

**Association of British Neurologists**  
**Guidelines for the use of Beta Interferons and Glatiramer Acetate in**  
**Multiple Sclerosis**  
**January 2001**

These guidelines have been drawn up by the Association of British Neurologists (ABN) MS guidelines advisory group and approved by the Council of the ABN. They update and replace previous guidelines formulated in June 1999.

**(A) SUMMARY**

The aim of these guidelines is to provide advice on the use of expensive new disease modifying treatments for multiple sclerosis for doctors, patients and health providers. They are based on data derived from double blinded, randomized, and placebo-controlled clinical trials. The ABN considers the evidence that the drugs are effective in a subgroup of patients with clinically active relapsing remitting MS to be conclusive. The beneficial effects can be clinically important, and in the absence of alternative disease modifying treatments, treatment should be available to this well-defined subgroup (approximately 10% patients) in all parts of the UK. It should be prescribed and supervised by a consultant neurologist, using the starting and stopping criteria outlined in these guidelines, and long term outcome should be systematically monitored by audit. Such a provision of treatment would meet an important clinical need in a debilitating neurological disease, would represent best clinical practice based on current evidence, and would be in accordance with standard clinical practice elsewhere in the EU.

**(B) TREATMENT CRITERIA**

**B.1 Beta Interferon**

**B.1.1. Relapsing-Remitting MS**

Beta interferon (using any one of the three preparations licensed for this indication) is appropriate treatment and should be offered to patients with relapsing-remitting MS who fulfill the following four criteria:

1. *Able to walk independently.* By way of illustration, the trials in relapsing remitting MS studied patients who were able to walk at least 100 metres without assistance (EDSS 5.5). A similar 30% reduction in relapse rate was observed in the secondary progressive trials which included more disabled patients, who could walk at least 10 metres with assistance (EDSS 6.5). We recommend treatment more strongly in the former group (EDSS 5.5), as the potential for long term benefits, such as delaying the time until walking is no longer possible, appears greater.
2. *At least two clinically significant relapses in the last two years.* Where possible, the patient's history of relapses should have been confirmed by neurological examination, or from another source e.g. hospital or general practitioner's records, or by discussion with the patient's main carer.
3. *Adult age group (18 years or older).* No recommendations are possible in the paediatric age group, since trials have not been performed in this cohort.
4. *There are no contraindications* See sections C.4 & C.7

**B.1.2 Clinically isolated syndromes**

Because: (i) the treatment effect on relapse rate appears similar but not superior to that seen in established relapsing remitting MS, and (ii) many patients will *not* have new relapses in the

early years (e.g. 50% of placebo patients in the CHAMPS trial did not have further relapses during the 3 years of follow up), treatment is not currently recommended at presentation with a clinically isolated syndrome. Should a relapse occur during the first two years of follow up, the patient then has relapsing remitting MS and the treatment criteria in B.1.1. should be used. Current efforts are being made to develop MRI criteria which enable an earlier diagnosis of MS at or near presentation with a clinically isolated syndrome and to identify those who have a *high* probability of early clinical relapses; such criteria may lead in future to guidelines for earlier treatment after the first clinical event.

### B.1.3 Secondary Progressive MS

A consideration of all three trials suggests that beta interferon is not effective in slowing progression in disability in patients with a non relapsing secondary progressive course. It is therefore not recommended in such patients. In patients with relapsing secondary progressive MS, treatment should only be considered when relapses are the dominant cause of the increasing disability. Specifically, the following criteria should be fulfilled:

1. *Able to walk at least 10 metres with or without assistance.*
2. *At least two disabling relapses in the last two years*
3. *Any increase in disability due to slow progression over the last two years has been minimal.*
4. *Adult age group (18 years or older).* No recommendations are possible in the paediatric age group, since trials have not been performed in this cohort.
5. *There are no contraindications* See sections C.4 & C.7

### B.1.4 Primary progressive MS

There is currently no evidence for clinical benefits in this form of MS and beta interferon should not be used.

### B.1.5 Stopping Criteria

In some patients, discontinuation of treatment may become necessary because of intolerable adverse effects, or when a pregnancy is planned. Treatment should be discontinued when it is no longer effective. The following features are likely to indicate lack of efficacy and should normally be used as stopping criteria:

- (i) Two *disabling* relapses, as defined by the examining neurologist, within a 12 month period.
- (ii) Secondary progression with an increase in disability observable over 6 months.
- (iii) Loss of ability to walk, with or without assistance, persistent for at least 6 months (studies have excluded patients with such disability).

The stopping criteria should be made known to patients and agreed before treatment is begun. For all patients, it is recommended that a formal review of the treatment takes place at two years. If the patient and their neurologist agrees that the treatment is having a beneficial effect, it should be continued.

