP Products GmbH	20.12.1999	19.12.2019
C09CA03	VAL	Diovan	80/160	28/98	Novartis Pharma Schweiz AG	23.03.2001	04.08.2023
C09CA03	VAL	Valsartan Axapharm	80/160	28/98	Axapharm AG	15.05.2013	14.05.2023
C09CA03	VAL	Valsartan Helvepharm	80/160	28/98	Helvepharm AG	03.08.2011	25.07.2021
C09CA03	VAL	Valsartan Sandoz	80/160	28/98	Sandoz Pharmaceuticals AG	24.11.2010	23.11.2020
C09CA03	VAL	Valsartan Spirig HC	80/160	28/98	Spirig HealthCare AG	02.03.2011	01.03.2021
C09CA03	VAL	Valtan Mepha	40/80	28/98	Mepha Pharma AG	16.06.2010	15.06.2020
C09CA04	IRB	Aprovel 150	150/300	28/98	Sanofi-Aventis (Suisse) SA	15.08.1997	07.09.2023
C09CA04	IRB	Irbesartan Mepha	150/300	28/98	Mepha Pharma AG	09.02.2011	08.02.2021
C09CA04	IRB	Irbesartan Sandoz	150/300	28/98	Sandoz Pharmaceuticals AG	25.02.2010	24.02.2020
C09CA04	IRB	Irbesartan Spirig HC	150/300	28/98	Spirig HealthCare AG	24.05.2012	23.05.2022
C09CA04	IRB	Irbesartan Zentiva	150/300	28/98	Helvepharm AG	26.07.2011	25.07.2021
C09CA06	CAN	Atacand	4/8/16/32	7/28/98	AstraZeneca AG	26.08.1997	26.04.2022

ATC code	Substance	Brand name	Dosage mg*	Package size*	Marketing authorisation holder	Date of first approval	Approval valid until
C09CA06	CAN	Blopress	4/8/16/32	7/28/98	Takeda Pharma AG	26.08.1997	21.12.2021
C09CA06	CAN	Candesartan Helvepharm	4/8/16/32	10/30/100	Helvepharm AG	03.02.2012	02.02.2022
C09CA06	CAN	Candesartan Sandoz	4/8/16/32	7/28/98	Sandoz Pharmaceuticals AG	13.04.2010	12.04.2020
C09CA06	CAN	Candesartan Spirig HC	4/8/16/32	7/28/98	Spirig HealthCare AG	04.08.2016	03.08.2021
C09CA06	CAN	Candesartan Takeda	4/8/16/32	7/28/98	Takeda Pharma AG	12.03.2012	11.03.2022
C09CA06	CAN	Cansartan Mepha	4/8/16/32	7/28/98	Mepha Pharma AG	30.11.2010	29.11.2020
C09CA06	CAN	Pemzek	4/8/16/32	7/28/98	AstraZeneca AG	06.01.2012	05.01.2022
C09CA07	TEL	Kinzal	40/80	28/98	Bayer (Schweiz) AG	25.02.2003	07.10.2022
C09CA07	TEL	Micardis	40/80	28/98	Boehringer Ingelheim (Schweiz)	16.12.1998	04.12.2023
C09CA07	TEL	Telmisartan Helvepharm	40/80	30/100	Helvepharm AG	13.06.2013	12.06.2023
C09CA07	TEL	Telmisartan Mepha	40/80	28/98	Mepha Pharma AG	23.01.2014	22.01.2024
C09CA07	TEL	Telmisartan Sandoz	40/80	28/98	Sandoz Pharmaceuticals AG	09.10.2012	30.05.2022
C09CA07	TEL	Telmisartan Spirig HC	40/80	28/98	Spirig HealthCare AG	17.12.2013	16.12.2023
C09CA08	OLM	Olmesartan Mepha Lactab	10/20/40	30/100	Mepha Pharma AG	15.03.2016	14.03.2021
C09CA08	OLM	Olmesartan Sandoz	10/20/40	30/100	Sandoz Pharmaceuticals AG	28.09.2016	27.09.2021
C09CA08	OLM	Olmesartan Spirig HC	10/20/40	30/100	Spirig HealthCare AG	16.12.2016	15.12.2021
C09CA08	OLM	Olmetec	10/20/40	30/100	Daiichi Sankyo (Schweiz) AG	15.04.2005	14.04.2020
C09CA08	OLM	Votum	10/20/40	28/98	A. Menarini AG	31.05.2005	30.05.2020
C09CA09	AZI	Edarbi	20/40/80	28/98	Takeda Pharma AG	31.08.2012	30.08.2022

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; EPR = eprosartan; IRB = irbesartan; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

* According to the SL

Sources: www.spezialitätenliste.ch as of 9 August 2019 and www.swissmedicinfo.ch as of 30 July 2019

Table 21: Sartans: reimbursed combination preparations and authorisation status in Switzerland

ATC code	Substance	Brand name	Dosage mg	Pack size*	Marketing authorisation holder	Date of first approval	Approval valid until
C09DA01	LOS + HCTZ	Co-Losartan Sandoz	100/12.5; 10/25; 50/12.5	28/98	Sandoz Pharmaceuticals AG	09.06.2009	08.06.2024
C09DA01	LOS + HCTZ	Co-Losartan Spirig HC	50/12.5; 100/12.5; 100/25	28/98	Spirig HealthCare AG	14.04.2010	13.04.2020
C09DA01	LOS + HCTZ	Cosaar Plus	50/12.5; 100/12.5; 100/25	28/98	MSD Merck Sharp & Dohme AG	28.02.1997	26.11.2022
C09DA01	LOS + HCTZ	Losartan HCT Axapharm	50/12.5; 100/12.5; 100/25	28/98	Axapharm AG	20.12.2011	19.12.2021
C09DA01	LOS + HCTZ	Losartan HCT Helvepharm	50/12.5; 100/12.5; 100/25	28/98	Helvepharm AG	14.02.2011	13.02.2021
C09DA01	LOS + HCTZ	Losartan HCT Mepha	50/12.5; 100/12.5; 100/25	28/98	Mepha Pharma AG	19.05.2009	18.05.2019
C09DA02	EPR + HCTZ	Teveten Plus	600/12.5	28/98	Mylan Pharma GmbH	07.06.2002	20.06.2022
C09DA02	EPR + HCTZ	Eprotan Mepha plus, Lactabs	600/12.6	28/99	Mepha Pharma AG	19.03.2007	18.03.2022
C09DA03	VAL + HCTZ	Co-Diovan	80/12.5; 160/12.5; 320/12.5; 320/25	28/98	Novartis Pharma Schweiz AG	28.01.1998	05.02.2024
C09DA03	VAL + HCTZ	Co-Valsartan Sandoz	80/12.5; 160/12.5; 160/25	28/98	Sandoz Pharmaceuticals AG	14.12.2010	13.12.2020
C09DA03	VAL + HCTZ	Co-Valsartan Mepha	80/12.5; 160/12.5; 160/25	28/98	Mepha Pharma AG	16.03.2010	15.03.2020
C09DA03	VAL + HCTZ	Valsartan HCT Actavis	not in the Spezialitätenliste	28/56/98	Mepha Pharma AG	04.04.2011	03.04.2021
C09DA03	VAL + HCTZ	Valsartan HCT Axapharm	80/12.5; 160/12.5; 160/25	28/56/98	Axapharm AG	15.05.2013	14.05.2023
C09DA03	VAL + HCTZ	Valsartan HCT Helvepharm	80/12.5; 160/12.5; 160/25	28/56/98	Helvepharm AG	13.09.2011	12.09.2021
C09DA03	VAL + HCTZ	Co-Valsartan Spirig HC	80/12.5; 160/12.5; 160/25	28/98	Spirig HealthCare AG	12.04.2011	11.04.2021
C09DA04	IRB + HCTZ	Co-Irbesartan Sandoz	150/12.5; 300/12.5; 300/25	28/98	Sandoz Pharmaceuticals AG	06.11.2012	05.11.2022
C09DA04	IRB + HCTZ	Co-Irbesartan Spirig HC	150/12.5; 300/12.5; 300/25	28/98	Spirig HealthCare AG	05.03.2013	04.03.2023
C09DA04	IRB + HCTZ	Irbesartan HCT Mepha	150/12.5; 300/12.5; 300/25	28/98	Mepha Pharma AG	08.02.2011	07.02.2021
C09DA04	IRB + HCTZ	Irbesartan HCT Zentiva	150/12.5; 300/12.5; 300/25	28/98	Helvepharm AG	27.07.2011	26.07.2021
C09DA04	IRB + HCTZ	CoAprovel, Filmtabl	150/12.5; 300/12.5; 30/25	28/98	Sanofi-Aventis (Suisse) SA	10.02.1999	19.12.2019

