

**INTERIM GUIDANCE ON DONEPEZIL
FOR PRIMARY AND SECONDARY CARE
CLINICIANS**

**REPORT BY THE WORKING GROUP
ON
NEW DRUGS FOR DEMENTIA**

February 1998



This booklet has been published by the Clinical Resource Efficiency Support Team (CREST) which is a small committee of doctors established under the auspices of the Central Medical Advisory Committee. Its aim is to promote clinical efficiency in the health service in Northern Ireland while ensuring the highest possible standard of clinical practice is maintained.

Crest wish to thank Dr James Kelly and the Working Group on New Drugs for Dementia for producing this guidance.

Special thanks are due to Dr Maura Briscoe for the major contribution which she made to the production of this booklet.

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Introduction

In June 1997 Dr Henrietta Campbell, Chief Medical Officer for Northern Ireland convened a working group under the chairmanship of Dr James Kelly, Consultant Geriatrician in the Erne Hospital. The Working Group was asked to produce advice for clinicians on recently licensed drugs in dementia.

This guidance on donepezil recommends a shared care approach between primary and secondary care clinicians for the management of those patients who are considered suitable for treatment. The long-term efficiency of this new drug will require further research and evaluation. Physicians will wish to assess the health care needs of the individual and carefully weigh up any advantages, which may be obtained from this drug against established services and treatments. Careful monitoring of patient outcomes is encouraged in order to provide evidence of possible benefits.

The Working Group on New Drugs for Dementia will review these guidelines within 1 year to take account of emerging evidence. The principals outlined in this guidance are also applicable to other drugs currently under trial for Alzheimer's disease unless superseded by further guidance from the Group.

This Group has now been incorporated into the CREST Drugs Advisory Group which was recently convened to:

provide advice to facilitate the managed introduction of recently licensed drugs;

promote rational cost effective and safe prescribing of such drugs;

promote equity of access to treatment and supply of such drugs for all patients; and

monitor the overall prescribing of such drugs in Northern Ireland.

