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DRAFT

GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

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GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

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EXECUTIVE SUMMARY

The present document should be considered as general guidance on the development for medicinal products for the treatment of dementia and its subtypes, and should be read in conjunction with other EMEA and ICH guidelines, which may apply to these conditions and patient populations.

Based on efficacy and safety data several drugs have been approved for symptomatic improvement of dementia of the Alzheimer Type and one for the symptomatic improvement of dementia associated with Parkinson's Disease. However, established treatment effects must be considered as modest. Randomized clinical trials in other subtypes of dementia (e.g. vascular dementia) have not been able to demonstrate clinically relevant symptomatic improvement nor was it yet possible to establish disease modifying effects in any dementia syndrome or its subtypes. Recent progress in basic science and molecular biology of the dementias has now fostered new interest for more efficacious symptomatic treatments as well as for disease modifying approaches in the dementias.

For regulatory purposes this requires better standardization and refinement of diagnostic criteria, which allow the study of homogeneous disease populations in specialized academic centres as well as in the general community setting. Depending on the disease stages (early versus late, mild to moderate to severe impairment) and disease entities distinct assessment tools for cognitive, functional and global endpoints should be used or newly developed. The typical design to show symptomatic improvement is a randomized, double-blind, placebo-controlled, parallel group study comparing change in two primary endpoints, one of them reflecting the cognitive domain and the second preferably reflecting the functional domain of impairment. The changes must be robust and clinically meaningful in favour of active treatment versus placebo.

If a treatment claim for prevention of the emergence, slowing or stabilizing deterioration is strived for, it has to be shown that the treatment has an impact on the underlying neurobiology and pathophysiology of the dementing process. Establishing such an effect in an highly variable progressing syndrome is complex and difficult, however, a variety of trial designs has been provided including baseline designs, survival designs, randomized start or randomized withdrawal designs with or without incorporation of biomarkers as surrogate endpoints (e.g. magnetic resonance tomography, emission tomography, cerebrospinal fluid markers). To be accepted as a surrogate endpoint such a biomarker ideally should respond to treatment, predict clinical response and be compellingly related to the pathophysiological process of the dementing condition. However, careful and sufficient validation of the proposed biomarkers as a potential surrogate endpoint is a prerequisite for acceptance by regulatory bodies.

1. INTRODUCTION

The term dementia describes a syndrome characterised by memory impairment, intellectual deterioration, changes in personality and behavioural abnormalities (DSM-IV-TR, ICD-10). These symptoms are of significant severity to interfere with social activities and occupational functioning. Moreover, the observed cognitive deficits must represent a decline from a higher level of function. In general, the disorders constituting the dementia syndromes share a common symptom presentation and are identified and classified on the basis of different etiologic factors and separate pathophysiological pathways. However, distinct subtypes of dementia syndromes are identifiable based on etiologic factors, clinical presentation, and pattern of impairment, natural course of the dementia syndrome and laboratory or neuroimaging tools. Alzheimer's Disease (AD) is the most common cause of dementia, followed by vascular dementia (VaD) or mixed forms of Alzheimer's disease and vascular dementia (MIXD). Other forms of neurodegenerative disorders as Parkinson's disease (PD), Lewy-Body disease (LBD), Huntington's disease and others are accompanied in a subset of patients with dementia as well. Thus based on these distinct aetiologies and clinical features there will be probably be no single "anti-dementia" drug, but different drugs should be developed directed towards either symptomatic change or to modification of aetiological and pathophysiological processes.

The main goals of treatment for dementing conditions are:

- Symptomatic improvement, which may consist in enhanced cognition, more autonomy and/or improvement in neuropsychiatric and behavioural dysfunction.
- Disease modification with slowing or arrest of symptom progression of the dementing process.
- Primary prevention of disease by intervention in key pathogenic mechanisms at a pre-symptomatic stage.

It should be recognised that the treatment of AD and other dementias is still an open research field. For symptomatic treatment the development and use of reliable and sensitive instruments to measure cognition, functional and behavioural symptoms, particularly for the assessment of activities of daily living (ADL), and neuropsychiatric symptoms is encouraged.

Currently there is a lack of agreement on the appropriate methodology to demonstrate slowing or arrest of the dementing process. Ideally proof of a disease modifying effect would require demonstration of clinically relevant changes in key symptoms of the dementia syndrome and in addition hints for change in the underlying disease process based on validated biological markers, e.g. a neuroimaging marker as serial MRI of the hippocampal region of the brain.

Data on prevention of dementing conditions are still very limited and have been disappointing up to now. Taking into consideration vascular dementia modification and control of the major risk factors for cardiovascular and cerebrovascular disorders has been shown effective in preliminary results from observational epidemiological studies. Another prevention strategy takes into account that several of the traditional cardiovascular risk factors are associated with AD as well. Prevention studies in dementia need to be large, may last for many years and due to that must take into consideration high drop out rates, may be partly due to these problems up to know no positive results are available for secondary prevention in dementing conditions. However, enrichment strategies and the development of better screening and measurement tools for asymptomatic or very mild forms of dementia combined with biomarkers may help to gain more data in the future.