ATC code	Substance	Brand name	Dosage mg	Pack size*	Marketing authorisation holder	Date of first approval	Approval valid until
C09DA06	CAN + HCTZ	Blopress plus	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	Takeda Pharma AG	11.02.2000	05.09.2020
C09DA06	CAN + HCTZ	Candesartan HCT Helvepharm	8/12.5; 16/12.5;32/12.5; 32/25	28/100	Helvepharm AG	30.01.2012	29.01.2022
C09DA06	CAN + HCTZ	Candesartan Mepha plus	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	Mepha Pharma AG	24.01.2011	23.01.2021
C09DA06	CAN + HCTZ	Candesartan Plus Takeda	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	Takeda Pharma AG	12.03.2012	11.03.2022
C09DA06	CAN + HCTZ	Co-Candesartan Sandoz	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	Sandoz Pharmaceuticals AG	18.07.2011	17.07.2021
C09DA06	CAN + HCTZ	Co-Candesartan Spirig HC	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	Spirig HealthCare AG	23.09.2016	22.09.2021
C09DA06	CAN + HCTZ	Pemzek Plus	8/12.5; 16/12.5; 32/12.5; 32/25	28/98	AstraZeneca AG	06.01.2012	05.01.2022
C09DA06	CAN + HCTZ	Atacand Plus	8/12.5; 16/12.5; 32/12.5; 32/26	28/99	AstraZeneca AG	24.03.1999	19.12.2019
C09DA07	TEL + HCTZ	Co-Telmisartan Sandoz	80/12.5; 80/25	28/98	Sandoz Pharmaceuticals AG	27.02.2014	26.02.2024
C09DA07	TEL + HCTZ	Co-Telmisartan Spirig HC	80/12.5; 80/25	28/98	Spirig HealthCare AG	05.09.2016	04.09.2021
C09DA07	TEL + HCTZ	Kinzal Plus	80/12.5; 80/25	28/98	Bayer (Schweiz) AG	25.02.2003	07.10.2022
C09DA07	TEL + HCTZ	Micardis Plus	80/12.5; 80/25	28/98	Boehringer Ingelheim (Schweiz) GmbH	30.08.2002	23.07.2022
C09DA07	TEL + HCTZ	Telmisartan HCT Mepha	80/12.5; 80/25	28/98	Mepha Pharma AG	08.04.2015	07.04.2020
C09DA07	TEL + HCTZ	Telmisartan HCT Zentiva	80/12.5; 80/25	28/98	Helvepharm AG	03.02.2016	02.02.2021
C09DA08	OLM + HCTZ	Co-Olmesartan Spirig HC	20/12.5; 20/25; 40/12.5; 40/25	28/98	Spirig HealthCare AG	01.03.2017	28.02.2022
C09DA08	OLM + HCTZ	Olmesartan HCT Mepha	20/12.5; 20/25; 40/12.5; 40/25	28/98	Mepha Pharma AG	22.09.2016	21.09.2021
C09DA08	OLM + HCTZ	Olmesartan Plus Sandoz	20/12.5; 20/25; 40/12.5; 40/25	28/98	Sandoz Pharmaceuticals AG	08.02.2017	07.02.2022
C09DA08	OLM + HCTZ	Olmetec Plus	20/12.5; 20/25; 40/12.5; 40/25	28/98	Daiichi Sankyo (Schweiz) AG	12.07.2005	11.07.2020
C09DA08	OLM + HCTZ	Votum Plus	20/12.5; 20/25; 40/12.5; 40/25; 80/12.5; 80/25	28/98	A. Menarini AG	07.10.2005	06.10.2020
C09DA08	OLM + HCTZ	Olmesartan HCT Mylan	20/12.5; 20/25; 40/12.5; 40/25	28/98	Mylan Pharma GmbH	19.07.2018	18.07.2023
C09DA09	AZI + HCTZ	Edarbyclor	40/12.5; 40/25	28/98	Takeda Pharma AG	28.10.2014	27.10.2019

ATC code	Substance	Brand name	Dosage mg	Pack size*	Marketing authorisation holder	Date of first approval	Approval valid until
C09DB01	VAL + CCBs	Exforge	5/80; 10/160	28/98	Novartis Pharma Schweiz AG	22.12.2006	21.12.2021
C09DB01	VAL + CCBs	Amlodipin-Valsartan-Mepha	5/80; 5/160; 10/160	28/98	Mepha Pharma AG	14.07.2016	13.07.2021
C09DB01	VAL + CCBs	Valsartan Amlo Spirig HC	5/160/12.5; 5/160/25; 10/160/12.5; 10/160/25	28/99	Spirig HealthCare AG	20.06.2016	19.06.2021
C09DB02	OLM + CCBs	Olmesartan Amlodipin Sandoz	20/5; 40/5; 40/10; 20/12.5	28/98	Sandoz Pharmaceuticals AG	03.10.2017	02.10.2022
C09DB02	OLM + CCBs	Olmesartan-Amlodipin-Mepha	20/5; 40/5; 40/10	28/98	Mepha Pharma AG	07.12.2016	06.12.2021
C09DB02	OLM + CCBs	Sevikar	20/5; 40/5; 40/10	28/98	Daiichi Sankyo (Schweiz) AG	08.10.2008	07.10.2023
C09DB02	OLM + CCBs	Olmesartan Amlo Spirig HC	20/5; 40/5; 40/10	30/100	Spirig HealthCare AG	10.01.2018	10.01.2023
C09DB02	OLM + CCBs	Vascord	20/5; 40/5; 40/10	28/98	A. Menarini AG	05.12.2008	04.12.2023
C09DB04	TEL + CCBs	Micardis Amlo	40/5; 80/5; 80/10; 80/12.5; 80/25	28/98	Boehringer Ingelheim (Schweiz) GmbH	08.11.2010	07.11.2020
C09DX01	VAL + CCBs + HCTZ	Exforge HCT	5/160/12.5; 5/60/125; 10/160/12.5	28/98	Novartis Pharma Schweiz AG	16.09.2009	unlimited
C09DX01	VAL + CCBs + HCTZ	Amlodipin Valsartan HCT Mepha	5/160/12.5; 5/60/125; 10/160/12.5	28/99	Mepha Pharma AG	02.11.2016	01.11.2021
C09DX01	VAL + CCBs + HCTZ	Co-Valsartan Amlo Spirig HC	5/160/12.5; 5/60/125; 10/160/12.5	28/98	Spirig HealthCare AG	07.06.2018	06.06.2023
C09DX03	OLM + CCBs + HCTZ	Sevikar HCT	20/5/12.5; 40/5/12.5; 40/10/12.5; 40/5/25; 40/10/25	28/98	Daiichi Sankyo (Schweiz) AG	30.05.2011	29.05.2021
C09DX03	OLM + CCBs + HCTZ	Olmesartan Amlodipin HCT Sandoz	not in the Spezialitätenliste		Sandoz Pharmaceuticals AG	25.04.2019	24.04.2024
C09DX03	OLM + CCBs + HCTZ	Vascord HCT	20/5/12.5; 40/5/12.5; 40/10/12.5; 40/5/25; 40/10/25	28/98	A. Menarini AG	09.08.2011	08.08.2021

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; CCBs = Calcium channel blockers; EPR = eprosartan; HCTZ = hydrochlorothiazide; IRB = irbesartan; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

* According to the SL

Sources: www.spezialitätenliste.ch as of 30 July 2019 and www.swissmedicinfo.ch as of 30 July 2019

14.2 Appendix B: Selection criteria and search strategy

Table 22: Search strategies for EFF, SAF and ECO (search for scoping report incl. search update)

Search strategy Medline via OVID

Search for scoping report: **Search date: 24 October 2018** **Databases: Ovid MEDLINE® ALL 1946 to 24 October 2018, Publisher, In-Data-Review, In-Process and PubMed-not-MEDLINE records from NLM**			**Search update:** **Search date: 11 June 2019** **Databases: Ovid MEDLINE® ALL (1946 to Daily Update), Publisher, In-Data-Review, In-Process and PubMed-not-MEDLINE records from NLM Ovid MEDLINE(R) ALL 1946 to 11 June 2019**	
1	exp Essential Hypertension	2035	2117	Search for disease (MeSH and free text)
2	exp Hypertensive Retinopathy/	152	163	
3	"essential hypertens*".ab,ti.	23338	23504	
4	"Primar* Hypertens*".ab,ti.	1993	2040	
5	"idiopathic* hypertens*".ab,ti.	84	87	
6	exp Hypertension/	241623	245538	
7	exp Blood Pressure/	278331	282188	
8	"hypertens*".ab,ti.	395922	407199	
9	"blood pressur*".ab,ti.	276652	283990	
10	"systemic* hypertens*".ab,ti.	4422	4484	
11	"systolic* pressur*".ab,ti.	14092	14379	
12	"diastolic* pressur*".ab,ti.	14984	15167	
13	"arterial pressur*".ab,ti.	58731	59774	
14	"bloodpressur*".ab,ti.	43	44	
15	exp Antihypertensive Agents/	245485	253285	
16	"antihypertens*".ab,ti.	45580	46716	
17	"anti hypertens*".ab,ti.	4249	4423	
18	"spontan* hypertens*".ab,ti.	19332	19547	
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	929537	Linking search for disease with OR
20	exp Olmesartan Medoxomil/	402	407	Search for intervention (olmesartan as mono- and any combination therapy (MeSH and free text))
21	"Olmesartan*".af.	1517	1551	
22	20 or 21	1517	1551	Linking search for intervention with OR

23	19 and 22	1182	1214	Intervention AND disease
24	limit 23 to (English or German)	1140	1171	Limit to English or German
25	exp Animals/	21858262	22369939	Exclude animal studies
26	humans.sh.	17349859	17782134	
27	25 not 26	4508403	4587805	
28	26 not 27	860	887	Total hits
29	from 28 keep 1-860	860	887	Total hits exported to Endnote
30	exp Randomised Controlled Trials as Topic/	121307	126838	Search filter for RCTs excluding case reports, letters, historical articles
31	exp randomised controlled trial/	470739	484017	
32	exp Random Allocation/	96305	99260	
33	exp Double-Blind Method/	147990	151649	
34	exp single-blind method/	25830	26863	
35	exp clinical trial/	810025	828063	
36	clinical trial, phase i.pt.	18433	18997	
37	clinical trial, phase ii.pt.	29720	30668	
38	clinical trial, phase iii.pt.	14283	15112	
39	clinical trial, phase iv.pt.	1607	1712	
40	controlled clinical trial.pt.	92722	93106	
41	randomised controlled trial.pt.	470336	483466	
42	multicentre study.pt.	240681	251462	
43	clinical trial.pt.	512937	516498	
44	exp Clinical Trials as Topic/	318582	326661	
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	1297412	
46	(clinical adj trial*).tw.	318279	334729	
47	((singl* or doubl* or treb* or tripl*) adj (blind* or mask*)).tw.	159764	164221	
48	randomly allocated.tw.	25096	26358	
49	(allocated adj2 random*).tw.	28183	29517	
50	46 or 47 or 48 or 49	473432	493947	
51	45 or 50	1456963	1504956	
52	case report.tw.	278351	289381	
53	exp letter/	1004514	1030266	
54	exp historical article/	383676	388621	
55	52 or 53 or 54	1651968	1693207	
56	51 not 55	1423446	1470425	
57	29 and 56	**444**		Hits for RCT (scoping report)