**Guidance on Donepezil
for
General Practitioners**

SUMMARY OF GUIDANCE ON DONEPEZIL FOR GENERAL PRACTITIONERS

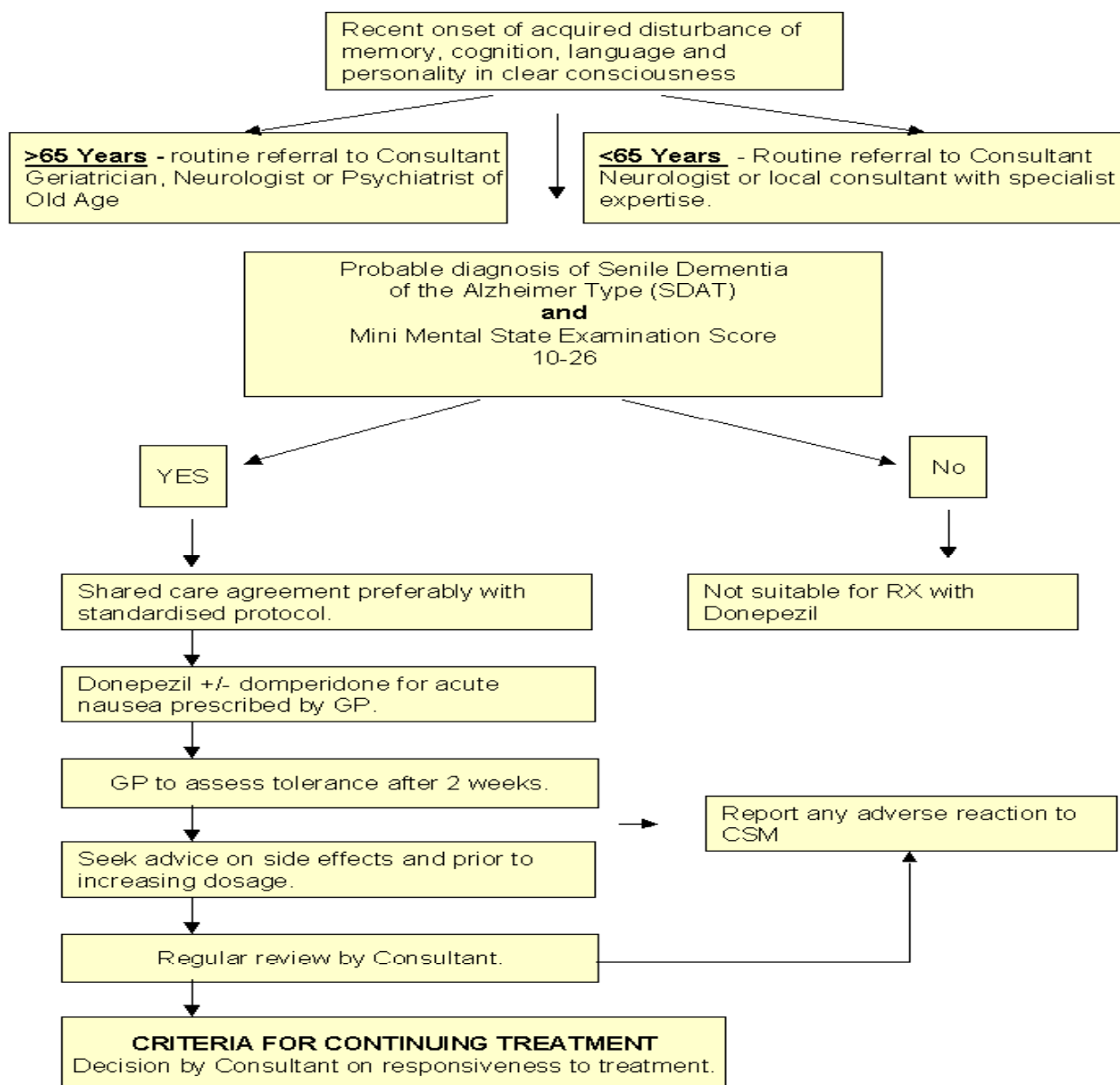
Donepezil is licensed for the treatment of mild to moderate Alzheimer's disease. Consideration should be given to the clinical significance of the published evidence prior to a decision on treatment.

Treatment with Donepezil gives only a modest short-term improvement in cognitive function. It does not alter the underlying disease process.

Patients should be referred for specialist evaluation prior to commencement of treatment. Only those patients who fulfil the diagnostic criteria and who have a Mini-Mental State Examination score of 10-26 should be commenced on treatment.

Management should normally be by a shared care approach, which should clearly define the responsibilities of both the general practitioner and the consultant.

The decision on duration of treatment will be consultant led, depending on responsiveness to treatment.



CLINICAL GUIDANCE ON DONEPEZIL FOR GENERAL PRACTITIONERS

1.0 Introduction

- 1.1 Donepezil hydrochloride (Aricept) has recently been licensed in the UK for the treatment of mild to moderate Alzheimer's disease. Currently there is no published evidence of its beneficial effects on multi-infarct dementia. Donepezil provides symptomatic treatment. It acts by inhibiting the enzyme responsible for metabolising acetylcholine, thereby enhancing neurotransmitter levels. As the cholinergic neurones degenerate, the benefits derived from treatment are likely to reduce over time.
- 1.2 To date two trials have been published in full. There is some evidence that donepezil gives a modest, short-term improvement in cognitive function but it does not appear to alter the underlying disease process. Its maximum benefits are derived early in the treatment and cognitive changes are probably equivalent to approximately a 3-6 month delay in disease progression. It is generally well tolerated but as acetylcholine is found in cells throughout the body side effects may occur.
- 1.3 The Drug and Therapeutics Bulletin of October 1997 highlights that the clinical significance of these changes for patients and their carers is uncertain and, on the basis of the published evidence, the Bulletin does not recommend the use of Donepezil. However, since this was written the journal Neurology, in January 1998, published an article highlighting the benefits of treatment with Donepezil. Doctors should, therefore, carefully consider all available evidence prior to prescribing this drug.

