## COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

## NOTE FOR GUIDANCE ON MEDICINAL PRODUCTS IN THE TREATMENT OF ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)</td>
<td>October 1992</td>
</tr>
<tr>
<td>TRANSMISSION TO THE CPMP</td>
<td>December 1992</td>
</tr>
<tr>
<td>TRANSMISSION TO INTERESTED PARTIES</td>
<td>December 1992</td>
</tr>
<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>June 1993</td>
</tr>
<tr>
<td>RE-SUBMISSION TO THE EFFICACY WORKING PARTY</td>
<td>June 1996</td>
</tr>
<tr>
<td>DISCUSSION IN THE AD-HOC WORKING GROUP AND EFFICACY WORKING PARTY</td>
<td>October 1996</td>
</tr>
<tr>
<td>RE-TRANSMISSION TO THE CPMP</td>
<td>December 1996</td>
</tr>
<tr>
<td>RE-TRANSMISSION TO INTERESTED PARTIES</td>
<td>December 1996</td>
</tr>
<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>March 1997</td>
</tr>
<tr>
<td>RE-SUBMISSION TO THE EFFICACY WORKING PARTY</td>
<td>July 1997</td>
</tr>
<tr>
<td>APPROVAL BY THE CPMP</td>
<td>July 1997</td>
</tr>
<tr>
<td>DATE FOR COMING INTO OPERATION</td>
<td>January 1998</td>
</tr>
</tbody>
</table>
INTRODUCTION

The term dementia describes a syndrome characterised by dysmnesia, intellectual deterioration, changes in personality and behavioural abnormalities (DSM-III-R, DSM-IV, ICD-10). These symptoms result in social and occupational decline. The dementia syndrome can have multiple aetiologies and pathophysologies. Thus there can probably be no single "antidementia" drug, but different drugs should be developed directed towards either symptomatic change or to modification of aetiological and pathophysiological processes.

The principles of the present guidelines are mainly applicable to Alzheimer's disease (AD), but may be adapted for use in preparing guidance for drug trials in other specific forms of dementia.

It should be recognised that the symptomatic treatment of AD is still an open research field. The development and use of relevant reliable and sensitive instruments to measure, among others, activities of daily living (ADL), instrumental activities of daily living (IADL) and behavioural symptoms is encouraged.

I. DIAGNOSIS

1. Dementia

The clinical syndrome of dementia and the criteria for its severity are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III. Revised 1988 and DSM-IV of the American Psychiatric Association) and in ICD-10 (F00-F03) of the WHO.

According to these definitions, the diagnosis of dementia is 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. These impairments should not be explained by another major primary psychiatric disorder. Simple screening tests, such as the Mini Mental State Examination (MMSE) are useful to document cognitive dysfunction.

2. Severity of dementia

The DSM-IV and ICD 10 include criteria for mild, moderate and severe dementia. The severity of cognitive impairment and behavioural changes and the resulting changes in self-care and other ADL can be documented using a variety of specific and global rating instruments. The degree of severity of dementia of the included patients should be assessed and the method used should be stated.
3. The diagnosis of Alzheimer's dementia

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. Patients with brain biopsy proven definite AD are seldom available. Currently the most appropriate group in whom to study the effects of drugs are patients with probable AD, according to the NINCDS-ADRDA criteria.

4. Selection criteria for Alzheimer's disease

As stated above, the diagnosis of AD consists of two steps: first, the clinical diagnosis of dementia and second, the exclusion of other causes of dementia. This relies on a careful history with a clinical neurological examination and technical and laboratory methods. As the latter are evolving rapidly, no complete list is presented here. Other causes of dementia to be excluded with pertinent method include in particular vascular dementia, infections of CNS (e.g. HIV, syphilis), Creutzfeld-Jakob disease, Huntington’s disease, and Parkinson's 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 following methods are strongly recommended:

- Brain imaging, such as CT or MRI to exclude major structural brain diseases. These include ischaemic infarcts, subdural haematoma, communicating hydrocephalus and brain tumours.
- The NINDS AIREN(1993) criteria to render vascular dementia unprobable.
- Blood tests to exclude infectious, endocrine, and other systemic disorders.
- History and laboratory screening to exclude drug use and abuse. Neuroleptics, hypnotics, alcohol, opioids, benzodiazepines, other sedatives and illicit drugs should be considered, as likely or contributing causes.