	Limit 29 and 56 to publication from 24/10/2018 to Current		**4**	Hits for RCT (search update)
58	exp meta-analysis as topic/	16991	17811	Search filter for systematic reviews and meta-analyses excluding comments, editorials, letters
59	exp meta-analysis/	93528	101732	
60	"meta analy*".tw.	135331	148123	
61	"metaanaly*".tw.	1881	1952	
62	(systematic adj (review$1 or overview$1)).tw.	129746	143977	
63	"Review Literature as Topic"/	7537	7408	
64	58 or 59 or 60 or 61 or 62 or 63	240296	260795	
65	cochrane.ab.	64682	71098	
66	embase.ab.	69159	76747	
67	(psychlit or psyclit).ab.	913	913	
68	(psychinfo or psycinfo).ab.	25326	29267	
69	(cinahl or cinhal).ab.	21997	24172	
70	science citation index.ab.	2820	2952	
71	reference list$.ab.	15768	16514	
72	bibliograph$.ab.	16165	16794	
73	hand-search$.ab.	6082	6371	
74	relevant journals.ab.	1074	1103	
75	selection criteria.ab.	27581	28535	
76	data extraction.ab.	17020	18341	
77	75 or 76	42493	44694	
78	"review"/	2444155	2520935	
79	77 and 78	28391	28426	
80	65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	131183	144689	
81	exp comment/ or exp editorial/ or exp letter/	1667993	1733117	
82	64 or 79 or 80	288704	313356	
83	82 not 81	277674	301434	
84	29 and 83	**35**		Hits for systematic reviews, meta-analysie (scoping report)
	Limit 29 and 83 to publication from 24/10/2018 to Current		**5**	Hits for systematic reviews, meta-analyses (search update)
85	Economics/	26962	27046	Search filter for economy
86	"Costs and Cost Analysis"/	46487	47296	
87	"Cost Allocation"/	1988	1997	
88	Cost-Benefit Analysis/	74416	76714	

89	"Cost Control"/	21261	21366	
90	"Cost Savings"/	10930	11217	
91	"cost of illness"/	24125	25163	
92	"Cost Sharing"/	2376	2430	
93	"Deductibles and Coinsurance"/	1683	1712	
94	Medical Savings Accounts/	524	528	
95	Health Care Costs/	35782	36981	
96	direct service costs/ or drug costs/ or employer health costs/ or hospital costs/	26168	26923	
97	health expenditures/ or capital expenditures/	19899	20770	
98	"Value of Life"/	5624	5647	
99	exp Economics, Hospital/	23151	23615	
100	exp Economics, Medical/	14059	14102	
101	Economics, Nursing/	3982	3986	
102	Economics, Pharmaceutical/	2808	2862	
103	exp "Fees and Charges"/	29449	29742	
104	exp Budgets/	13395	13515	
105	(low adj cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	46156	50302	
106	(high adj cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12388	13137	
107	(health?care adj cost*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9372	10178	
108	(fiscal or funding or financial or finance).tw.	126449	133452	
109	(cost adj estimate*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2022	2107	
110	(cost adj variable).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	39	41	

111	(unit adj cost*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2245	2348	
112	(economic* or pharmacoeconomic* or price* or pricing).tw.	259902	274262	
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	676380	
114	(cost adj effectiv*).tw.	116901	122982	
115	(cost adj utility).tw.	3949	4216	
116	(cost adj benefit*).tw.	10012	10291	
117	(cost adj consequenc*).tw.	494	524	
118	"budget impact analys*".tw.	540	586	
119	113 or 114 or 115 or 116 or 117 or 118	715910	749058	
120	29 and 119	**33**		Hits for economy (scoping report)
	Limit 29 and 119 to publication from 24/10/2018 to Current		**1**	Hits for economy (search update)

Table 23: Search strategies for observational studies for SAF (widened search for HTA report)

Search strategy Medline via OVID

Search date: 13 May 2019

Databases: Ovid MEDLINE® ALL (1946 to Daily Update), Publisher, In-Data-Review, In-Process and PubMed-not-MEDLINE records from NLM Ovid MEDLINE(R) ALL 1946 to 13 May 2019

1	exp Essential Hypertension/	2101
2	exp Hypertensive Retinopathy/	162
3	"essential hypertens*".ab,ti.	23462
4	"Primar* Hypertens*".ab,ti.	2034
5	"idiopathic* hypertens*".ab,ti.	87
6	exp Hypertension/	244807
7	exp Blood Pressure/	281435
8	"hypertens*".ab,ti.	403692
9	"blood pressur*".ab,ti.	282138
10	"systemic* hypertens*".ab,ti.	4449
11	"systolic* pressur*".ab,ti.	14305
12	"diastolic* pressur*".ab,ti.	15124
13	"arterial pressur*".ab,ti.	59516
14	"bloodpressur*".ab,ti.	44
15	exp Antihypertensive Agents/	252852

16	"antihypertens*".ab,ti.	46413
17	"anti hypertens*".ab,ti.	4363
18	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	924215
19	exp Olmesartan Medoxomil/	406
20	"Olmesartan*".af.	1539
21	19 or 20	1539
22	"spontan* hypertens*".ab,ti.	19499
23	18 or 22	924215
24	21 and 23	1205
25	limit 24 to (english or german)	1162
26	exp Animals/	22271563
27	humans.sh.	17697042
28	26 not 27	4574521
29	25 not 28	879
30	epidemiologic studies/	7938
31	exp case-control studies/	988108
32	exp Cohort Studies/	1850198
33	Case control.tw.	114975
34	(cohort adj (study or studies)).tw.	174892
35	"Cohort analy*".tw.	6943
36	(Follow up adj (study or studies)).tw.	46731
37	(observational adj (study or studies)).tw.	91399
38	Longitudinal.tw.	220789
39	Retrospective.tw.	467286
40	Cross-sectional.tw.	307247
41	Cross-sectional Studies/	292332
42	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	2748429
43	29 and 42	177

Search strategy Embase via OVID

Search date: 13 May 2019

1	exp essential hypertension/	27332
2	exp hypertension retinopathy/	1195
3	"essential hypertens*".ab,ti.	30024
4	"Primar* Hypertens*".ab,ti.	2919
5	"idiopathic* hypertens* ".ab,ti.	122
6	exp hypertension/	681035
7	exp blood pressure/	524297
8	"hypertens*".ab,ti.	599533
9	"blood pressur*".ab,ti.	400875
10	"systemic* hypertens*".ab,ti.	6024
11	"systolic* pressur*".ab,ti.	22489
12	"diastolic* pressur*".ab,ti.	20302
13	"arterial pressur*".ab,ti.	76425
14	"bloodpressur*".ab,ti.	306

15	exp antihypertensive agent/	661039
16	"antihypertens*".ab,ti.	67819
17	"anti hypertens*".ab,ti.	8803
18	"spontan* hypertens*".ab,ti.	24143
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	1695564
20	exp olmesartan/	4420
21	"Olmesartan*".af.	4740
22	exp amlodipine plus olmesartan/	207
23	exp hydrochlorothiazide plus olmesartan/	120
24	exp amlodipine plus hydrochlorothiazide plus olmesartan/	62
25	20 or 21 or 22 or 23 or 24	4740
26	19 and 25	4705
27	limit 26 to (english or german)	4528
28	exp animal/	24293481
29	exp non-human/	5847863
30	28 or 29	25959955
31	exp human/	19830490
32	30 not 31	6129465
33	27 not 32	3856
34	clinical study.sh.	154219
35	exp case control study/	159939
36	exp family study/	26018
37	exp longitudinal study/	127197
38	exp retrospective study/	788464
39	exp prospective study/	529294
40	exp "randomised controlled trial (topic)"/	163455
41	39 not 40	523833
42	exp cohort analysis/	478681
43	(Cohort adj (study or studies)).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]	265769
44	(Case control adj (study or studies)).tw.	123889
45	(follow up adj (study or studies)).tw.	60117
46	(observational adj (study or studies)).tw.	146366
47	(epidemiologic* adj (study or studies)).tw.	100828
48	(cross-sectional adj (study or studies)).tw.	190485
49	34 or 35 or 36 or 37 or 38 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	2404892
50	33 and 49	397

Table 24: Search strategies for ethical and social domain (widened search for HTA report)

Search strategy Medline via OVID

Search date: 18 June 2019

Databases: Ovid MEDLINE® ALL 1946 to 18 June 2019

1	exp Essential Hypertension/	2122
2	exp Hypertensive Retinopathy/	163
3	"essential hypertens*".ab,ti.	23507
4	"Primar* Hypertens*".ab,ti.	2041
5	"idiopathic* hypertens*".ab,ti.	87

6	exp Hypertension/	245671
7	exp Blood Pressure/	282310
8	"hypertens*".ab,ti.	407431
9	"blood pressur*".ab,ti.	284181
10	"systemic* hypertens*".ab,ti.	4485
11	"systolic* pressur*".ab,ti.	14389
12	"diastolic* pressur*".ab,ti.	15166
13	"arterial pressur*".ab,ti.	59784
14	"bloodpressur*".ab,ti.	44
15	exp Antihypertensive Agents/	253357
16	"antihypertens*".ab,ti.	46742
17	"anti hypertens*".ab,ti.	4429
18	"spontan* hypertens*".ab,ti.	19559
19	exp Animals/	22384927
20	humans.sh.	17795451
21	19 not 20	4589476
22	exp Ethics/	141774
23	"ethics*".ti.	25698
24	"ethical*".ti.	24777
25	"sociological* aspect*".ti.	160
26	"social* aspect*".ti.	1349
27	exp Socioeconomic Factors/	427913
28	"patient* experience*".ti.	3632
29	"patient* attitude*".ti.	840
30	exp Physician-Patient Relations/	70030
31	exp Practice Patterns, Physicians'/	55414
32	exp Health Communication/	1831
33	"physician* patient* communication*".ab,ti.	835
34	"doctor* patient* communication*".ab,ti.	1030
35	exp Health Services Accessibility/	104801
36	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	767843
37	exp Angiotensin II Type 1 Receptor Blockers/	17288
38	"sartan*".ab,ti.	294
39	"Azilsartan*".ab,ti.	179
40	"Candesartan*".ab,ti.	2572
41	"Irbesartan*".ab,ti.	1596
42	"Losartan*".ab,ti.	8306
43	"Telmisartan*".ab,ti.	2085
44	"Valsartan*".ab,ti.	3300
45	"olmesartan*".af.	1552
46	exp Olmesartan Medoxomil/	408
47	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	23666
48	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	929976
49	47 and 48	18576
50	limit 49 to (english or german)	17361
51	50 not 21	10640
52	36 and 51	100