## **B.2 Glatiramer acetate**

### B.2.1 Relapsing-remitting MS

With the caution that clinical efficacy has been limited to reducing relapse rate but not preventing sustained increase in disability in only one substantial placebo-controlled trial to

date, glatiramer acetate is an appropriate treatment to reduce relapse frequency in patients with relapsing-remitting MS provided they fulfill all the following criteria:

1. *Able to walk at least 100 metres without assistance*
2. *At least two clinically significant relapses in the last two years.* Where possible the patient's history of relapses should have been confirmed by neurological examination, or from another source, eg hospital or general practitioner's records, or by discussion with the patient's main carer
3. *Age group 18 years or older.* No recommendations are possible for the paediatric age group, as trials have not been performed in this cohort.

### B.2.2 Secondary and primary progressive MS and clinically isolated syndromes

As there are currently no data from controlled trials to indicate efficacy in these cohorts, glatiramer acetate should not be used.

### B.2.3 Stopping criteria

In some patients, discontinuation of treatment may become necessary because of intolerable adverse effects, or when a pregnancy is planned. Treatment should be discontinued when it is no longer effective. The following features should normally be used as stopping criteria:

- (i) Two *disabling* relapses, as defined by the examining neurologist, within a 12 months period.
- (ii) Development of secondary progressive MS (there is currently no data on the effectiveness of glatiramer acetate in this form of MS).
- (iii) Loss of ability to walk, with or without assistance, persistent for at least 6 months (studies have excluded patients with such disability).

The stopping criteria should be made known to and agreed with patients before treatment is begun. For all patients, it is recommended that a formal review of the treatment takes place at two years. If the patient and their neurologist agrees that the treatment is having a beneficial effect, it should be continued.

## **(C) BACKGROUND INFORMATION: BETA INTERFERONS**

### **1. Introduction**

In the last 8 years the results of eight large, randomised, double-blind, placebo-controlled trials of beta interferon preparations in MS or clinically isolated syndromes suggestive of MS have been published [1-5] or presented at scientific meetings [6-8]. Three trials have been performed in relapsing-remitting MS, 3 in secondary progressive MS, and 2 in clinically isolated syndromes. The results provide the basis for the present guidelines for the use of beta interferon in MS. Three brands of beta interferon are available. Beta interferon-1b (Betaferon) is produced in a bacterial system and differs slightly from natural human beta interferon. Beta interferon-1a (Avonex and Rebif) is produced in mammalian cells and is thought to be similar to natural human beta interferon. The differences between beta interferon-1b and beta interferon-1a, and in route of administration of the 1a preparations, make dosage comparisons difficult.

### **2. Evidence of Efficacy**

#### **2.1 Relapsing-Remitting MS**

The three placebo-controlled trials have been of beta interferon-1b (Betaferon) 1.6 million units (mU) and 8 mU subcutaneously on alternate days [1](372 patients were studied in the trial);

beta interferon-1a (Avonex) 30µg (6mU) intramuscularly once per week [2](301 patients); and beta interferon-1a (Rebif) 22 µg (6mU) and 44 µg (12mU) subcutaneously three times per week [3](560 patients). In all three trials, patients were ambulant without assistance at the time of entry, had at least two relapses in the preceding two years and entered at a maximum Kurtzke expanded disability status scale (EDSS) of 5.5 (Betaferon), 5.0 (Rebif) and 3.5 (Avonex) respectively.

Over a two year period, Betaferon, at the higher dose, and Rebif, at both doses, were associated with a significant reduction in the frequency and severity of relapses. Betaferon at the higher dose (8mU) was associated with a 34% reduction in relapse rate after 2 years. Rebif was associated with a reduction in relapse frequency of 27% at the lower dose (22µg) and 33% at the higher dose (44µg). Avonex treatment was associated with an overall reduction in relapse frequency of 9% at the end of year one and 18% at the end of the trial. This study was terminated early, so that only 57% were followed for 2 years, and their reduction in relapse rate was 32%. Treatment with both Rebif and Avonex was associated with a slowing in the accumulation of neurological impairment or disability (defined as a one point increase in the EDSS sustained for three [3] or six [2] months) over the two year study periods; this was not demonstrated with Betaferon [1]. Treatment with Betaferon and Rebif was associated with significantly fewer hospitalisations[1,3] and courses of steroids[3] to treat MS relapses.

