Pharmacotherapeutic report, summary

Donepezil (hydrochloride) Aspen® for the indication 'symptomatic treatment of mild to moderately severe Alzheimer's dementia'
Recommendation by CVZ dated 24-6-2013, based on Evaluation by the WAR (Scientific Advisory Committee)

The WAR has drawn up a pharmacotherapeutic report for the medicine donepezil (hydrochloride) Aspen® film-coated tablets. Its therapeutic value was determined via comparison with rivastigmin and galantamin.. They reached the following conclusions.
- the therapeutic value of donepezil is equal to that of rivastigmin and galantamin for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

Medicine. Donepezil (hydrochloride) Aspen®, film-coated tablet

Registered indication. Symptomatic treatment of mild to moderately severe Alzheimer's dementia.

Posology. 5 mg/day; after a minimum of one month, based on a clinical evaluation, the dose may be increased to a maximum recommended dose of 10 mg/day.

Mechanism of action. Donepezil is a specific and reversible inhibitor of acetylcholinesterase.

Specific details. Decentralised assessment procedures for market registration have demonstrated bioequivalence between donepezil (hydrochloride) Aspen® and the respective reference product, donepezil (Aricept®). The efficacy of donepezil has not been studied in patients with severe Alzheimer's dementia, other types of dementia and other types of memory disorders.

Summary of the therapeutic value

Intended effects. Based on both direct and indirect comparisons, the effects of donepezil on cognition are comparable to those of galantamin and rivastigmin in patients with mild to moderately severe Alzheimer's disease. Statistically significant effects that were more favourable for rivastigmin, as found in the direct comparative study between donepezil and rivastigmin, are limited to secondary endpoints including ADL , of which their clinical relevance is unknown. Based on the indirect comparison, donepezil may be slightly more effective than galantamin on a behavioural observation scale and the global domain. A limitation of the direct comparisons it that it is unclear whether these results can be extrapolated to patients with moderately severe dementia (MMSE > 20). These patients were included in the indirect comparison, but the limitation here is that it took place on the basis of placebo-controlled studies with a heterogeneous set-up and study population and most of which have a lower methodological quality than the direct comparative studies. Taken together, it can be concluded that the favourable effects of donepezil are equal to those of galantamin and rivastigmin.

Unintended effects. The side effects of donepezil, rivastigmin and galantamin often lead to discontinuing treatment. There are no major differences in the side effects of these three products. Nor are there any major differences in the incidence of severe side effects of the various products. A long follow-up did not reveal any advantage to one of the products with respect to ceasing treatment, however, galantamin may lead a higher frequency of nausea and

vomiting than donepezil. The conclusion is that there are not major differences in the nature and incidence of side effects of donepezil, galantamin and rivastigmin.

Experience. Donepezil has been marketed internationally since 1996, galantamin since 1991 and rivastigmin since 1997. Ample experience has therefore been gained with all three products.

Applicability. There are no major differences in applicability between donepezil and galantamin. However, the applicability of rivastigmin is greater than of donepezil.

Ease of use. There are no major differences between donepezil, rivastigmin and galantamin.

Final conclusion on therapeutic value.

Based on both the direct and indirect comparisons, donepezil has similar effects on cognition to galantamin and rivastigmin in patients with mild to moderately severe Alzheimer's dementia. Small differences between the products is limited to secondary endpoints that are of unknown clinical relevance. Possible small differences in side effects are insufficient to speak of a therapeutic advantage for one of these products. These products must be used strictly in accordance with professional treatment guidelines on the medicinal treatment of dementia and conditions pertaining to Appendix 2 of the GVS apply unabatedly.

The therapeutic value of donepezil for the treatment of mild to moderately severe Alzheimer's dementia is equal to that of rivastigmin and galantamin.

*The original text of this excerpt from a **WAR-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's WAR-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.