Search strategy Embase via OVID

Search date: 18 June 2019

1	exp essential hypertension/	27309
2	exp hypertension retinopathy/	1192
3	"essential hypertens*".ab,ti.	30004
4	"Primar* Hypertens*".ab,ti.	2909
5	"idiopathic* hypertens* ".ab,ti.	122
6	exp hypertension/	678638
7	exp blood pressure/	522669
8	"hypertens*".ab,ti.	597772
9	"blood pressur*".ab,ti.	399816
10	"systemic* hypertens*".ab,ti.	6010
11	"systolic* pressur*".ab,ti.	22448
12	"diastolic* pressur*".ab,ti.	20269
13	"arterial pressur*".ab,ti.	76271
14	"bloodpressur*".ab,ti.	306
15	exp antihypertensive agent/	659666
16	"antihypertens*".ab,ti.	67658
17	"anti hypertens*".ab,ti.	8770
18	"spontan* hypertens*".ab,ti.	24111
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	1690500
20	exp olmesartan/	4410
21	"Olmesartan*".af.	4730
22	exp amlodipine plus olmesartan/	206
23	exp hydrochlorothiazide plus olmesartan/	120
24	exp amlodipine plus hydrochlorothiazide plus olmesartan/	62
25	exp angiotensin 1 receptor antagonist/	5473
26	"sartan*".ab,ti.	654
27	"Azilsartan*".ab,ti.	321
28	"Candesartan*".ab,ti.	3691
29	"Irbesartan*".ab,ti.	2464
30	"Losartan*".ab,ti.	11624
31	"Telmisartan*".ab,ti.	3515
32	"Valsartan*".ab,ti.	5516
33	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	32012
34	exp ethics/	280067
35	"ethics*".ti.	27301
36	"ethical*".ti.	28131
37	"sociological* aspect*".ti.	104
38	"social* aspect*".ti.	1020
39	"patient* experience*".ti.	5216
40	"patient* attitude*".ti.	1051
41	exp socioeconomics/	354856
42	exp doctor patient relation/	112667
43	exp medical information/	70004

44	"physician* patient* communication*".ti.	280
45	"doctor* patient* communication*".ti.	344
46	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	790085
47	19 and 33	31432
48	limit 47 to (english or german)	29466
49	exp animal/	24219672
50	exp non-human/	5827608
51	49 or 50	25881733
52	exp human/	19766891
53	51 not 52	6114842
54	48 not 53	19625
55	46 and 54	167

Table 25: Search strategies for organisational domain (widened search for HTA report)

Search strategy Medline via OVID

Search date: 18 June 2019

Databases: Ovid MEDLINE® ALL 1946 to 18 June 2019

1	exp Essential Hypertension/	2122
2	exp Hypertensive Retinopathy/	163
3	essential hypertens*.ab,ti.	23507
4	Primar* Hypertens*.ab,ti.	2041
5	idiopathic* hypertens*.ab,ti.	87
6	exp Hypertension/	245671
7	exp Blood Pressure/	282310
8	hypertens*.ab,ti.	407431
9	blood pressur*.ab,ti.	284181
10	systemic* hypertens*.ab,ti.	4485
11	systolic* pressur*.ab,ti.	14389
12	diastolic* pressur*.ab,ti.	15166
13	arterial pressur*.ab,ti.	59784
14	bloodpressur*.ab,ti.	44
15	exp Antihypertensive Agents/	253357
16	antihypertens*.ab,ti.	46742
17	anti hypertens*.ab,ti.	4429
18	spontan* hypertens*.ab,ti.	19559
19	exp Animals/	22384927
20	humans.sh.	17795451
21	19 not 20	4589476
22	exp Drug Substitution/	3168
23	drug switch*.ab,ti.	194
24	(olmesartan adj2 switch*).ab,ti.	7
25	drug substitut*.ab,ti.	359
26	(olmesartan adj2 substitut*).ab,ti.	1
27	disinvest*.ab,ti.	239
28	changeover*.ab,ti.	905

29	medication switch*.ab,ti.	165
30	medication replace*.ab,ti.	5
31	drug replace*.ab,ti.	42
32	(olmesartan adj2 replace*).ab,ti.	0
33	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	4986
34	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	929976
35	exp Angiotensin II Type 1 Receptor Blockers/	17288
36	sartan*.ab,ti.	294
37	Azilsartan*.ab,ti.	179
38	Candesartan*.ab,ti.	2572
39	Irbesartan*.ab,ti.	1596
40	Losartan*.ab,ti.	8306
41	Telmisartan*.ab,ti.	2085
42	Valsartan*.ab,ti.	3300
43	olmesartan*.af.	1552
44	exp Olmesartan Medoxomil/	408
45	35 or 36 or 37 or 38 or 39 or 40 or 41 42 or 43 or 44	23666
46	34 and 45	18576
47	limit 46 to (english or german)	17361
48	47 not 21	10640
49	33 and 48	51

Search strategy Embase via OVID

Search date: 18 June 2019

1	exp essential hypertension/	27309
2	exp hypertension retinopathy/	1192
3	"essential hypertens*".ab,ti.	30004
4	"Primar* Hypertens*".ab,ti.	2909
5	"idiopathic* hypertens* ".ab,ti.	122
6	exp hypertension/	678638
7	exp blood pressure/	522669
8	"hypertens*".ab,ti.	597772
9	"blood pressur*".ab,ti.	399816
10	"systemic* hypertens*".ab,ti.	6010
11	"systolic* pressur*".ab,ti.	22448
12	"diastolic* pressur*".ab,ti.	20269
13	"arterial pressur*".ab,ti.	76271
14	"bloodpressur*".ab,ti.	306
15	exp antihypertensive agent/	659666
16	"antihypertens*".ab,ti.	67658
17	"anti hypertens*".ab,ti.	8770
18	"spontan* hypertens*".ab,ti.	24111
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	1690500
20	exp olmesartan/	4410
21	"Olmesartan*".af.	4730

22	exp amlodipine plus olmesartan/	206
23	exp hydrochlorothiazide plus olmesartan/	120
24	exp amlodipine plus hydrochlorothiazide plus olmesartan/	62
25	exp angiotensin 1 receptor antagonist/	5473
26	"sartan*".ab,ti.	654
27	"Azilsartan*".ab,ti.	321
28	"Candesartan*".ab,ti.	3691
29	"Irbesartan*".ab,ti.	2464
30	"Losartan*".ab,ti.	11624
31	"Telmisartan*".ab,ti.	3515
32	"Valsartan*".ab,ti.	5516
33	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	32012
34	exp drug substitution/	38526
35	"drug switch*".ab,ti.	379
36	(olmesartan adj2 switch*).ab,ti.	15
37	"drug substitut*".ab,ti.	555
38	(olmesartan adj2 substitut*).ab,ti.	2
39	"medication switch*".ab,ti.	297
40	"medication replace*".ab,ti.	14
41	"drug replace*".ab,ti.	83
42	(olmesartan adj2 replace*).ab,ti.	0
43	"disinvest*".ab,ti.	318
44	"changeover*".ab,ti.	1110
45	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	40772
46	19 and 33 and 45	268
47	Limit 46 to (english or german)	251
48	exp animal/	24219672
49	exp non-human/	5827608
50	48 or 49	25881733
51	exp human/	19766891
52	50 not 51	6114842
53	47 not 52	249

Table 26: Selection criteria for EFF, SAF and ECO

I 1	Patients (≥18 years) with essential (primary) arterial hypertension that requires antihypertensive pharmacotherapy The study focus is essential hypertension.However study populations with existing co-morbidities were not excluded from the analyses when the primary target of the study was the treatment of essential hypertension.
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
I 3 a	Control: domain efficacy: 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
I 3 b	Control: domain safety for comparative safety assessment same as I 3 a, no control for single-arm studies
I 4	Including one or more of the critical or important outcomes as formulated in PICO
I 5	Study design domain efficacy/effectiveness: randomised controlled trials (direct comparisons), follow-up at least 2 months
I 5 a	Study design domain efficacy/effectiveness: for long-term outcomes (morbidity, mortality) non-randomised controlled trials and observational studies: prospective cohort studies, retrospective cohort studies
I 6	Study design for domain safety: randomised controlled trial (direct comparisons)
I 6 a	Study design for domain safety: non-randomised controlled trials, observational studies: prospective cohort studies, retrospective cohort studies, case-control studies, uncontrolled longitudinal studies (single-arm studies for prevalence of adverse events)
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
I 9	Formal aspects: language (English, German), Search period: no restriction
I 10	Full publication available
I 11	Duration of treatment: a minimum of 8 weeks for the efficacy domain (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” and more than 8 weeks for the safety domain
I 12	Study design/questions allows safety assessment

I = inclusion criteria with number

Table 27: Documentation of queries

Study/domain	Content of query	Reply received yes/no	Content of reply
Regulatory status/Organisational domain	- Inquiry Main Association of Austrian Social Security Institutions about experiences with withdrawal of OLM from reimbursement as of 1 January 2019	Yes	- Massive decline in prescriptions for all preparations containing the active ingredient OLM from 1st quarter 2019 compared with 4th quarter 2018 - No statement possible on the exact figures within sartans - Inquiries from patients (10 inquiries at Main Association of Austrian Social Security Institutions) regarding the reasons for delisting and possible alternatives - Complaint by the manufacturing company to the Federal Administrative Court dismissed
Regulatory status/Organisational domain	- Inquiry Assurance Maladie/France 19 June 2019 about consequences in France regarding deleting OLM from reimbursement and if there were any organisational issues	No	-
Regulatory status/Organisational domain	- Inquiry Haute Autorité de Santé/France 17 July 2019 about consequences in France regarding deleting OLM from reimbursement and if there were any organisational issues; 2nd inquiry 27 July 2019	No	-
Regulatory status	- Inquiry TLV (The Dental and Pharmaceutical Benefits Agency) 19 June 2019 regarding market availability of olmesartan in Sweden	Yes	- OLM was available between 2014 and 2019 – however only from time to time in very limited quantities (about 10 to 50 packs per year)
Budget impact	- Inquiry physician(s) experiences in Austria regarding delisting OLM, prescription behaviour	Yes	- Substitution of mono- with mono-preparations and combi- with combi-preparations within sartans, no switching to ACE preparations; mainly substitution within mono-preparations to the Austrian market leader CAN followed by VAL and to a lesser extent to LOS and TEL. Combination preparations: VAL and HCTZ and CCBs (50%), 20% to CAN and HCTZ and 30% to VAL and HCTZ (these are also the market leaders in Austria).

