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Introduction

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In June 2011, Dr. Willmar Schwabe Pharmaceuticals sponsored a two-day expert meeting in Amsterdam, The Netherlands. The meeting brought together 19 dementia experts from a range of disciplines and countries to review preclinical and clinical data on *Ginkgo biloba* special extract EGb 761® in the context of recent developments in the diagnosis and treatment of age-related cognitive decline and Alzheimer's disease (AD). *Ginkgo biloba* special extract EGb 761® is formally approved and reimbursed for the symptomatic treatment of age-related cognitive decline or dementia by numerous authorities worldwide. The meeting therefore focused on relevant research questions and potential study designs with appropriate target populations to prove the efficacy of *Ginkgo biloba* special extract EGb 761® as a disease-modifying product in AD and to reveal further relevant modes of action.

This supplement summarizes the key presentations and discussions from the meeting. The first two papers set the scene by looking at the current status of research in the field of brain aging and AD in general. Professor Christian Behl argues that research has tended to focus on particular pathways and mechanisms at the expense of other theories and so might be slowing progress in the field. He proposes new avenues for research exploration that may lead to a better understanding of the pathophysiology of AD and therefore to improved approaches to its prevention and treatment. Professor Harald Hampel discusses the challenges that face those developing therapies for AD, with many drugs that show promise at one stage of research falling at the next hurdle and many drugs currently under investigation acting perhaps too late in the disease process to have meaningful effects. He proposes new models of disease, biomarkers, outcomes and endpoints that may allow targeting of specific mechanism-derived therapies at different points in the disease process in order to increase opportunities for preventative intervention in the early stages.

In the next three papers, the focus turns to preclinical research with *Ginkgo biloba* special extract EGb 761®. Dr. Anne Eckert describes the role of oxidative stress and mitochondrial failure in the early stages of AD development. She reviews data showing that a combination of several compounds within *Ginkgo biloba* special extract EGb 761® produces protective effects such as a reduction in oxidative stress and long-term regulation of mitochondria. Professor Walter Müller and colleagues describe data showing that the active fractions of *Ginkgo biloba* special extract EGb 761® improve neuroplasticity, which is increasingly impaired as people age and in patients with AD. The enhancement of endogenous neurogenesis employing *Ginkgo biloba* special extract EGb 761® might therefore be a promising option for the treatment of AD. Professor J. Kehr *et al.* describe a study investigating the effects of *Ginkgo biloba* standardized extract EGb 761® on extracellular levels of neurochemicals in rats. The study provides evidence that subacute treatment with EGb 761® and its flavonol constituents increases release of dopamine and acetylcholine release in the rat medical prefrontal cortex and suggest that *Ginkgo*- specific acylated flavonol glycosides actively contributed to these effect. The direct involvement of these two flavonol derivatives in the increase of dopaminergic and cholinergic neurotransmission in the prefrontal cortex may be one of the underlying mechanisms behind the reported effects of EGb 761® on improvement of cognitive functions.

Two further papers look at data available from clinical research with *Ginkgo biloba* special extract EGb 761®, which has been ongoing for many years. Professor Ralf Ihl reviews the clinical data obtained with *Ginkgo biloba* special extract EGb 761® in patients with dementia, which show that this product improves cognitive function, neuropsychiatric symptoms, activities of daily living and quality of life in patients with mild to moderate dementia compared with placebo. It also proves to be at least as effective as memantine, galantamine and donepezil regarding improvements in neuropsychiatric symptoms, and has no important safety concerns. Professor Siegfried Kasper reviews the body of research into

early intervention for AD and dementia, which has involved cohort data from large epidemiological studies and specifically designed intervention trials. Although conclusions from the large trials are limited by poor medication adherence, *Ginkgo biloba* special extract EGb 761®, with its long history of use and excellent safety record, does seem to have potential benefits in terms of reduced incidence of dementia of the AD type, reduced progression in terms of the clinical dementia ratings, and improvements in attention and memory.

In the final paper, Professor Nicola Lautenschlager and colleagues summarize the conclusions of the meeting. *Ginkgo biloba* special extract EGb 761® is a multi-target compound with activity on distinct pathophysiological pathways in AD and age-related cognitive decline. Although symptomatic efficacy in dementia and mild cognitive impairment has been demonstrated, interpretation of data from dementia prevention trials is complicated by important methodological issues. Bridging pre-clinical and clinical research as well as deciding on suitable study designs for future trials with EGb 761® remain important questions. The wealth of promising pre-clinical and clinical data makes future research with the compound targeting cognitive impairment in old age a worthwhile activity.

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