Alignment of European regulatory and health technology assessments: a review of licensed products for Alzheimer's disease

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Facts & Figures

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Challenge

Alzheimer's disease (AD) is the most common cause of dementia worldwide. Currently, four symptomatic treatments are available: donepezil, galantamine, rivastigmine, and memantine. These treatments provide only temporary and modest improvement in AD symptoms, so a large unmet medical need still remains in AD.

In order to make new drugs available to the larger public, pharmaceutical companies need to satisfy the requirements of both regulatory and health technology assessment (HTA) bodies. In this study we evaluated similarities and differences in evidence requirements between regulatory and HTA bodies of AD-approved products. The overall aim is to facilitate regulatory learning to promote collaboration and alignment.

Approach & Methodology

The European regulatory application dossiers of the licensed AD drugs were screened to identify the phase III trials that were included in these dossiers. Next, we evaluated the regulatory assessment reports and European public assessment reports (EPARs) to determine which outcomes were used in the risk/benefit analyses. Likewise, we screened the assessment reports of the National Institute of Health and Care Excellence (NICE, UK) and Zorginstituut Nederland (ZiN, the Netherlands) to identify the studies and outcomes used in their appraisals.

Results

The marketing authorisation dossiers of donepezil, galantamine, rivastigmine and memantine contained 16 phase III randomized controlled trials in total. All of these trials were also included in HTA appraisals of ZiN*. NICE excluded istudies that were not published (n=2) or trials that also included patients with other types of dementia (n=3). In the risk/benefit analyses of the regulatory assessments the focus was on cognitive and global outcomes, and to some extent on function. In the assessment of the clinical effectiveness of NICE and ZiN also other domains were covered including: function, behaviour and mood, and, occasionally, quality of life and obser-vational data. In the economic analyses of NICE only two domains, cognition and function, were included.

Value of IMI collaboration

In this project CBG-MEB and NICE closely collaborated and had access to old dossiers. During the general assembly meetings of ROADMAP all stakeholders, including EFPIA partners, were informed on the results and gave input for new research directions.

Impact & take home message

Our study shows that in case of established AD, evidence requirements of regulatory and HTA assessments were not that far apart as usually perceived. Further alignment might be possible if regulatory authorities use the totality of evidence, including secondary endpoints, explicitly in their benefit-risk assessments and anticipate on collecting real world data to monitor drugs over its life-cycle.

Table 1. Evidence sources of regulatory and HTA assessments

	Regulation	NICE TA217	ZiN*
Regulatory application dossiers	16 phase III trials	11/16 phase III trials	12/12* phase III trials
Additional evidence of HTA assessments	-	25 RCTs 7 head-to-head trials 1 systematic review Submissions from consultees# & personal statements^	2 RCTs 2 head-to-head trials 2 systematic reviews Registration texts, including SmPC's / EPARs

*The ZiN assessment report of galantamine was not available, #Consultees consisted of professional and patient organisations, and manufacturers. ^Statements from carers and professional experts.

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