2. SCOPE

The rapid increase of ageing populations with its accompanying set of chronic illnesses and the age-dependent exponential rise in the prevalence of dementia is recognized. In the last decades significant progress has been made in basic and clinical research in dementing conditions. Therefore the aim of this updated document is to provide guidance in the development of clinical studies for the treatment of dementia incorporating new research data and experience from recent clinical trials and development programs. The present document addresses not only Alzheimer's disease as the most common form of dementia, but other common forms of dementia as vascular dementia and dementia associated with Parkinson's disease and Lewy Body Disorder as well. Special emphasis is given to diagnostic criteria of these conditions and their implications for inclusion and exclusion criteria on the one hand, and to new assessment tools suitable as primary and secondary endpoints on the other hand. Recently in addition to symptomatic treatment new emphasis is given to possible disease modifying approaches. A lot of research focused on biomarkers as possible surrogate endpoints, however, yet none has been sufficiently validated. This together with new treatment options with distinct modes of action requires different study designs, which have to be adjusted for their particular conditions.
Validation or qualification of a certain biomarker as supportive evidence or as a surrogate endpoint is out of the scope of this guideline.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83/EC as amended and relevant CHMP Guidelines, among them:

- Dose-Response information to Support Drug Registration (CPMP/ICH/378/95 (ICH E4))
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96 (ICH E9))
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 (ICH E10))
- Adjustment for Baseline covariate (CPMP/EWP/2863/99)

- Missing data (CPMP/EWP/177/99)
- Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95 (ICH E1A))
- Studies in support of special populations: geriatrics (CPMP/ICH/379/99 (ICH E7))
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Investigation of Drug Interactions (CPMP/EWP/560/95)
- Note for Guidance on the Clinical Evaluation of Vaccines **(C**HMP/VWP/164653/2005)

4. MAIN GUIDELINE TEXT

4.1 Diagnostic Criteria

4.1.1 Diagnosis of Dementia

The clinical syndrome of dementia and the criteria for its severity are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR of the American Psychiatric Association) and in ICD-10 (F00-F03) of the WHO. For the effective and consistent evaluation of patients with dementia a stable diagnostic framework must be followed.

According to these definitions, the diagnosis of dementia remains primarily clinical. It is based on a careful history, obtained from the patient and their relatives and care givers. The history should demonstrate a typical progressive deterioration of cognitive and non-cognitive functions and some functional and behavioural consequences of this deterioration. At neurological and neuropsychological examination, there must be explicit impairments in memory and other cognitive domains, in the absence of developmental deficits.

One particular shortcoming of these criteria is the strong focus on memory deficits, which is adequate for patients with Alzheimer's disease, whereas dementia syndromes with aetiology frequently may present without prominent memory impairment. The request of a progressive deterioration in any two cognitive domains resulting in impairment of social and occupational function may be more adequate, and needs to be established and further validated.

These impairments should not be explained by another major primary psychiatric disorder.

4.1.2 Severity of dementia

The DSM-IV-TR and ICD 10 incorporate criteria for mild, moderate and severe dementia. The degree of severity of dementia of the included patients should be assessed and the method used should be stated. Simple screening tests, such as the Mini Mental State Examination (MMSE), have been used to document the extent of cognitive dysfunction, e.g. mild to moderate versus severe impairment. Revised definitions should rely not only on the cognitive dimension, but also take into account levels of functional disability and neuropsychiatric symptoms. Outcome measures in very mild, mild to moderate or moderate to severe patient populations must be able to assess the stage specific symptoms, which are of clinical relevance. Therefore the severity of cognitive impairment and behavioural changes and the resulting changes in self-care and other ADL should be documented using a variety of specific and global rating instruments.

There is a need to start treatment as soon as possible before many irreversible changes have been established. However, the emergence and the experience with terms like "mild cognitive impairment" have shown that it is necessary to develop more sensitive and diagnostic criteria for early disease, which at the same time are valid and reliable (see also Section 4.1.5).

4.1.3 The diagnosis of Alzheimer's disease and other dementias

The probability that a dementia syndrome is caused by AD is essentially based on a history of a steadily progressive course and on the absence of evidence for any other clinically diagnosable cause of the dementia. It can be further specified by using the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association). Knowledge about AD is accumulating rapidly, thus the diagnostic criteria used may need revision and updating. Whereas sensitivity has been shown very good to excellent, specificity has been much lower in many studies, and assessment of inter-rater reliability has shown high variability. Patients with brain biopsy proven definite AD are usually not available. Currently patients with

probable AD according to the NINCDS-ADRDA criteria are the most appropriate group in whom to study the effects of drugs.

However, there are clear limitations of the NINCDS-ADRDA criteria to exclude patients with mixed AD-VaD or other dementia syndromes.