2.0 Patient Selection

- 2.1 When treatment is being considered, the early, accurate diagnosis of patients with mild to moderate Alzheimer's disease is essential. Therefore, where there is a suspicion of *an acquired disturbance of memory, cognition, language and personality in clear consciousness* **it is recommended that the patient should be referred for specialist evaluation prior to commencement of treatment.** Consultants in neurology, psychiatry of old age and geriatric medicine are best placed to establish the accurate diagnosis of mild to moderate dementia of Alzheimer's disease. A patient with a Mini-Mental State Examination giving rise to a score of 10-26 would fulfil the grading criteria associated with mild to moderate dementia. Patients should be referred in the usual way unless there is a high index of suspicion of major pathology requiring urgent treatment.
- 2.2 Those patients who are under the age of 65 years and who have a possible diagnosis of dementia should be referred to a consultant neurologist or other local specialist with expertise. There may be a requirement for referral to a specialist centre for screening for familial dementia.
- 2.3 A detailed medical and drug history needs to be included in the referral in order to ensure there is no interaction between the proposed treatment and other drug treatments or conditions such as cardiovascular, gastrointestinal, pulmonary, genitourinary and neurological conditions.

3.0 Initiation of Prescribing

- 3.1 It is recommended that general practitioners should not commence treatment prior to referral. If the patient is suitable for treatment, the consultant may advise that domperidone for acute nausea should be prescribed with the initial prescription.

As most patients will be home-based, it is considered that this prescription should be available in a primary care setting.

4.0 Patient Monitoring

- 4.1 It is anticipated that the majority of patients will be managed by a *shared-care approach*, preferably using a standardised protocol. When a general practitioner is asked to participate in a shared-care arrangement, this protocol will specify the respective responsibilities of the consultant and general practitioner.

- 4.2 A review of the patient after 2 weeks of treatment should normally be undertaken by the general practitioner to assess tolerance to the drug. Side effects appear to be dose dependent. The most common side effects are due to increased gastrointestinal activity with nausea, vomiting and diarrhoea occurring in approximately 5% of patients. General practitioners should also be aware that donepezil may cause bradycardia; syncope has also been reported. More information on adverse effects, contraindications and precautions may be obtained from the data sheet produced by Eisai/Pfizer.

The general practitioner may wish to seek advice from the secondary care clinician if major side effects occur. This is also recommended if an increase in dosage is being considered at any stage.

- 4.3 The patient will be regularly reviewed by the secondary care clinician.

5.0 Criteria for Continuing Treatment

- 5.1 The decision on duration of treatment should normally be left to specialist expertise. In the event of an adverse reaction, however, donepezil may be stopped abruptly. All adverse reactions should be reported to the Committee on Safety of Medicines (CSM).

6.0 Advice to Carers

- 6.1 A carer should be identified to assist in treatment compliance. The carer should be advised that patients who have been on donepezil for a significant period of time may rapidly deteriorate if the drug is withdrawn.