14.3 Appendix C: Effectiveness/Safety

Table 28: Study quality assessment for RCTs: outcome diastolic blood pressure

Study	Basic quality of evidence (study design)	Lack of allocation concealment	Lack of blinding	Incomplete accounting of patients and outcomes	Selective out-come reporting	Other limitations	Modified quality of evidence
Tsutamoto et al. 2010[44]	High	Unclear	Yes	Unclear	No	Yes	Moderate
Ushijima et al. 2015[45]	High	Unclear	Yes	Unclear	No	Yes	Moderate
Fogari et al. 2008[36]	High	No	Yes	No	No	No	Moderate
Kalikar et al. 2017[38]	High	No	Yes	No	No	Yes	Moderate
Liau et al. 2005[39]	High	No	No	Yes	No	No	Moderate
Oparil et al. 2001[41]	High	Unclear	No	No	No	No	Moderate
Morii et al. 2012[40]	High	Unclear	Yes	Yes	No	Yes	Moderate
Ball et al. 2001[31]	High	Unclear	No	Unclear	No	No	Moderate
Brunner et al. 2003[22]	High	Unclear	No	No	No	No	Moderate
Crush 2012[35]	High	No	No	Unclear	No	No	Moderate
De Luis et al. 2010a[32]	High	No	Yes	Unclear	No	Yes	Moderate
De Luis et al. 2010b[33]	High	Unclear	Yes	Unclear	No	No	Moderate
Giles et al. 2007[23]	High	Unclear	No	No	No	No	Moderate
Destro et al. 2005[34]	High	Unclear	Yes	Unclear	No	No	Moderate
Ramesh et al. 2018[42]	High	Unclear	Unclear	Yes	No	No	Moderate
Shiga et al. 2017[43]	High	Unclear	Unclear	Unclear	No	Yes	Moderate
Kakio et al. 2017[37]	High	Unclear	Yes	No	No	Yes	Moderate

Table 29: Study quality assessment for cohort studies: outcome enteropathy and long-term effectiveness outcomes

Study	Failure to develop and apply appropriate eligibility criteria	Flawed measurement of both exposure and outcome	Failure to adequately control confounding	Incomplete or inadequately short follow-up	Modified quality of evidence
Dong et al. 2018[51]	No	No	No	No	Moderate
You et al. 2019[58]	Yes	No	Yes	No	Very low
Malfertheiner et al. 2018[54]	Yes	No	Yes	No	Very low
Basson et al. 2015[49]	Yes	No	Yes	No	Very low
De Bortoli et al. 2017[50]	Yes	No	Yes	Yes	Very low
Swindle et al. 2011[46]	Yes	Yes	Unclear	No	Low

Table 30: Study characteristics and SAE occurrences in single-arm studies as well as single arms of RCTs/cohort studies

Study design	STUDY	Population	Follow-up (weeks)	Participants	SAE number	Events projected for one year per 1'000 participants
OLM arms from RCTs	Barrios et al. 2007[83]	HT	14	627	7	41
	Fogari et al. 2008[84]	HT + DM	48	74	0	0
	Hirohata et al. 2012[85]	HT + SAP/PCI	16	126	8	206
	Malacco et al. 2012[86]	HT + elder	36	284	0	0
	Mazza et al. 2016[87]	HT	26	69	0	0
	Nielsen et al. 2018[88]	HT + HF	117	484	6	6
	Omboni et al. 2015[90]	HT + elder	12	712	0	0
	OSCAR 2012[89]	HT + DM	156	1'164	98	28
	Sakata et al. 2015[92]	HT + CHF	229	578	192	75
	SEVITENSION[91]	HT	24	244	4	36
	Williams et al. 2017[82]	HT	52	225	13	58

Study design	STUDY	Population	Follow-up (weeks)	Participants	SAE number	Events projected for one year per 1'000 participants
OLM arms from cohort studies	Angeloni et al. 2015[93]	HT + elder	26	142	0	0
	Bramlage et al. 2011[94]	HT	14	8'241	3	1
	Kawai et al. 2011[95]	HT	24	68	0	0
	OMEGA 2012[99]	HT + DM	156	14'721	281	6
	Saito et al. 2008[96]	HT	26	554	0	0
	Saito et al. 2012[97]	HT	12	1'246	0	0
	Scholze et al. 2014[98]	HT + CKD	52	7'724	45	6
	Toh et al. 2012[100]	HT	52	92'973	1	0
Single-arm studies with OLM	Bramlage et al. 2014[61]	HT	24	10'995	24	5
	Bramlage et al. 2015[60]	HT	24	5'831	5	2
	Buendia et al. 2017[62]	HT	12	428	0	0
	CRUSH 2012[74]	HT	12	999	12	52
	Dohi et al. 2011[63]	HT	12	25	0	0
	Germino et al. 2012[64]	HT	12	178	0	0
	Gomes et al. 2008[65]	HT + elder	9	144	0	0
	Heagerty et al. 2009[66]	HT	53	1'621	40	24
	HONEST 2018[75]	HT + elder	104	21'591	123	3
	Izzo et al. 2007a[67]	HT + elder	17	170	8	141
	Izzo et al. 2007b[68]	HT stage II	13	250	1	16
	Jung et al. 2015[69]	HT stage II	12	385	4	45
	Kereiakes et al. 2010[70]	HT	12	192	0	0
	Neutel et al. 2006[72]	HT	24	86	5	126

Study design	STUDY	Population	Follow-up (weeks)	Participants	SAE number	Events projected for one year per 1'000 participants
	OMEGA 2015[79]	HT stage I + stage II HT	36	13'052	195	22
	Punzi et al. 2010[73]	HT + elder	12	185	0	0
	Saito et al. 2008[76]	HT	12	2'221	0	0
	Sezai et al. 2011[77]	HT	52	56	0	0
	Tada et al. 2015[78]	HT	12	25	0	0
	Wang et al. 2012[80]	HT + stroke	24	357	7	42
	WIN OVER 2014[71]	HT	26	8'940	0	0
	Zemmrich et al. 2013[81]	HT	18	191	1	15

HT = essential hypertension; CKD = chronic kidney disease; DM = diabetes mellitus; elder = elderly patients; SAE = severe adverse events

Source: authors' own calculations

Table 31: Case-control studies evaluating OLM-induced cases of enteritis

STUDY	Country	Population	COI
Kung et al. 2018[141]	USA	N.A.	No COI
Viola et al. 2015[142]	Global (World Health Organization Global Individual Case Safety Report database, VigiBase)	HT + photosensitivity	No COI
Greywoode et al. 2014[143]	USA	Patients undergoing endoscopy	No COI
Marthey et al. 2014[139]	France	N.A.	Some COI
Douros et al. 2013[144]	Germany	HT + pancreatitis	No COI

HT = hypertension; COI = conflict of interest; N.A. = not applicable

14.4 Appendix D: Costs, cost effectiveness and budget impact

Table 32: Equivalent doses

Valsartan	Azilsartan	Candesartan	Eprosar-tan	Irbesar-tan	Losartan	Olmesartan	Telmisartan
-	-	2 mg	-	-	12.5 mg	-	-
40 mg	20 mg	4 mg	300 mg*	75 mg*	25 mg	10 mg	20 mg*
80 mg	40 mg	8 mg	600 mg	150 mg	50 mg	20 mg	40 mg
120 mg*	60 mg*	12 mg*	900 mg*	225 mg*	75 mg*	30 mg*	60 mg*
160 mg	80 mg	16 mg	1200 mg*	300 mg	100 mg	40 mg	80 mg
320 mg	-	32 mg	-	-	-	-	-

* Not in SL 2018

Source: Deutsche Apothekerzeitung[110]

Table 33: Evidence table domain ECO (systematic literature search)

Study/country	Study design	Population	Interven-tion	Compara-tor	Main outcomes	Statistical validation	Sponsor	Source clinical /cost data	Perspec-tive
Belsey 2011,[116] UK	Probalistic cost-benefit simulation (Monte-Carlo) linked to blood pressure targets Budget impact	Parent cohort patients (number not reported) with normally distributed BPs about mean values of 170 mmHg and 105 mmHg No subclasses for age, sex or co-morbidity	OLM	CAN	*Lowering BP* *Mean treatment cost per patient/year (2010)* *Systolic target* 150 mmHg: OLM/CAN: ' GBD 171.36 vs. 189.91 *Systolic target 140 mmHg: OLM/CAN* GBD 304.50 vs. 441.96 Diastolic target 90 mmHg: *OLM/CAN* GBD 156.11 vs. 189.13 OLM = cost saving	No	Daiichi-Sankyo UK	Clinical trial data – indirect comparison: Karlson et al. 2009; Chrysant et al. 2008, Oparil et al. 2010 Drug Tariff and British National Formulary	Payer: National Health Service
Boersma et al. 2010,[112] NL	Cost-effectiveness simulation model, Extrapolation 1 and 5 years BP control: <140/90 mmHg	Hypothetical cohort with essential hypertension combined with daily-practice prescription data No subclasses analysed	OLM	LOS VAL IRB	Net costs/cardiovascular complication averted for cohort of 100'000 compared with do-nothing (2006), after 1 year: OLM: EUR 39'100 LOS: EUR 77'100 VAL: EUR 70'700 IRB: EUR 50'900 OLM = cost saving	No	Daiichi-Sankyo NL	Clinical trial data: Oparil et al. 2001 Dutch drug prices	Payer