In clinical trials vascular dementia has traditionally been diagnosed by the Hachinski-Score and its modified versions or the criteria of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). Similarly to the NINCDS-ADRDA criteria in AD the NINDS-AIREN criteria allow the distinction of possible and probable disease, they show high specificity but low sensitivity for vascular dementia. In some trials on vascular dementia the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centres have been used as inclusion criteria, sensitivity using these criteria is high, however, specificity is lower. Independent of the criteria used for VaD inter-rater reliability is lower than in AD. So it is not surprising that in comparative studies different patient populations have been identified by the different criteria. For regulatory purposes therefore the NINDS-AIREN criteria with there high specificity are still preferred until better criteria are available.

A large proportion of patients with dementia shows evidence of multiple overlapping neuropathological processes with combination of neurodegenerative and vascular changes (30 to 40%). AD and VaD very often coexist and constitute the large group of patients with mixed dementia (MIXD). Up to now no consistent diagnostic framework has been established to distinguish these mixed forms of dementia from "pure" forms of vascular or Alzheimer's dementia. However, use of structural neuroimaging is standard in all dementia therapeutic trials and is considered as an essential part within the work-up of patients with dementia to allow determination of vascular elements in the differential diagnosis. Due to the large proportion of these patients in the dementia population treatment options should be available, therefore in clinical trials a specific diagnostic and assessment framework must be developed for these patients as efficacious treatments in "pure" AD or VaD cannot be extrapolated. It is recommended to start development in "pure" disease forms and thereafter extend the scope of development to the "mixed" forms.

Based on recent research Parkinson Disease with Dementia (PDD) and dementia with Lewy bodies (DLB) are subsumed under the umbrella term "Lewy body disorders" with impaired α-synuclein metabolism. However, based on the differing temporal sequence of key symptoms and clinical features of PDD and DLB distinction of these concise subtypes is still justified.

Patients with Parkinson's disease show an increased risk for dementia based on epidemiological studies. Based on systematic reviews patients with Parkinson's disease suffer from additional dementia in 24 to 31 % and 3 to 4 % of dementia burden is due to Parkinson's disease. Operationalised criteria for patients with PDD have been proposed recently, however data on sensitivity and specificity have not been fully established. A current pragmatic approach requires at least one year of major parkinsonian motor symptoms before the onset of symptoms of dementia.

The criteria by McKeith et al. have become a standard for studies in dementia with Lewy Bodies (DLB), which show a very high specificity but low sensitivity. Clinical core features of DLB consist of rapid fluctuations in cognition, recurrent visual hallucinations and spontaneous and fluctuating features of parkinsonism, these are further supported by high sensitivity for extrapyramidal side effects to neuroleptics and rapid eye movement sleep behaviour disorder.

In a very preliminary stage for regulatory purposes are the criteria for fronto-temporal dementia and its subtypes.

4.1.4 Selection criteria for Alzheimer's disease and other dementias

As stated above, the diagnosis of AD and other dementias consists of three steps: first, the clinical diagnosis of dementia; second, the exclusion of other causes of dementia and third, diagnostic classification of the dementia subtype. This relies on a careful history with a clinical neurological examination and technical (e.g. brain imaging modalities using MRI or emission tomography based techniques) and laboratory methods (e.g. beta-amyloid, tau-protein, phospho-tau, proteomics in the cerebrospinal fluid). The latter is evolving rapidly and preliminary data show, that it may be possible to better define patient populations by distinguishing AD and other dementias with higher sensitivity and specificity. Other causes of dementia to be excluded with appropriate methods include in

particular treatable causes of dementia as infections of the CNS (e.g. HIV, syphilis) or Creutzfeld-Jakob disease. Subdural haematoma, communicating hydrocephalus, brain tumours, drug intoxication, alcohol intoxication, thyroid disease, parathyroid disease, and vitamin or other deficiencies also need to be excluded when appropriate.

The inclusion criteria, exclusion criteria, examinations, methods of examination and evaluation should be carefully described and documented in the study protocol.

4.1.5 Early and advanced stages of disease

Based on the modest progress in the treatment of dementing conditions with moderate to severe impairment interest has grown to diagnose and treat subsyndromal or very early stages of these diseases as soon as possible. So recently, mild cognitive impairment (MCI) was proposed as a nosological entity in elderly patients with mild cognitive deficits but without the complete picture of dementia and as such has become an area of high research interest. The rationale behind the development of this term is that an individual patient will pass through a stage of impaired cognition without social or occupational impairment and that the start of treatment in this early stage will result in greater benefits. This new term shows overlapping with other definitions as “benign senescent forgetfulness”, “age associated memory impairment”, “age associated cognitive decline” and “cognitively impaired not demented”. However, the concept of MCI is still in progress and suffers from several limitations. Estimations of prevalence from epidemiological studies are highly variable depending on the used definitions and criteria. A high proportion of patients diagnosed with MCI returned to normal without progression to dementia, on the other hand in several studies rates of progression from MCI to the full spectrum of dementia up to 12 percent per year have been described. Data from clinical trials using cholinesterase-inhibitors and other medicinal products with different mechanisms of action in patients with MCI have not shown efficacy in the predefined primary endpoints. Thus up to now MCI is not considered as a homogeneous clinical entity and more work on characterization of meaningful diagnostic criteria is needed, particularly the multiplicity of MCI definitions, the role of aetiological subtypes (e.g. amnestic type of MCI) and the development of appropriate assessment tools has to be refined. Currently epidemiological and clinical studies are underway to establish validated criteria for definition of “pre-dementia stages”.