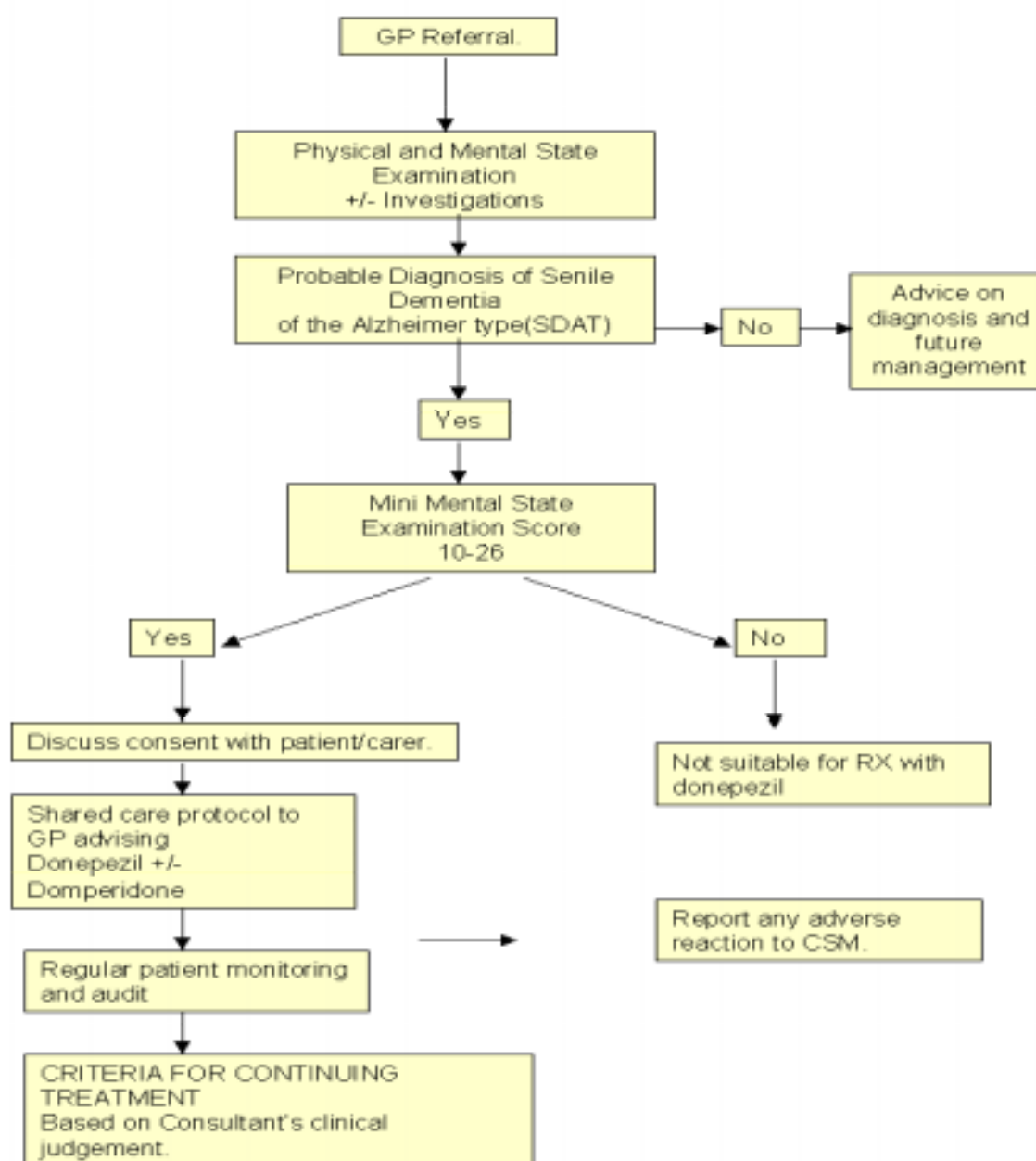
They should be encouraged to report any side effects to their general practitioner and should be aware that donepezil is likely to exaggerate muscle relaxation during anaesthesia and, therefore, they should inform hospital doctors if a procedure involving general anaesthesia is being considered.

- 6.2 General practitioners may wish to inform carers that advice sheets on donepezil are available from the Alzheimer's Disease Society.

**Guidance on Donepezil
for
Secondary Care Clinicians**

SUMMARY OF GUIDANCE ON DONEPEZIL FOR SECONDARY CARE CLINICIANS

- Mental state and physical examination combined with relevant investigations will help confirm or clarify the diagnosis of mild to moderate dementia of Alzheimer's disease.
- Consideration should be given to the clinical significance of the published evidence prior to a decision on treatment.
- Consultant initiated treatment should be reserved for patients who have a Mini-Mental State Examination Score of 10-26 inclusive.
- GPs should be invited to participate in a shared care agreement, preferably using a standardised protocol.
- Regular monitoring and audit should be undertaken by the Consultant to determine effectiveness of the drug.