Study/country	Study design	Population	Interven-tion	Compara-tor	Main outcomes	Statistical validation	Sponsor	Source clinical /cost data	Perspec-tive
Miller et al. 2010,[114] USA	Cost-effectiveness model (decision analytic model) based on medical chart data	Cohort of 121 472 patients -> 1600 randomly selected with >140/90 mmHg for uncomplicated hypertension and >130/80 mmHg for patients with diabetes; Average age 57.1 years 53.5% females	OLM Mono- and with HCTZ	LOS VAL IRB Mono- and with HCTZ	Cost per patient reaching BP goal (2006): all causes/ (hypertension attributable): OLM: USD 8'964(2'704) LOS: USD 10'484(3'291) VAL: USD 10'557(3'577) IRB: USD 13'335(4'325) OLM = cost saving	Yes	Daiichi-Sankyo, USA	Medical chart data Administrative claims cost data	Payer
Mazza et al. 2017,[113] I	"Cost-benefit analysis" stated by author, however no values cost/benefit/effectiveness shown Retrospective cross-sectional study	114 patients (>18 years) with essential hyper-tension – target: <140 mmHg Excluded: severe hypertension >180/110 mmHg and cardiovascular events, severe obesity, dementia	OLM Mono- and with HCTZ	CAN IRB LOS TEL VAL Mono- and with HCTZ	BP 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	No	N/R	Retrospective cross-sectional study Pharmacy dispensing records	N/R

Study/country	Study design	Population	Interven-tion	Compara-tor	Main outcomes	Statistical validation	Sponsor	Source clinical /cost data	Perspec-tive
Simons 2003,[115] USA	Cost effectiveness Modelling long-term events based on Framingham Heart Study Budget impact (health expenditure savings)	Hypothetical cohort of 100'000 individuals	OLM	LOS VAL IRB	Incremental benefit after 5 years for 100'000 patients (1999): OLM vs. LOS CVD: USD 15'149'000 CHD: USD 11'107'000 MI: USD 1'437'000 Stroke: USD 1'437'000 OLM vs. VAL CVD: USD 16'231'000 CHD: USD 11'955'000 MI: USD 14'505'000 Stroke: USD 1'741'000 OLM vs. IRB CVD: USD 5'410'000 CHD: USD 3'975'000 MI: USD 2'430'000 Stroke: USD 497'000 OLM has the potential to reduce overall cost of medical care	Yes	Sankyo Pharma Inc.	Clinical trial data: Oparil et al. 2001 Predicting CV: Framingham Heart Study Cost: managed care database	Payer

Study/country	Study design	Population	Interven-tion	Compara-tor	Main outcomes	Statistical validation	Sponsor	Source clinical /cost data	Perspec-tive
Swindle et al. 2011,[46] USA	Retrospective observational study with cardiac and economic outcomes Healthcare costs Regression analysis	Limited study sample with 65'579 subjects (=without pre-existing conditions or risk factors) Follow-up 861 to 933 days (mean: 2.5 years)	OLM Mono- and with HCTZ	LOS VAL IRB Mono- and with HCTZ	Healthcare cost (2009): Predicted overall costs – all causes per member and month: OLM: USD 555 VAL: USD 592 LOS: USD 577 IRB: USD 590 Predicted hypertension attributable costs per member and month: OLM: USD 213 VAL: USD 239 LOS: USD 225 IRB: USD 228 OLM was associated with lower risk of cardiac events and lower healthcare resource utilisation and costs (=association rather than causality)	Yes	Daiichi-Sankyo, USA	Data from USA Managed Health Plan	Healthcare payer

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

Table 34: Results average cost/pack 2018

ATC code	Substance	Number reimbursed packs 2018	Pharmaceutical expenditure 2018 in CHF	Market share packs	Average cost/pack 2018 in CHF
Mono-preparations					
C09CA01	LOS	148’782	8’016’136	13%	53.88
C09CA02	EPR	3’595	343’962	0%	95.68
C09CA03	VAL	184’584	10’424’620	16%	56.48
C09CA04	IRB	141’026	10’241’590	12%	72.62
C09CA06	CAN	503’259	22’593’229	44%	44.89
C09CA07	TEL	50’271	3’892’243	4%	77.42
C09CA08	OLM	111’470	8’985’977	10%	80.61
C09CA09	AZI	12’296	1’134’116	1%	92.24
Subtotal mono-preparations		1’155’282	65’631’873	100%	56.81
Combination preparations					
C09DA01	LOS + HCTZ	104’492	8’018’621	8%	76.74
C09DA02	EPR + HCTZ	4’487	463’906	0%	103.40
C09DA03	VAL + HCTZ	150’089	9’144’689	12%	60.93
C09DA04	IRB + HCTZ	157’352	11’897’029	13%	75.61
C09DA06	CAN + HCTZ	291’434	17’341’935	23%	59.51
C09DA07	TEL + HCTZ	33’358	3’252’963	3%	97.52
C09DA08	OLM + HCTZ	63’975	5’580’711	5%	87.23
C09DA09	AZI + HCTZ	14’660	1’345’218	1%	91.76
C09DB01	VAL + CCBs	122’455	14’283’841	10%	116.65
C09DB02	OLM + CCBs	81’501	7’620’926	7%	93.51
C09DB04	TEL + CCBs	8’808	878’456	1%	99.74

ATC code	Substance	Number reimbursed packs 2018	Pharmaceutical expenditure 2018 in CHF	Market share packs	Average cost/pack 2018 in CHF
C09DX01	VAL + HCTZ + CCBs	142’882	17’946’561	11%	125.60
C09DX03	OLM + HCTZ + CCBs	75’524	9’443’880	6%	125.04
Subtotal combination preparations		1’251’016	107’218’735	100%	85.71
Total mono- and combination preparations		2’406’298	172’850’608		71.83

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; CCBs = calcium channel blocker; EPR = eprosartan; HCTZ = hydrochlorothiazide; IRB = irbesartan; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

Sources: authors’ own calculations; data source: Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]

Table 35: Costs per event (in CHF 2018, per patient, per year)

Event	Costs per severity					
	Fatal		Non-fatal		Maintenance	Total
	Costs	Probability	Costs	Probability		
Myocardial infarction	CHF 8'385	30%	CHF 35'739	70%	CHF 3'226	CHF 29'791
Stroke	CHF 9'789	50%	CHF 49'228	50%	CHF 16'584	CHF 37'801
Heart failure	CHF 8'499	70%	CHF 33'778	30%	CHF 11'744	CHF 19'606
Ischemic heart disease	CHF 5'886	25%	CHF 17'398	75%	CHF 2'426	CHF 16'339
Cardiac event	**CHF 8'140**	**44%**	**CHF 34'036**	**56%**	**CHF 8'495**	**CHF 27'485**

Source: authors’ own calculations based on Brändle et al.[103]

Table 36: Effects per pharmaceutical (part I)

Event	OLM				VAL						
	Swindle et al. (2011)	Bootstrapped (based on Swindle 2011)			Swindle et al. (2011)	Bootstrapped (based on Swindle et al. 2011)					
	Probability	Effect (Probability)			Probability	Probability			Incremental effect (OLM vs. VAL)		
		Average	Minimum	Maximum		Average	Minimum	Maximum	Average	Minimum*	Maximum**
Myocardial infarction	0.67%	0.60%	0.16%	1.55%	0.75%	0.68%	0.19%	1.67%	0.08%	-0.98%	1.16%
Stroke	0.80%	0.73%	0.22%	1.74%	1.13%	1.05%	0.40%	2.21%	0.31%	-0.87%	1.59%
Heart failure	1.74%	1.64%	0.77%	3.02%	2.71%	2.58%	1.43%	4.18%	0.91%	-0.84%	2.77%
Ischemic heart disease	0.61%	0.54%	0.12%	1.46%	0.79%	0.72%	0.21%	1.73%	0.16%	-0.86%	1.24%
Cardiac event	**3.42%**	**3.25%**	**1.94%**	**5.02%**	**4.81%**	**4.54%**	**2.97%**	**6.55%**	**1.27%**	**-1.09%**	**3.67%**

OLM = Olmesartan; VAL = valsartan
* 95% confidence interval lower bound (means a low effect for OLM)
** 95% confidence interval upper bound (means a high effect ****of OLM)

Sources: Swindle et al.[46] and authors' own bootstrapping results

Table 37: Effects per pharmaceutical (part II)

Event	LOS							IRB						
	Swin-dle et al. (2011)	Bootstrapped (based on Swindle et al. 2011)						Swindle et al. (2011)	Bootstrapped (based on Swindle et al. 2011)					
	Prob-ability	Effect (Probability)			Incremental effect (OLM vs. LOS)			Probability	Effect (Probability)			Incremental effect (OLM vs. IRB)		
		Avg.	Min	Max	Avg.	Min*	Max**		Avg.	Min	Max	Avg.	Min*	Max**
Myocardial infarction	0.79%	0.72%	0.21%	1.72%	0.11%	-0.93%	1.21%	0.62%	0.55%	0.13%	1.46%	-0.04%	-1.07%	0.96%
Stroke	1.36%	1.28%	0.53%	2.52%	0.53%	-0.70%	1.88%	1.27%	1.19%	0.48%	2.39%	0.45%	-0.76%	1.78%
Heart failure	3.24%	3.08%	1.81%	4.80%	1.42%	-0.41%	3.39%	2.92%	2.77%	1.59%	4.43%	1.11%	-0.67%	3.01%