In advanced stages of dementia the focus of the impairments for the patients and carers is changing. Beside the cognitive deficiencies functional impairments are more and more pronounced and stabilization or improvement in ADL may be more important endpoints. Behavioural problems with agitation and aggression do occur with major impact on patients and carers. Not many studies have been performed in patients with severe dementia, so there is a need for adaptation of assessment tools, which allow a comprehensive evaluation of the cognitive and the functional domains with special emphasis on ADL and neuro-behavioural abnormalities.

4.2 Assessment of Therapeutic Efficacy

4.2.1 Criteria of efficacy

4.2.1.1 Symptomatic improvement

Improvement of symptoms should be assessed in the following three domains:

1) cognition, as measured by objective tests (cognitive endpoint);

2) activities of daily living (functional endpoint).

3) overall clinical response, as reflected by global assessment (global endpoint).

Efficacy variables should be specified for each of the three domains. Two primary endpoints should be stipulated reflecting the cognitive and the functional domain. The study should be designed to show significant differences in each of the two primary variables. Global assessment should be evaluated as a secondary endpoint.

If this is achieved, then an assessment should be made of the overall benefit (response) in individual patients, and the effect of treatment should be illustrated in terms of the proportion of patients who achieve a clinically meaningful benefit (response). For a claim of short term treatment, responders (in patient populations with AD, PDD or DLB) may be defined at 6 months as improved to a relevant pre-specified degree in the cognitive endpoint and at least not worsened in the two other domains.

Depending on the natural course of the dementia subtype longer duration of clinical trials are required, e.g. in VaD it has been shown that at least 12 months seem to be necessary. Other definitions of responders are possible, but should be justified by the applicant, taking into account the clinical relevance of the outcome.

Secondary endpoints of interest may include neuropsychiatric and behavioural symptoms. For a claim in these symptoms, a specific trial should be designed with neuropsychiatric and behavioural symptoms as the primary variable measured according to a specific and validated scale.

In the more advanced forms of the disease, changes in cognitive performance may be less relevant to quantify. Hence choice of functional and global domains as primary endpoints may be more appropriate to establish clinically relevant symptomatic improvement in this severely impaired population.

4.2.1.2 Disease modifying effects

Up to now no clinical trial has led to a successful claim of disease modification in dementing conditions. For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. Consequently a true disease modifying effect cannot be established solely based on clinical outcome data, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. As this is difficult to achieve without an adequately validated biomarker, a two-step approach may be more suitable. If in a first step delay in the natural course of progression of the disease based on clinical signs and symptoms of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.

4.2.1.3 Primary prevention

The overall goal of primary prevention in dementia is to reduce the incidence of the disease. This will be accomplished by promoting the initiation and maintenance of good health or by removing potential causes of disease in non-demented individuals or individuals with potentially modifiable (e.g. hypertension, high cholesterol) or unmodifiable (APOE4 status, high age) risk factors for dementia. Cognitive endpoints in primary prevention trials have been dementia (based on cut-off scores), significant cognitive decline and change in cognitive function based on longitudinal performance on certain tests. Unfortunately trials so far have not given conclusive results, however, this may be due to methodological reasons, e.g. high baseline variability and inhomogeneous populations, ceiling effects of assessment tools, rarity of proposed outcome, etc. Therefore in future prevention trials baseline populations, length of follow-up, timing in relation to possible dementia onset, use of valid outcomes, which are sensitive to change, etc. must be considered and should be justified (see also Section 4.1.5).

4.2.2 Study design and methods

4.2.2.1 Run-in period

The screening and run-in period, preceding randomisation to treatment is used for wash-out of previously administered medicinal products which are incompatible with the trial, and for the qualitative and quantitative baseline assessment of patients. Patients with major short term fluctuations of their condition should be excluded. Placebo can be given during this period to assess compliance with medication.

4.2.2.2 Choice of control group

In many countries symptomatic treatment of dementia with cholinesterase-inhibitors is considered as standard of care, particularly in mild to moderate Alzheimer's disease. Therefore in the future new treatments for dementia may be evaluated more and more by using add-on-designs, particularly in long term studies the "pure" use of placebo control for demonstration of efficacy may be difficult to justify. However, substantial differences between placebo patients in the different trials and distinct subtypes of dementia have been shown, therefore placebo controlled studies are still necessary.

