Question

Should **combination therapy** vs. **monotherapy with cholinesterase inhibitors** be used for **Alzheimer's disease**?	
POPULATION:	Alzheimer's disease
INTERVENTION:	Combination therapy (cholinesterase inhibitor + memantine)
COMPARISON:	Monotherapy with cholinesterase inhibitors
MAIN OUTCOMES:	**Critically important**: Delay in nursing home placement; Cognition; Activities of daily living; Clinical Global Impression; Behavioural and psychological symptoms of dementia **Important**: Withdrawal from study; Adverse events; Caregiver burden or distress; Quality of life All outcomes are assessed both for short-term (up to 9 months) and long-term follow-up (> 9 months)
PERSPECTIVE:	Clinical recommendation: Population perspective

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Desirable effects, short-term follow up**: Improvement with combination therapy in: cognition, activities of daily living, clinical global impression (critically important outcomes) and caregiver burden (important outcome) No difference in: behavioural and psychological symptoms (critically important outcome) Not reported: quality of life **Desirable effects, long-term follow up:** No difference: delay in nursing home placement, cognition, activities of daily living (critically important outcomes) Not reported: clinical global impression, behavioural and psychological symptoms, quality of life.	Clinical significance of improvement is modest. Delay in nursing home placement: results come from a single study and are for a max. follow-up of 48 months. However, after the first 12 months physicians and patients were unblinded and free to choose their treatment.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ●Small ○ Trivial ○ Varies ○ Don't know	**Undesirable effects, short-term follow up**: Worse with combination therapy: adverse events (important outcome) No difference: Withdrawal from study (important outcome) **Undesirable effects, long-term follow up**: Worse with combination therapy: withdrawal from study (important outcome) No difference: adverse events (important outcome)	Inconsistent reporting of adverse events. Most adverse events were similar in both groups. More serious adverse events with monotherapy than with combination therapy (results not pooled). Details in supplementary material.
QUALITY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ●Very low ○ Low ○ Moderate ○ High ○ No included studies	Based on the critical outcomes, the overall certainty of the evidence is **very low.**	For details, see the Summary of Findings tables in Appendix 1 of the Appraisal Report.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ●Probably no important uncertainty or variability ○ No important uncertainty or variability	No separate literature review focusing on patient or caregiver values was conducted during assessment. Utility values: The lowest estimated QALY difference in the included studies was 0.02752 and the highest 0.26	Utility and probability estimates may be biased and may not correspond to the Swiss context. Outcomes are valued most probably at the same degree by everyone involved. Variability might exist for some outcomes such as delay in nursing home placement. Uncertainty might exist on how different stakeholders (health professionals, patients/caregivers and taxpayers) value some outcomes.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ●Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Small benefits and small harms	Most desirable effects were small and observed during short-term follow-up only. Uncertainty about nature and severity of adverse events. Difference in QALYs are probably over-estimated.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ●Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Budget impact analysis: The overall healthcare costs for Alzheimer's disease might reach CHF 5.87 billion. Cost for cholinesterase monotherapy in 2016 was estimated at CHF 14.6 million. If combination therapy was included the total cost would be CHF 18.8 million. Updated drug cost estimation for 2016 shows a cost reduction of about CHF 3 million as compared to 2010.	Analysis does not report the cost share of combination therapy Uncertainty about whether healthcare cost estimates were reliable
QUALITY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Numerous limitations of cost data used and estimations made
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	Cost-utility analyses favour combination therapy.	The analyses are heavily driven by the claimed benefits with delaying nursing home placement. However, there is no clear evidence that combination therapy is effective in delaying placement of patients in nursing homes.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No separate literature review focusing on health equity for Alzheimer's disease patients with different treatments was conducted.	Relative effectiveness of the intervention is probably the same for everyone, including disadvantaged groups. Inequality might be caused due to the fact that combination therapy is not currently reimbursed by statutory health insurance in Switzerland. Patients with multliple medications (e.g. due to comorbidities) might find it more difficult to adhere to taking an additional drug.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No separate literature review focusing on aspects of acceptability was conducted during assessment.	Based on anecdotal evidence and data from other countries, it is estimated that at least 19% of Alzheimer's patients are already prescribed combination therapy. Taxpayers might not be willing to accept increased costs for small benefits. Patients who already take a lot of drugs might not accept taking an additional one.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No information on the current prescription practice in Switzerland or the overall prevalence of combination therapy	It is not uncommon to prescribe combination therapy in Switzerland. Some legal challenges exist for making combination therapy payable through statutory health insurance.

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should combination therapy vs. monotherapy with cholinesterase inhibitors be used for Alzheimer's disease?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	We recommend not to use combination therapy (as compared to monotherapy) in the pharmacological treatment of patients with moderate to severe Alzheimer's disease. This is in line with the current policy of the Federal Office of Public Health.				
JUSTIFICATION	The benefits and harms of combination therapy are closely balanced and the confidence in the effect estimates is limited. The Appraisal Committee judged that the small short-term benefits observed with combination therapy do not outweigh the potential harms. In addition, combination therapy might be more costly.				
SUBGROUP CONSIDERATIONS	None				
IMPLEMENTATION CONSIDERATIONS	Physicians should discuss with patients or their caregivers, if the patient is incompetent, and weight the possible benefits and harms of pharmacological treatment options. Shared decision making of patients, their caregivers and health professionals should include communication about (i) the limited evidence supporting either combination therapy or monotherapy, (ii) the need to consider individual aspects such as adherence to daily medication and perceived importance of any gains in terms of overall quality of life, and (iii) information on costs. Some patients or their caregivers might be willing to try combination therapy in order to gain some beneficial effects, at least in the short term. They might choose to stop it if any undesirable effects become serious or frequent. If such undesirable effects are not serious, the case-by-case assessment might also take into account the patient's comorbidities and other medications. Patients may wish to continue combination therapy if they improve in important or critically important outcomes without major undesirable effects.				
MONITORING AND EVALUATION	When a patient with moderate to severe Alzheimer's disease receives combination therapy, the individual response should be monitored and evaluated regularly to determine whether it should be continued or stopped.				
RESEARCH PRIORITIES	More long-term studies are needed, especially assessing any effect on delays in nursing home placement, as well as patient-important outcomes such as cognition and quality of life.				