Ischemic heart disease	0.83%	0.76%	0.23%	1.78%	0.21%	-0.83%	1.32%	0.84%	0.77%	0.24%	1.80%	0.22%	-0.82%	1.33%
Cardiac event	**5.56%**	**5.20%**	**3.51%**	**7.32%**	**1.93%**	**-0.47%**	**4.43%**	**5.17%**	**4.85%**	**3.21%**	**6.92%**	**1.60%**	**-0.78%**	**4.05%**

Avg. = average; Min = minimum; Max = maximum; OLM = olmesartan; LOS = losartan; IRB = irbesartan
* 95% confidence interval lower bound (means a low effect for OLM)
** 95% confidence interval upper bound (means a high effect ****of OLM)

Sources: Swindle et al.[46]swindle and authors' own bootstrapping results

Table 38: Sensitivity analysis results for incremental costs and effects (Scenario A)

Event	Comparison	Scenario A: optimistic (high effect OLM, low effect VAL/LOS/IRB)		Basic scenario (mean effect OLM/VAL/LOS/IRB)		Scenario A: pessimistic (low effect OLM, high effect VAL/LOS/IRB)	
		Incremental costs	**Increm. effects**	**Incremental costs**	**Increm. effects**	**Incremental costs**	**Increm. effects**
MI	OLM vs. VAL	-CHF 408	1.16%	CHF 19	0.08%	CHF 446	-0.98%
	OLM vs. LOS	-CHF 329	1.21%	CHF 100	0.11%	CHF 534	-0.93%
	OLM vs. IRB	-CHF 295	0.96%	CHF 110	-0.04%	CHF 516	-1.07%
Stroke	OLM vs. VAL	-CHF 710	1.59%	-CHF 80	0.31%	CHF 548	-0.87%
	OLM vs. LOS	-CHF 736	1.88%	-CHF 71	0.53%	CHF 592	-0.70%
	OLM vs. IRB	-CHF 729	1.78%	-CHF 81	0.45%	CHF 572	-0.76%
Heart failure	OLM vs. VAL	-CHF 625	2.77%	-CHF 140	0.91%	CHF 355	-0.84%
	OLM vs. LOS	-CHF 653	3.39%	-CHF 146	1.42%	CHF 374	-0.41%
	OLM vs. IRB	-CHF 622	3.01%	-CHF 126	2.77%	CHF 375	-0.67%
IHD	OLM vs. VAL	-CHF 219	1.24%	CHF 13	0.16%	CHF 247	-0.86%
	OLM vs. LOS	-CHF 135	1.32%	CHF 101	0.21%	CHF 337	-0.83%
	OLM vs. IRB	-CHF 179	1.33%	CHF 58	0.22%	CHF 295	-0.82%
Cardiac event	**OLM vs. VAL**	**-CHF 1'572**	**3.67%**	**-CHF 311**	**1.27%**	**CHF 605**	**-1.09%**
	OLM vs. LOS	**-CHF 1'343**	**4.43%**	**-CHF 400**	**1.93%**	**CHF 550**	**-0.47%**
	OLM vs. IRB	**-CHF 1'275**	**4.05%**	**-CHF 346**	**1.60%**	**CHF 590**	**-0.78%**

IHD = ischemic heart disease; MI = myocardial infarction; OLM = olmesartan; LOS = losartan; IRB = irbesartan; VAL = valsartan

Source: authors' own calculations

Table 39: Sensitivity analysis results for incremental costs and effects (Scenario B)

Event	Comparison	Scenario B: optimistic (low costs OLM, high costs VAL/LOS/IRB)		Basic scenario (mean costs OLM/VAL/LOS/IRB)		Scenario B: pessimistic (high costs OLM, low costs VAL/LOS/IRB)	
		Incremental costs	Increm. effects	Incremental costs	Increm. effects	Incremental costs	Increm. effects
MI	OLM vs. VAL	-CHF 101	0.08%	CHF 19	0.08%	CHF 94	0.08%
	OLM vs. LOS	-CHF 117	0.11%	CHF 100	0.11%	CHF 177	0.11%
	OLM vs. IRB	-CHF 53	-0.04%	CHF 110	-0.04%	CHF 179	-0.04%
Stroke	OLM vs. VAL	-CHF 263	0.31%	-CHF 80	0.31%	CHF 48	0.31%
	OLM vs. LOS	-CHF 369	0.53%	-CHF 71	0.53%	CHF 70	0.53%
	OLM vs. IRB	-CHF 330	0.45%	-CHF 81	0.45%	CHF 55	0.45%
Heart failure	OLM vs. VAL	-CHF 358	0.91%	-CHF 140	0.91%	CHF 16	0.91%
	OLM vs. LOS	-CHF 482	1.42%	-CHF 146	1.42%	CHF 25	1.42%
	OLM vs. IRB	-CHF 405	2.77%	-CHF 126	2.77%	CHF 36	2.77%
IHD	OLM vs. VAL	-CHF 72	0.16%	CHF 13	0.16%	CHF 53	0.16%
	OLM vs. LOS	-CHF 80	0.21%	CHF 101	0.21%	CHF 141	0.21%
	OLM vs. IRB	-CHF 82	0.22%	CHF 58	0.22%	CHF 99	0.22%
Cardiac event	**OLM vs. VAL**	**-CHF 799**	1.27%	**-CHF 311**	**1.27%**	**CHF 99**	**1.27%**
	OLM vs. LOS	**-CHF 1'027**	1.93%	**-CHF 400**	**1.93%**	**CHF 37**	**1.93%**
	OLM vs. IRB	**-CHF 908**	1.60%	**-CHF 346**	**1.60%**	**CHF 77**	**1.60%**

IHD = ischemic heart disease; MI = myocardial infarction; OLM = olmesartan; LOS = losartan; IRB = irbesartan; VAL = valsartan

Source: authors' own calculations

Table 40: Mono-preparations: pharmaceutical expenditures and packs reimbursed by health insurance in Switzerland in 2018

ATC code	Substance	Market share pharmaceutical expenditures	Market share packs	Number preparations (incl. different pack size)
C09CA01	LOS	12.2%	12.9%	30
C09CA02	EPR	0.5%	0.3%	4
C09CA03	VAL	15.9%	16.0%	33
C09CA04	IRB	15.6%	12.2%	24
C09CA06	CAM	34.4%	43.6%	77
C09CA07	TEL	5.9%	4.4%	28
C09CA08	OLM	13.7%	9.6%	30
C09CA09	AZI	1.7%	1.1%	6
Total		**100%**	**100%**	**232**

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; EPR = eprosartan; IRB = irbesartan; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

Sources: Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]

Table 41: Fixed-dose combinations: pharmaceutical expenditures and packs reimbursed by health insurance in Switzerland in 2018

ATC Code	Substance	Market share pharmaceutical expenditures	Packs	Number prepara-tions (incl. diff. pack size)
C09DA01	LOS + HCTZ	7.5%	8.4%	42
C09DA02	EPR + HCTZ	0.4%	0.4%	4
C09DA03	VAL + HCTZ	8.5%	12.0%	50
C09DA04	IRB + HCTZ	11.1%	12.6%	36
C09DA06	CAN + HCTZ	16.2%	23.3%	76
C09DA07	TEL + HCTZ	3.0%	2.7%	24
C09DA08	OLM + HCTZ	5.2%	5.1%	48
C09DA09	AZI + HCTZ	1.3%	1.2%	8
C09DB01	VAL + HCTZ	13.3%	9.8%	18
C09DB02	OLM + CCBs	7.1%	6.5%	30
C09DB04	TEL + CCBs	0.8%	0.7%	6
C09DX01	VAL + HCTZ + CCBs	16.7%	11.4%	28
C09DX03	OLM + HCTZ + CCBs	8.8%	6.0%	20
Total		**100.0%**	**100.0%**	**390**

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; CCB = calcium channel blocker; IRB = irbesartan; EPR = eprosartan; HCTZ = hydrochlorothiazide; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

Sources: Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]

Table 42: Scenario 1: budget impact – substitution of OLM, allocation corresponding to market shares 2018 (at single product level, base total market share mono- or combination preparations, valued at average cost/pack 2018)

ATC code	Substance/Description	No. reimbursed packs 2018	Base Case: pharma-ceutical expenditure 2018 in CHF	Market share packs 2018	Market share packs New after OLM substitu-tion	Scenario 1: budget impact* in CHF
C09CA01	LOS	148’782	8’016’136	13%	14%	8’872’188
C09CA02	EPR	3’595	343’962	0%	0%	380’694
C09CA03	VAL	184’584	10’424’620	16%	18%	11’537’876
C09CA04	IRB	141’026	10’241’590	12%	14%	11’335’302
C09CA06	CAN	503’259	22’593’229	44%	48%	25’005’987
C09CA07	TEL	50’271	3’892’243	4%	5%	4’307’900
C09CA08	OLM	111’470	8’985’977	10%	0%	0
C09CA09	AZI	12’296	1’134’116	1%	1%	1’255’229
Subtotal mono-preparations		1’155’282	65’631’873	100%	100%	62’695’178
I. Budget impact mono-preparations						-2’936’695
C09DA01	LOS + HCTZ	104’492	8’018’621	8%	10%	9’739’102
C09DA02	EPR + HCTZ	4’487	463’906	0%	0%	563’442
C09DA03	VAL + HCTZ	150’089	9’144’689	12%	15%	11’106’780
C09DA04	IRB + HCTZ	157’352	11’897’029	13%	15%	14’449’665
C09DA06	CAN + HCTZ	291’434	17’341’935	23%	28%	21’062’818
C09DA07	TEL + HCTZ	33’358	3’252’963	3%	3%	3’950’921
C09DA08	OLM + HCTZ	63’975	5’580’711	5%	0%	0
C09DA09	AZI + HCTZ	14’660	1’345’218	1%	1%	1’633’850
C09DB01	VAL + CCBs	122’455	14’283’841	10%	12%	17’348’593
C09DB02	OLM + CCBs	81’501	7’620’926	7%	0%	0