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

II ASSESSMENT OF THERAPEUTIC EFFICACY IN ALZHEIMER’S DISEASE

1. Criteria of efficacy

The main goals of AD treatments may be:

- Symptomatic improvement, which may be manifest in enhanced cognition, more autonomy and/or improvement in behavioural dysfunction.
- Slowing or arrest of symptom progression.
• Primary prevention of disease by intervention in key pathogenic mechanisms at a presymptomatic stage.

This guideline will concentrate on assessment of symptomatic improvement in so far as, for the time being, experience is lacking in either slowing, arresting symptom progression or in the primary prevention of disease.

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 variables should be stipulated, one of which evaluates the cognitive endpoint. The other should reflect the clinical relevance of the improvement in cognition. The protocol should specify this second primary variable and to which domain (global, or preferably functional) it relates. The study should be designed to show significant differences in at least each of the two primary variables.

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 meaningful benefit (response). For a claim of short term treatment, responders may be defined at 6 months as improved to a relevant prespecified degree in the cognitive endpoint and not worsened in the two other domains. Other definitions of responders are possible, but should be justified by the applicant, taking into account the clinical relevance of the outcome.

Other end-points of interest may include behavioural symptoms. For a claim in these symptoms, a specific trial should be designed with 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 a statistically significant improvement on the functional and global endpoints may be considered as primary evidence of clinically relevant symptomatic improvement in this population.

2. Study design and methods

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.

2.2 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 or sub-populations of different social, educational and cultural backgrounds in order to have validated norms available for the interpretation of the results.

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 Alzheimer’s drugs because:

a) there is no single test that encompasses the broad range of heterogeneous manifestations of dementia in AD;

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. Relatives or nurses evaluations should therefore be part of the assessment, even though the risk of bias should not be underestimated.

For each domain one instrument should be specified in the protocol as primary. If this is not done, then the resulting multiplicity issues must be addressed.

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.

2.2.1 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 psycho-motor 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. However this remains an open research field.
As the ADAS-Cog is recorded on a categorical scale and response may be related to baseline in a non-linear manner, due consideration should be given to the appropriate analysis of treatment effects determined by changes from baseline.

2.2.2 Self care and activities of daily living
These measurements usually rely largely upon the reports of relatives or carers in close and regular contact with the patient.

ADL assessment is useful to evaluate the impact of a medicinal product-linked improvement in everyday functioning. 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 or instrumental activities of daily living, such as shopping, cooking, doing laundry, handling finances, using transportation, driving and phoning.

2.2.3 Global assessment
Global assessment refers to an overall subjective independent rating of the patient's condition by a clinician experienced in the management of AD patients. Despite certain limitations, the clinician's global assessment can serve as a useful measure of the clinical relevance of a medicinal product's antidementia effect.

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 (see 2.2.4 Comprehensive assessment). Although 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 AD as it represents a way to validate results obtained in comprehensive scales or objective tests.

The Clinician's Interview Based Impression Of Change is recognised to be less responsive to drug effect than psychometric tests alone.

2.2.4 Comprehensive assessment
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) should be encouraged.

2.2.5 Quality of life
Although quality of life is an important dimension of the consequences of diseases, the lack of validation of its assessment in AD does not allow specific recommendations to be made as yet. When adequate instruments to assess this dimension in patients and their care givers become available, quality of life assessment may be justified in AD trials.
III GENERAL STRATEGY

The following recommendations apply mainly to AD but can be adapted to other forms of dementia (e.g. vascular dementia).

1. Phase I. Early pharmacology and pharmacokinetic studies

In the early phases of the development of antidementia 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.


2. Phase II. 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.

3. Phase III. Controlled clinical trials

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 should last at least 6 months. Such studies should include placebo and/ or comparators where appropriate. However studies of one year or more would be desirable to evaluate the maintenance of efficacy. The results of such extended studies might have an impact on labelling of compounds demonstrating efficacy.
Open label follow-up of at least 12 months 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 (cf. Note for Guidance on Clinical Investigation of Medicinal Products for Long-Term Use, Vol. III of The Rules Governing Medicinal Products in the European Union), at least 100 good quality cases of patients followed-up for 1 year or more should be available.

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 AD or other dementias.

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

- Apo lipoprotein E genotype
- 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.

5. Concomitant treatments

In order to eliminate any interference or bias, it is desirable, particularly in Phase II 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.