Active control parallel group trials comparing the new treatment to an already approved treatment are

needed in order to give the comparative benefit/risk ratio of the new treatment, at least in those treatments intended for symptomatic improvement. However, due to missing assay sensitivity the use of a non-inferiority design versus active control only, will not be accepted as proof of efficacy. Therefore three-arm studies with placebo, test product and active control or a superiority trial are the preferred design options. As feasibility of long term placebo controlled studies have become seriously limited due to the evidence of efficacy of available treatments, a second option is to compare the new treatment to placebo in a short duration trial (e.g. 6 or 12 months depending on the dementia subtype) and thereafter to switch placebo patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment.

4.2.2.3 Choice of tools

Measurement tools (cognitive, functional or global) should be externally validated, pertinent in terms of realistically reflecting symptomatic severity, sufficiently sensitive to detect modest changes related to treatment, reliable (inter-rater; test/retest reliability) and as far as possible easy to use and of short duration, allowing the possibility of easy combination with other tests. They should be calibrated in relation to various populations with distinct dementia syndromes and subpopulations of different social, educational and cultural backgrounds in order to have validated norms available for the interpretation of the results. Particularly in early stages of the distinct dementia subgroups better tools for cognitive, functional or global assessments with higher sensitivity to change are needed and would be welcomed.

They should be standardised for use in different languages and cultures. Some tools (e.g. memory tests) should be available in several equivalent forms to allow for the effect of training with repeated administration.

Applicants may need to use several instruments to assess efficacy of putative drugs for treatment of dementing conditions because:

a) there is no single test that encompasses the broad range of heterogeneous manifestations of dementia and its specific subtypes

b) there is no ideal measurement instrument at the present time. Whilst a large number of methods for evaluation of cognitive functions and behavioural changes have been suggested, none has convincingly emerged as the reference technique, satisfying the above set of requirements. Hence the choice of assessment tools should remain open, provided that the rationale for their use is presented, and justified

c) demented patients are poor observers and reporters of their own symptoms and behaviour self-report measures tend therefore to be less sensitive to treatment effects than observer-related instruments, particularly in moderate to severe disease stages. Relatives or nurses evaluations should therefore be part of the assessment, even though the risk of bias should not be under estimated.

For each domain one instrument should be specified in the protocol as primary. It is recommended that each domain is assessed by a different investigator who should be independent of and blind to all other ratings of outcome. If side effects exist which can unblind the investigator all outcome raters should be denied access to this information as far as possible.

The applicant will be required to justify the instruments selected with respect to their qualities.

- **Objective cognitive tests**

Objective tests of cognitive function must be included in the psychometric assessment; such tests or batteries of tests must cover more than just memory as impairments in domains other than memory are mandatory for the diagnosis of AD and the assessment of its severity. Within the domain of memory, several aspects should be assessed. These are learning of new material, remote as well as recent memory, and recall and recognition memory for various modalities (including verbal and visuo-spatial). Other cognitive domains such as language, constructional ability, attention/concentration and psychomotor speed should be assessed as well.

The Alzheimer's Disease Assessment Scale (ADAS) cognitive subscale, dealing with memory, language, construction and praxis orientation, is widely used and can be considered as standard in trials on patients with mild to moderate Alzheimer’s disease. However, due to ceiling and floor

effects, its sensitivity to change is limited in early and late stages of the disease. . If new instruments are developed, data are needed to provide empirical support for the construct validity and reliability of the new measurement tools (e.g. test-retest, inter-rater, internal consistency, etc). Moreover, for correct interpretation of the described results validation of these tests in normal controls and different disease states including influences by age, gender, level of education, time interval of testing etc. is necessary. Otherwise the clinical meaningfulness is not assessable. For instance the ADAS-cog has been adapted to vascular dementia by adding assessment of executive function as Vascular dementia Assessment Scale (VaDAS), however, comprehensive data on validity and reliability have not been published yet.

Alternatives to the ADAS like the "Neuropsychological Test Battery for Use in Alzheimer's Disease" (NTB) have been validated and may be used. However, it has to be taken in consideration that every scale must be adapted and validated for the distinct subtypes of dementia, and within subtypes the original validated scale should be used without further adaptations. If other scales than $ADAS_{cog}$ are used as primary outcome measure, estimations with the $ADAS_{cog}$ as secondary endpoint should supplement the results for consistency of interpretation.

- **Self-care and activities of daily living**

Activities of daily living (ADL) assessment is useful to evaluate the impact of a medicinal product-related improvement in everyday functioning. These measurements usually rely largely upon the reports of relatives or carers in close and regular contact with the patient, some items of measurement are gender- and culture-biased.