ATC code	Substance/Description	No. reimbursed packs 2018	Base Case: pharmaceutical expenditure 2018 in CHF	Market share packs 2018	Market share packs New after OLM substitution	Scenario 1: budget impact* in CHF
C09DB04	TEL + CCBs	8’808	878’456	1%	1%	1’066’938
C09DX01	VAL + HCTZ + CCBs	142’882	17’946’561	11%	14%	21’797’189
C09DX03	OLM + HCTZ + CCBs	75’524	9’443’880	6%	0%	0
Subtotal combination preparations		1’251’016	107’218’735	100%	100%	102’719’298
II. Budget impact combination preparations						-4’499’436
I. + II. Net budget impact pharmaceutical expenditures						-7’436’131
III. Additional visits (outpatient) 15'790 visits à CHF 163.92, OLM patients**						2’604’052
I + II + III Sum net budget impact						-4’832’079

ATC = anatomic therapeutic classification; AZI = azilsartan; CAN = candesartan; CCB = calcium channel blocker; IRB = irbesartan; EPR = eprosartan; HCTZ = hydrochlorothiazide; LOS = losartan; OLM = olmesartan; TEL = telmisartan; VAL = valsartan

* Calculated with pharmaceutical expenditure/pack and reimbursed packs 2018 at the level of individual products (includes out- and inpatient pharmaceuticals), the number of OLM products to be substituted is reallocated according to the market share of packs of the alternative preparations based on the total share of mono- or combination preparations)

** For each OLM patient switching to another sartan; number of patients calculated on the basis of reimbursed OLM packs in 2018; costs per visit based on Klazien Matter-Walstra et al.[107] costs converted with The Campbell and Cochrane Economics Methods Group converter tool to 2018 (CCEMG);[104] average number of visits based on Signorovitch et al. [108]

Sources: authors’ own calculations based on data from Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]

Table 43: Scenario 2: budget impact – substitution of OLM with equivalent doses and allocation with market share based on equivalence group, valued at average cost/pack 2018

ATC code/equivalence groups*	Description	No. reimbursed packs 2018 (aggregated to ATC code)	No. reimbursed packs OLM (aggregated to ATC code)	Base case: pharmaceutical expenditure in CHF	Scenario 2: budget impact** in CHF
CO9CA: 01 - 09: equivalent dose Equivalence groups: OLM 10 mg/30 pack; OLM 10 mg/100 pack, OLM 20 mg/100 pack, OLM 40 mg/30 pack, OLM 40 mg/100 pack	All mono-preparations	1'121'093	111'470	63'322'531	61'319'538
CO9CA: 01 - 09: no equivalent dose	All mono-preparations	34'189	0	2'309'342	2'309'342
Subtotal mono-preparations		*1'155'282*	*111'470*	*65'631'873*	*63'628'880*
I. Budget impact mono-preparations					-2'002'993
C09DA: 01 - 08: equivalent dose Equivalence groups: OLM 40/5 mg, OLM 40/10 mg, OLM 40/12.5 mg, OLM 40/25 mg/all packs; OLM 20/12.5 mg; OLM 20/5 mg, OLM 20/25 mg	Sartans + HCTZ	735'418	63'865	51'362'264	50'205'157
C09DB: 01 - 04: equivalent dose Equivalence groups: OLM 20/5 mg, OLM 20/12.5 mg, OLM 20/25 mg; OLM 40/5 mg; OLM 40/10 mg, OLM 40/12.5 mg, OLM 40/25 mg	Sartans + CCBs	212'764	81'501	22'783'223	24'576'620
C09DX: 01 + 03: equivalent dose Equivalence groups: OLM 20/5/12.5, OLM 40/10/12.5 mg, OLM 40/10/25 mg, OLM 40/5/12.5 mg, OLM 40/5/25 mg	Sartans + HCTZ + CCBs	218'406	75'524	27'390'441	27'432'738

ATC code/equivalence groups*	Description	No. reimbursed packs 2018 (aggregated to ATC code)	No. reimbursed packs OLM (aggregated to ATC code)	Base case: pharmaceutical expenditure in CHF	Scenario 2: budget impact** in CHF
C09DA: 01 - 08: no equivalent dose	Sartans + HCTZ	84'318	0	5'675'134	5'675'134
Subtotal combination preparations		*1'250'906*	*'220'891*	*107'211'062*	*107'889'649*
II. Budget impact combination preparations					678'586
I. + II. Net budget impact pharmaceutical expenditures					-1’323’407
III. Additional visits (outpatient)	15'790 visits à CHF 163.92, OLM patients***				2'604'052
I. + II. + III. Net budget impact pharmaceutical + visits					1’279’645

ATC = anatomic therapeutic classification; CCBs = calcium channel blocker: HCTZ = hydrochlorothiazidum,;OLM = olmesartan

* Equivalence groups summarised to ATC-code
** Calculated with pharmaceutical expenditure/pack and reimbursed packs 2018 at the level of single products (out- and inpatient pharmaceuticals), distributed to equivalent dose and reallocated with new market share within the equivalence group
*** For each OLM patient switching to another sartan; number of patients calculated on the basis of reimbursed OLM packs in 2018; costs per visit based on Klazien Matter-Walstra et al.[107] costs converted with The Campbell and Cochrane Economics Methods Group converter tool to 2018 (CCEMG);[104] average number of visits based on Signorovitch et al. [108]

Sources: authors’ own calculations based on data from Tarifpool ©SASIS AG, data processing: ©COGE GmbH[105]

Table 44: Scenario 3: budget impact – substitution of OLM with equivalent doses and allocation with market share based on equivalence group, valued with list prices as of 1 August 2019

ATC code/equivalence groups*	Description	No. reimbursed packs 2018 (aggregated to ATC code)	No. reimbursed packs OLM (aggregated to ATC code)	Base case: pharmaceutical expenditure 2018, OLM price 1.8.2019 in CHF	Scenario 3: budget impact** price 1.8.2019 in CHF
CO9CA: 01 - 09: equivalent dose Equivalence groups: OLM 10 mg/30 pack; OLM 10 mg/100 pack, OLM 20 mg/100 pack, OLM 40 mg/30 pack, OLM 40 mg/100 pack	All mono-preparations	1'121'093	111'470	63’371’081	62’157’007
CO9CA: 01 - 09: no equivalent dose	All mono-preparations	34'189	0	2'309'342	2'309'342
Subtotal mono-preparations		*1'155'282*	*111'470*	*65'680'424*	*64'466'350*
I. Budget impact mono-preparations					-1’214’074
C09DA: 01 - 08: equivalent dose *Equivalence groups: OLM 40/5 mg, OLM 40/10 mg, OLM 40/12.5 mg, OLM 40/25 mg/all packs; OLM 20/12.5 mg; OLM 20/5 mg, OLM 20/25 mg*	Sartans + HCTZ	735'418	63'865	51'405’621	50'747’526
C09DB: 01 - 04: equivalent dose Equivalence groups: OLM 20/5 mg, OLM 20/12.5 mg, OLM 20/25 mg; OLM 40/5 mg; OLM 40/10 mg, OLM 40/12.5 mg, OLM 40/25 mg	Sartans + CCBs	212'764	81'501	22'869’860	24'866’303
C09DX: 01 + 03: equivalent dose Equivalence group: OLM 20/5/12.5, OLM 40/10/12.5 mg, OLM 40/10/25 mg, OLM 40/5/12.5 mg, OLM 40/5/25 mg	Sartans + HCTZ + CCBs	218'406	75'524	27'823’084	27'673’732
C09DA: 01 - 08: no equivalent dose	Sartans + HCTZ	'84'318	0	5'675'134	5'675'134

ATC code/equivalence groups*	Description	No. reimbursed packs 2018 (aggregated to ATC code)	No. reimbursed packs OLM (aggregated to ATC code)	Base case: pharmaceutical expenditure 2018, OLM price 1.8.2019 in CHF	Scenario 3: budget impact** price 1.8.2019 in CHF
Subtotal combination preparations		*1'250'906*	*220'891*	*107'773'699*	*108'962'695*
II. Budget impact combination preparations					1'188'997
I. + II. Net budget impact pharmaceutical expenditures					-25'077
III. Additional visits (outpatient)	15'790 visits à CHF 163.92, OLM patients***				2'604'052
I. + II. + III. Net budget impact pharmaceutical + visits					2'578'975

ATC = anatomic therapeutic classification; CCBs = calcium channel blocker; HCTZ = hydrochlorothiazidum; OLM = olmesartan

* Equivalence groups summarised to ATC code

** Calculated with pharmaceutical expenditure/pack and reimbursed packs 2018 at the level of individual products (out- and inpatient pharmaceuticals), distributed to equivalent dose and reallocated with new market share in the equivalence group, valued with prices as of 1 August 2019 (Source: Spezialitätenliste)[106]

*** For each OLM patient switching to another sartan; number of patients calculated on the basis of reimbursed OLM packs in 2018; costs per visit based on Klazien Matter-Walstra et al.[107] costs converted with The Campbell and Cochrane Economics Methods Group converter tool to 2018 (CCEMG);[104] average number of visits based on Signorovitch et al. [108]

Sources: authors' own calculations based on data from Tarifpool ©SASIS AG, data processing: ©COGE GmbH;[105] Spezialitätenliste[106]

14.5 Appendix E: Quality assessment economic studies

1. Belsey, J. D. 2001

CHEC checklist*

	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			

*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.

2. Boersma, C. et al., 2010

CHEC checklist*

	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			

*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.

3. Miller L. et al., 2010

CHEC checklist*

	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: OLM group was younger and healthier Proportion of diabetes patients was lower in OLM group no detailed cost data shown no adverse events calculated no results for combination products shown			

*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.

4. Mazza, A. et al., 2017

CHEC checklist*

	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			

*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.

5. Simons, W. R., 2003

CHEC checklist*

	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; the assumed price of OLM is the same as all others (at that time OLM had no price in the USA), however the price was lower later on no adverse events included dosage like clinical trial, no real-world data			

*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.

6. Swindle, J. P., 2011

CHEC checklist*

	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: real-world data - however association and not causality not all unit data shown adverse events perhaps included, not desribed			

*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.