CLINICAL GUIDANCE ON DONEPEZIL FOR SECONDARY CARE CLINICIANS

1.0 Introduction

- 1.1 Donepezil hydrochloride (Aricept) has recently been licensed in the UK for the treatment of mild to moderate dementia of Alzheimer's disease. It is not licensed for the treatment of multi-infarct dementia. This is the first of the cholinesterase inhibitors for Alzheimer's disease to reach the market. Other agents are in development for the treatment of other forms of dementia.
- 1.2 General practitioners have been advised not to start treatment with donepezil without specialist evaluation. They have been asked to refer patients in which they consider there is a suspicion of acquired disturbance of memory cognition, language and personality in clear consciousness (part of the ICD10 classification for dementia). It is likely that the majority of patients will be referred to consultants in geriatric medicine, neurology and psychiatry of old age. GPs have been advised to refer patients who show symptoms of dementia under the age of 65 to a consultant neurologist; however, due consideration should be given to local specialist expertise.
- 1.3 The Drug and Therapeutics Bulletin of October 1997 highlights that the clinical significance of the changes for patients and their carers is uncertain and, on the basis of the published evidence, the bulletin does not recommend the use of Donepezil. However, since this was written the journal Neurology, in January 1998, published an article highlighting the benefits of treatment with Donepezil. Doctors should, therefore, carefully consider all available evidence prior to prescribing this drug.

2.0 Criteria for Diagnosis of Mild to Moderate Alzheimer's Disease

- 2.1 The diagnosis of dementia is a clinical matter which relies on a clear history from a patient and an informant. Mental state and physical examination combined with relevant investigations will help to clarify or confirm the clinical diagnosis. The diagnosis and classification of dementia should conform to accepted standards. The ICD10 classification of dementia is suggested for use in these guidelines. Physicians may wish to use the NINCDS/ADRDA criteria (McKhann criteria) for subclassification of Alzheimer's disease. This has the highest correlation of in-life diagnosis with post mortem findings.
- 2.2 Neuroimaging may be needed in certain cases, to exclude other forms of dementia or pathology. Therefore, access to CT scanning may be required depending on the clinical presentation. There may also be a need for blood tests and due consideration should be given to the necessity for an ECG as cholinesterase inhibitors may induce bradycardia.

3.0 Consent to Treatment

- 3.1 Consent in broad terms should be obtained from the patient, having discussed the possible benefits and side effects of the drug treatment with the patient (and carer). Careful thought will be needed where capacity for consent seems in doubt and in such circumstances, consideration should be given to the applicability of consent guidelines associated with mental health legislation and related law.

4.0 Initiation of Treatment

- 4.1 Treatment should normally be initiated by consultants or specialist registrars in geriatric medicine, neurology and psychiatry of old age. The initial starting dose is recommended to be 5mgs.

5.0 Criteria for Starting Treatment

- 5.1 The patient should have a mild to moderate dementia (SDAT) which normally correlates with a Mini-Mental State Examination score of 10-26 inclusive. Domperidone for acute nausea may also be recommended with the initial treatment.

6.0 Patient Monitoring

- 6.1 The initial assessment for tolerance of the drug should be undertaken after 2 weeks by the general practitioner who may wish to contact the consultant for advice on major side effects and prior to increasing dosage. The clinical responsibility for monitoring the patient should normally be under a shared care arrangement where the consultant invites the general practitioner to participate in a shared-care protocol which clearly defines the responsibilities of each doctor.
- 6.2 Consultants are encouraged to regularly monitor and audit the effectiveness of treatment in order that more information may be obtained on the usefulness of this drug. All adverse reactions should be reported to the Committee on Safety of Medicines (CSM).

7.0 Criteria for continuing treatment

- 7.1 This decision is based on the clinical judgement of the consultant. Continued deterioration or increase in rate of deterioration whilst on treatment suggests lack of clinical effectiveness. In some cases a "drug holiday" may be considered to assess the benefits of treatment or to assist in the decision of stopping treatment.