Several scales have been proposed to measure either basic activities of daily living (or self -care) which relate to physical activities, such as toileting, mobility, dressing and bathing (ADL) or instrumental activities of daily living, such as shopping, cooking, doing laundry, handling finances, using transportation, driving and phoning (IADL). However, this concentration on common self-care or domestic activities disregards many activities, which in recent times may be more appropriate, e.g. use of technology. This results in low sensitivity to change of most of the used assessment scales today. Separate measurement tools of ADL/IADL for early and advanced disease stages are needed, which add new dimensions to the existing assessment tools to allow better evaluation of a clinically meaningful change, e.g. in epidemiological studies impairments in four IADL items (handling medications, transportation, finances and telephone use) have been shown as most sensitive indicators of early stages of dementia whereas in advanced disease stages basic ADL as toileting, dressing and bathing are sensitive indicators of change. One of the major issues for use in clinical trials is non-linearity of these changes over time due to adaptation and coping strategies of the individual patient. However, in newer studies using the "Disability Assessment in Dementia" (DAD) or the "Alzheimer Disease Cooperative Study ADL scale" (ADCS-ADL) some initial results showed linearity in change over one year in mild to moderate AD.

As many instruments are under further study in the study protocol choice of the instrument for assessment and its applicability for the distinct dementia entity and early or advanced disease stages should be justified.

- **Global Assessment of Change**

Global assessment refers to an overall subjective independent rating of the patient's condition by a clinician experienced in the management of patients with dementia. Despite certain limitations, the clinician's global assessment can serve as a useful measure of the clinical relevance of a medicinal product's anti-dementia effect. Moreover, global assessment, being in general more unspecified, allows detection whatever changes occur within treatment.

A global scale allows a single subjective integrative judgement by the clinician on the patient's symptoms and performance, as opposed to assessing various functions by means of a composite scale or a set of tests (comprehensive assessment). The Clinician's Interview Based Impression of Change-plus (CIBIC-plus) allows assessment of the global clinical status of the demented patient relative to baseline, based on information from a semi-structured interview with the patient and the carer, without consideration of any cognitive performance from any source. The Alzheimer's Disease Cooperative Study Unit Clinician's Global Impression of Change (ADCS-CGIC) is another semi-structured interview based global measure incorporating information from both patient and carer. Compared to the CIBIC-plus it is more specified with focus on 15 areas including cognition, behaviour and social

and daily functioning. Although such a global assessment of patients benefit is less reliable than objective measurements of response and often appears insufficient to demonstrate by itself an improvement, it should be part of clinical trials in dementia as it represents a way to validate results obtained in comprehensive scales or objective tests, particularly when it is applied by an independent rater. The CIBIC-plus has been shown to be less responsive to drug effects than psychometric tests alone in some studies with anti-dementia drugs in AD, however, clinical global impression was more sensitive than standard measures of cognition and behaviour in a study in patients with PDD.

Contrary to global measurement of change, comprehensive assessment is meant to measure and rate together in an additive way several domains of the illness, e.g. cognitive deficits, language deficits, changes in affect and impulse control. Scores proven to be useful in describing the overall clinical condition should be used, such as the Clinical Dementia Rating (CDR).

However, rather than composite scores derived from summing or averaging scores in different domains, the use of a set of instruments to quantify individually the dimensions of impairment, disability and handicap (social participation) is encouraged by regulatory bodies.

- **Health related quality of life**

Although quality of life is an important dimension of the consequences of diseases, the lack of sufficient validation of its assessment in dementia does yet not allow specific recommendations to be made for regulatory acceptance. Further studies are required to validate adequate instruments for assessment of these dimensions in patients and their caregivers. In theory, both generic and disease specific questionnaires may be used in patients with dementia. However, in practice, it is very important to choose a questionnaire which addresses the key domains of the disease and is sensitive to reflect clinically meaningful changes. Depending on the disease stage information regarding quality of life can be obtained by the patient, by family members or professional caregivers. Based on the different perspectives of the respondent – patient or carer - the information may be divergent and sometimes even contradictory. This has to be taken into consideration in the process of validation of semi- or structured interviews and assessment scales before claims about improvement in quality of life can be achieved. The issue is further complicated by “response shift”. This term reflects on the change in the internal standards of the respondent: based on psychological, social and cultural background and resources coping processes will be facilitated, which may lead to an improvement in quality of life independent from treatment with medicinal products for dementia. These effects are clearly different in early and advanced stages of the dementing condition and must be taken into consideration.

Examples for disease specific quality of life measures in a sophisticated stage of development are the Alzheimer’s Disease-Related QOL (ADRQL) and the QOL-Alzheimer’s Disease (QOL-AD), both show sufficient psychometric properties and studies are ongoing to establish their sensitivity to change. Similar instruments should be developed for other dementing conditions as well.

4.3 General Strategy

The following recommendations apply to all dementing conditions but have to be adapted to the specific forms of dementia (e.g. Alzheimer’s disease, vascular dementia, etc.).

Exploratory Studies

4.3.1 Early pharmacology and pharmacokinetic studies

In the early phases of the development of anti-dementia medicinal products it is important to establish the pharmacological rationale on which the drug may be thought to be effective. Side effects and possible surrogate markers of pharmacological activity in volunteers, if available and relevant, might give some estimation of the appropriate dose.

Standard pharmacokinetic studies (see Note for Guidance on Pharmacokinetic Studies) must aim at defining the absorption, distribution, metabolism and elimination of the drug.

Pharmacokinetic interactions between the test drug, other anti-dementia drugs and other medicinal products, expected to be given concurrently in clinical practice, should be studied, unless clear mechanistic based evidence is available that no interaction could be expected.

Pharmacodynamic interactions between the test drug and any psychoactive medicinal product, expected to be given concurrently with the test drug in clinical practice, should be studied.

If relevant, pharmacokinetic studies of the test-drug in patients with hepatic and /or renal impairment should be performed.

4.3.2 Initial therapeutic trials

As it is difficult to seek improvement and probably unrealistic to expect recovery in advanced dementia, efficacy studies should be carried out mainly in patients suffering from mild or moderate forms of the disease. The inclusion of the same type of patients in Phases II and III should be advised, as safety issues may not be the same in different subgroups. Ideally such studies are carried out in the patient's everyday surroundings. These studies in well-characterised samples of demented patients have the following objectives:

- preliminary evaluation of efficacy
- assessment of short-term adverse reactions from a clinical and laboratory standpoint
- determination of pharmacokinetic characteristics
- definition of doses presumed to be effective
- determination of maximal tolerated doses

The duration of such trials will depend either upon the time of response that is expected, or may be one of the parameters to be assessed. Newer techniques as MRI (e.g. atrophy of entorhinal or parahippocampal cortex) may be used as biomarkers in such Phase II-trials. As the use of such biomarkers has been improved considerably they may be used as primary endpoint in proof of concept studies or as secondary endpoints in pivotal clinical trials.

Confirmatory Studies

4.3.3 Controlled clinical trials

4.3.3.1 Symptomatic improvement

Symptomatic improvement studies have the following main objectives:

- demonstrating efficacy of the drug and estimating the temporal course and duration of such effects
- assessing medium and long-term adverse effects.

Controlled clinical trials aimed at demonstrating short term improvement in AD should last at least 6 months. In epidemiological studies and clinical trials in patients with VaD it has been shown that cognitive and functional decline is slower than in AD, here study durations of at least 12 months seem to be necessary to show a difference between active and placebo treatment. These studies should include placebo and/or comparators where appropriate. However, even longer study durations are required to establish the maintenance of efficacy. The results of such extended studies might have an impact on labelling of compounds demonstrating efficacy. Depending on the subtype of dementia the possible influence of co-medication has to be taken into consideration, e.g. changes of dopaminergic treatment in PDD or changes of cardiovascular medication in patients with VaD.

Open label follow-up of at least 6 to 12 months more than in short term studies are recommended for demonstrating long term safety. This can be achieved with an extension of the trial over the initially scheduled period in patients considered as responders and/or asking for continuing the treatment. In addition to responding adequately to an ethical issue, this allows to accumulate data on medium/long term safety of the drug and to estimate the maximal duration of the symptomatic effects.

Periodic evaluation of efficacy and safety should be performed at regular intervals, depending on the anticipated rapidity of action of the medicinal product and the duration of the trial. After the end of the treatment administration, the state of the patients should be followed for possible adverse events related to withdrawal treatment for a period appropriate for the drug being tested.

With regard to safety, as in the case of medicinal products designed for prolonged use, at least 100 good quality cases of patients followed-up for 1 year or more should be available.

4.3.3.2 Disease modifying effects

From a regulatory point of view, a medicinal product can be considered as disease modifying, if the progression of the disease as measured by cognitive and functional assessment tools is reduced or slowed down and if these results are linked to an effect on the underlying disease process (see also Section 4.2.1.2).

In order to establish an impact on disease progression, distinction between symptomatic and disease modifying effects of a medicinal product has to be made: unfortunately there is no ideal study design to show unambiguously a disease modifying effect. Due to the characteristics of the underlying disease and if only slowing of the disease process is foreseen as a possible outcome, long-term placebo controlled trials are needed, and clinical outcomes in both study arms are measured at regular intervals to establish a clinically relevant effect. Clinical improvement must be shown over a time period that is relevant to the proposed claim taking into consideration the distinct subtype of dementia and its natural course. The minimum duration of confirmatory trials depends on the expected progression rate and the assumed activity of the experimental compound, e.g. in patients with mild to moderate Alzheimer's disease, duration of 18 months has been assumed to be sufficient in some currently ongoing trials. So in a first approximation a hypothesis of disease modification seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis). However, it should be taken into consideration that although it is known that the natural course of disease may be approximated with a linear model over time, it is yet unclear, whether a linearity assumption holds true in the situation of a clinical trial with an intervening (potentially disease modifying) treatment effect. Moreover, treatment effects are often different over the various disease stages (mild, moderate, severe) and many of the most commonly used outcome measures show a non-linear change, when used for time periods longer than one year.