REFERENCES

1. **Drug and Therapeutics Bulletin** Donepezil for Alzheimer's Disease? Vol. 35, No. 10, October 1997
2. **Folstein MF, Folstein SE and McHugh PA** Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *Psychiatr Res* 1975; 12:189-198
3. **London Alzheimer's Disease Treatment Working Group** Guidelines on drug treatments for Alzheimer's disease. *The Lancet* 1997; Vol 350:232-233
4. **Medical Sciences Bulletin** Donepezil Approved for Alzheimer's Disease - *Med Sci Bull* 1997; 20(3)
5. **McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM.** Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939-944
6. **Primary/Secondary Care Faculty** Setting Standards for the Diagnosis and Management of Alzheimer's Disease in Primary and Secondary Care. *Clinical Bulletin (Supplement to Geriatric Medicine)* March 1997
7. **Psychiatry of Old Age Group (NI)** Guidelines on Donepezil June 1997
8. **Rogers S, Farlow MR, Doody R, Friedhoff LT. et al.** A 24 week, double blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; 50: 136-144
9. **Royal College of Psychiatrists Section for the Psychiatry of Old Age** Interim Statement on Anti-Dementia Drugs - Implications, Concerns and Policy Proposals. April 1997
10. **The Wessex Institute** Donepezil in the treatment of mild to moderate senile dementia of the Alzheimer type (SDAT) June 1997 *Report* No. 69 <http://www.epi.bris.ac.uk/rd>
11. **World Health Organisation** The ICD-10 Classification of Mental band. Behavioural Disorders: clinical descriptions and diagnostic guidelines. *World Health Organisation, 1992; Geneva*

APPENDIX A MINI-MENTAL STATE EXAMINATION (MMSE)

Orientation: (score 1 if correct)

1. Name this hospital or building _____ / 1
2. What floor of the building are you on? _____ / 1
3. What city/town are you in now? _____ / 1
4. What country are you in? _____ / 1
5. What country is this? _____ / 1
6. What year is it? _____ / 1
7. What month is it? _____ / 1
8. What is the date today? _____ / 1
9. What day of the week is it? _____ / 1
10. What season of the year is it? _____ / 1

Registration

11. Name three objects and have the patient repeat them e.g. "penny, apple, table". (score 1 for each correct one) _____ / 3

Attention and calculation:

12. Subtract 7 from 100 in serial fashion to 65 (Maximum score 5 - 1 for each correct answer) _____ / 5

Recall:

13. Do you recall the three objects named before? (score 1 for each correct answer) _____ / 3

Language tests:

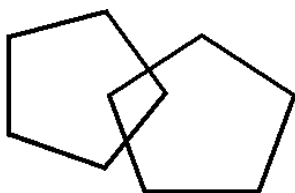
14. **Naming.** Point to watch and pen. Ask patient to name them. (Score 1 for each correct answer) _____ / 2
15. **Repetition.** Ask patient to repeat "No ifs and no buts". (score 1 if correct) _____ / 1
16. **Comprehension.** Instruct patient: "Pick up this piece of paper in your right hand, fold it in half and put it on the floor". (score 1 for each correct section of the 3 part instruction) _____ / 3
17. Read and perform this command: (score 1 if correct) _____ / 1

Close your eyes:

18. Write a sentence. (score 1 if subject, verb and object are present and correct) _____ / 1

Construction:

19. Copy the design below (score 1 for correct copy) _____ / 1



Total MMSE _____

APPENDIX B ACCURACY OF CLINICAL DIAGNOSIS NINCDS/ADRRA criteria (McKhann)

Probable Alzheimer's Disease

I Criteria include:

- presence of dementia
- deficits in at least two areas of cognition
- progressive deterioration
- no clouding of consciousness
- age between 40 and 90
- absence of systemic disorders

II Diagnosis supported by:

- progressive deterioration of individual cognitive function
- impaired activities of daily living
- family history of dementia
- normal LP, EEG, and evidence of atrophy (or progression) on CT scan

III Features consistent with the diagnosis:

- plateaus in the course of the disease
- associated psychiatric symptoms
- neurological signs
- seizures
- normal CT scan

IV Diagnosis of AD unlikely if:

- sudden onset
- focal neurological signs
- seizures or gait disturbance early in the disease

Possible Alzheimer's Disease

V Diagnosis of possible AD can be made:

- in the presence of atypical features
- in the presence of systemic disease (not the cause)
- in the presence of a single progressive cognitive deficit

Definite Alzheimer's Disease

VI Criteria for definite disease are:

- the clinical criteria for probable AD and histopathological evidence of the disorder

APPENDIX C CONSULTANT - INITIATED PRODUCTS

CRITERIA FOR CONSIDERING SHARED-CARE ARRANGEMENTS

Criteria for products which would not be approved for shared care (Red List)

Drugs which meet one or more of the following criteria should remain the prescribing responsibility of the consultant:

The drug does not hold a product licence.