In consequence it should be established that at two distinct time points the treatment effect in the pre-specified endpoints increases over time in a parallel group design. Such a study can be enhanced at the end of the trial with a phase of a randomized start or randomized withdrawal design. The magnitude of the treatment effect in terms of established outcomes, e.g. $ADAS_{cog}$ and IADL, is estimated based on the difference between placebo and experimental compound at study end. The possible disease modifying effect may be addressed by a slope analysis or by a survival design (e.g. time to progression to pre-specified clinical keystones of disease).

Both approaches to establish a disease modifying effect have their drawbacks and may be further hampered by possible placebo response, differences in drop out rates and missing data in general, poor adherence to treatment, change of treatment response with course of disease, etc. Therefore the choice of primary analysis and the fulfilment of underlying assumptions and requirements should be justified in detail in the study protocol. It may be considered to perform both analyses, e.g. a survival analysis as primary and slope analysis as secondary.

Independently from the study design chosen it may be difficult to differentiate unambiguously between symptomatic and disease modifying effects only on the clinical endpoints, therefore a full claim of "disease modification" can be supported by a validated biomarker, which is able to indicate an effect on the underlying pathophysiology of the dementing condition. Such a biomarker should reflect key aspects of the underlying disease process based on a plausible disease model (see also Section 4.2.1.2).

4.3.4 Adjustment for prognostic variables

Based on theoretical, experimental or observational considerations, the course of the disease and/or the efficacy of treatments may differ within subgroups of patients with dementia or its specific subtypes.

Some examples of prognostic factors to take into consideration could be as follows:

- apolipoprotein E genotype
- profile of betaamyloid and tau-protein in cerebrospinal fluid
- neuroimaging parameters (MRI, serial MRI, emission tomography)
- suspicion of Lewy body pathology (fluctuation of cognition, hallucinations, Parkinsonism)
- severity of dementia at inclusion

- presence of vascular risk factors.

The factor(s) to be taken into account in the analysis should be identified in the protocol, the rationale should be given, and the study should be powered to yield a sufficient number of patients with or without the factor(s) to allow a statistically valid conclusion. Moreover, some of these variables may be used to predefine homogeneous patient populations at risk ("enriched populations"), which may allow better evaluation off therapeutic efficacy in distinct populations.

4.3.5 Concomitant treatments

In order to eliminate any interference or bias, it is desirable, particularly in exploratory trials to avoid any treatment likely to impair alertness, intellectual function and behaviour. These include hypnotic, anxiolytic, antidepressant, antipsychotic, anticholinergic and memory enhancing drugs. If they cannot be avoided, the acceptable level of use of such medicinal products should be set a priori in the protocol and remain constant throughout the trial.

Pharmacodynamic interaction studies between the test drug and the drugs commonly used in the elderly should be conducted, including psychotropic drugs used to control behavioural disturbances as mentioned earlier.

4.4 Safety Evaluation

In general the content of ICH E1 should be taken into consideration.

Identified adverse events should be characterised in relation to the duration of treatment, the applied dosage, the recovery time, age (e.g. old and oldest-old patients) and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and electrophysiological recordings (e.g. electrocardiogram). It should be considered that the acceptance of adverse events in patients with early disease stages and minor impairment will be different in benefit-risk-assessment than in patients with advanced disease stages and severe impairment.

All adverse events occurring during the course of clinical trials must be fully documented with separate analysis of serious adverse drug events, adverse events leading to drop-outs and patients with a fatal outcome.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self poisoning should be provided, particularly in the patients with mild to moderate cognitive impairment.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated depending on the action on distinct receptor sites, e.g. cholinomimetic effects of cholinesterase inhibitors.

4.4.1 Neurological Adverse events

Depending on the dementia subtype special attention should be given to the occurrence or exacerbations of neurological adverse events, particularly extrapyramidal symptoms, disorientation, further impairment of gait, occurrence of seizures, etc.

Also the effect of withdrawal of the test drug should be systematically monitored.

4.4.2 Psychiatric Adverse events

Depending on the dementia subtype specific attention should be paid to the occurrence of hallucinations and other signs and symptoms of affective or psychotic disorders. Other neuro-behavioural abnormalities, particularly disorientation, agitation and aggressive behaviour should be recorded depending on the pharmacodynamic profile of the test drug. Specific claims in this respect, e.g. improvement of neuro-behavioural abnormalities, have to be based on specific studies.

4.4.3 Cardiovascular events

Depending on the dementia subtype and the pharmacodynamic profile of the medicinal product its effects on the cardiovascular system, e.g. occurrence of orthostatic hypotension or the potential to induce arrhythmias, should be examined.

4.4.4 Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see EC Guideline on population exposure), it should be considered that long term safety may be different in the distinct subtypes of dementia, e.g. AD vs. VAD and PDD.

For the moment, studies on morbidity and mortality are not required before marketing authorisation. However, effects on mortality should be monitored on a long term basis. This can be done post-marketing by implementing a risk minimization or risk management plan.

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Note: See http://publications.eu.int/code/en/en-250304.htm for guidance on referencing published information and http://publications.eu.int/code/en/en-130102.htm for guidance on referencing EU texts. References to related guidelines should also be included.