The drug is being used outside the terms of the product licence to an extent that a GP would not normally be expected to accept clinical responsibility.

The drug is being used as part of a hospital based clinical trial.

The individual GP is unable to monitor therapy sufficiently to oversee treatment or adjust the dose where necessary to ensure safety.

The drug is new and there may be issues around long term safety or its appropriate place in therapy.

The drug, dressing or appliance is only available through a hospital.

Criteria for products which may become part of shared care agreements (Amber List)

Circumstances, which meet all of the following criteria may allow a product to be used as part of a shared care arrangement, following agreement by both prescribing parties involved.

1. A shared care proposal has been drawn up following joint discussion of the parties.
2. The shared care agreement:
 - provides a comprehensive summary of treatment.
 - defines the responsibility of the consultant and GP for monitoring and adjusting treatment.
 - defines the referral procedures from hospital to GP.
 - defines the back-up facilities available to the GP from the hospital with which the agreement is made.
3. The GP is satisfied that he/she has all the information and support needed to prescribe and to monitor the patient.
4. If a product is not licensed for the proposed indication, full justification for its use is given by the consultant to the GP.

MODEL DOCUMENT

Dear Dr

SHARED CARE PROTOCOL FOR SPECIALISED TREATMENTS

I have prescribed _____
for your patient _____

Full details are given in the attached report.

This product is of a specialised nature */is being used for a specialised purpose outside the terms of the product license *. It is therefore subject to a Shared Care Protocol, which has been approved by the Northern Area Prescribing Liaison Forum. The protocol was prepared in response to Circular HSS (OPI) 2/92, a copy of which is available on request. It specifies the respective responsibilities of the consultant and the general practitioner when the latter is asked to participate in a shared care arrangement.

My responsibilities under the terms of the protocol are as follows:

- (i) to diagnose the condition
- (ii) to ensure that all necessary tests are undertaken
- (iii) to decide on the treatment and give the reasons
- (iv) to decide if shared care is appropriate for the patient with the diagnosed condition
- (v) where shared care is appropriate, to ask the general practitioner to participate
- (vi) to provide the general practitioner with relevant information, which may include:

diagnosis of the patient's clinical condition
other relevant clinical and product information
treatment to date (doses, times etc)
treatment to be undertaken by GP (dose, route, frequency etc)
information to be given to the patient
review arrangements
possible side effects of treatment
system for monitoring and recording side-effects
useful contact names/numbers

- (vii) to agree to reassess/review the patient's condition at any time when requested by the patient's general practitioner
- (viii) whenever the patient is seen by me to send a written summary within _ days to the patient's general practitioner
- (ix) to be available to provide further advice or information for the GP if required
- (x) to liaise with the hospital pharmacy, if necessary, in order to ensure continuity of supply

The general practitioner's responsibilities, in agreeing to accept clinical responsibility under a shared-care arrangement, are:

- (i) to ensure that he/she has the information and knowledge to understand the therapeutic issues relating to the patient's clinical condition
- (ii) to prescribe the necessary medication
- (iii) where appropriate, to administer the therapy in accordance with the written directions of the consultant
- (iv) to monitor and record the therapy in accordance with the written directions of the consultant
- (v) to report any adverse events to the consultant, as well as to the usual bodies
- (vi) to inform the Board's Family Practitioner Unit (Medical or Pharmaceutical Adviser) of this shared care agreement
- (vii) to liaise if necessary with the community pharmacy chosen by the patient, in order to ensure continuity of supply.

I enclose relevant information in accordance with paragraph (vi) on the first page of this letter. Please contact me at the above address if you have any concerns or queries about your role in this shared-care arrangement.

Yours sincerely,

(*delete as appropriate)