## **2.2 Clinically isolated syndromes**

Two recent large placebo controlled trials of beta interferon 1a in patients with a clinically isolated syndrome suggestive of MS and multiple abnormalities on T2-weighted brain MRI have been performed [4, 6]. Such patients are known to have substantial risk for future relapses leading to the diagnosis of clinically definite (CD) MS. Both studies showed that treatment delayed the time to development of CDMS and reduced the proportion of patients developing MS during the follow up period. Specifically: (i) in a trial of Avonex 30ug once per week vs placebo, CDMS developed after 3 years in 50% on placebo and 35% on beta interferon [4]; (ii) in a trial of Rebif 22ug once per week vs placebo, CDMS developed after two years in 45% on placebo and 34% on beta interferon[6]. These effects on relapses are similar to the effects demonstrated in relapsing remitting MS (section 2.1).

## **2.3 Secondary Progressive Multiple Sclerosis**

There have been two trials of beta interferon-1b (Betaferon) and one of beta interferon 1a (Rebif). The first trial of Betaferon involved 718 patients [5]. The maximum level of disability at inclusion required participants to walk 10 metres with bilateral assistance (EDSS 6.5). Over a two year period, treatment significantly delayed the development of increased disability (defined as a one point increase in EDSS if the baseline EDSS was 5.5, or a 0.5 point increase if the baseline EDSS was 6.0 or 6.5, in both instances sustained for three months), and fewer patients in the treatment group were more disabled (39% versus 50%) at the end of two years. The second trial of Betaferon involved 939 patients with two treatment arms (8mU alternate days and 5mU/m<sup>2</sup> alternate days) versus placebo [7]. There was no difference in the rate of increase in disability between the 3 arms over 3 years. The trial of Rebif involved 618 patients randomized to 3 arms (44ug and 22ug three times per week and placebo), and again there was no difference in the rate of progression between the 3 groups over 3 years [8]; a *post hoc* analysis of those patients who had experienced relapses in the two years before entry to this

trial revealed a trend for less progression in those treated with beta interferon. In all 3 studies, there was a 30% reduction in relapse rate.

In the first of these studies, 70% patients had experienced relapses in the two years prior to randomization. In the latter two studies fewer than 50% had experienced such relapses. Considering the studies overall, the most satisfactory interpretation is that interferon has no effect on secondary progression *per se*, but reduces the accumulation of disability from superimposed relapses; the positive effect on disability seen in the first trial only may reflect the higher frequency of relapses in that cohort.

#### **2.4 Primary progressive MS**

A single centre, investigator-lead, placebo-controlled two year trial of Avonex (30ug and 60ug once weekly) involving 50 patients has recently been completed [9]. There was no difference in the evolution of disability between treatment groups.

### **3. MRI Outcomes**

All trials have shown significant and striking beneficial effects of beta interferons in stabilizing total T2 lesion volume and in reducing the number of new T2 and/or gadolinium enhancing lesions. The effects were generally more marked with the higher dose preparations - about 70% reduction in new enhancing lesions with Rebif and Betaferon and 50% reduction with Avonex. Two recent studies examining the effect of treatment on progressive cerebral atrophy suggested slowing of atrophy in the second year of a relapsing remitting trial [10] and no significant effect in a 3 year study of secondary progressive MS [11]. Further reports of the effect of beta interferons on brain atrophy are awaited with interest.

### **4. Adverse Effects**

Beta interferon is usually well tolerated. Most patients experience flu-like symptoms, myalgia, fever, and sometimes headache during the first weeks or months of treatment. These symptoms usually subside with time, and can be prevented or ameliorated by concurrently taking a non-steroidal anti-inflammatory agent (NSAID e.g. Ibuprofen 400 mg up to three times per day) or paracetamol (500 mg up to four times per day). Flu-like symptoms can be alleviated by injecting immediately before going to bed and taking NSAIDs at that time. The subcutaneous preparations (Betaferon and Rebif) are often associated with injection site reactions (areas of redness or bruising), and rarely (1-2%) with skin necrosis. Injection site reactions may be effectively managed by having a good technique and careful site rotation - patients are often able to decide for themselves on the best sites. Minor reductions in white blood cell count and abnormal liver function tests are not uncommon, but rarely severe enough to require discontinuation of treatment. In the first Betaferon trial in relapsing remitting MS, there was an increased frequency of suicide attempts and depressive symptomatology in the treatment versus placebo arm. However, in subsequent trials (including the Betaferon secondary progressive trials) there was no difference between treatment or placebo groups in the risk of depression or suicide attempts. Caution is always needed when managing patients with MS who have a history of serious depression, and particularly if they are actively depressed at the time treatment is considered.

To date, no untoward long term adverse effects have appeared, although the widespread use of beta interferon is limited to 7-8 years in the United States and 4-5 years in the United

Kingdom. As beta interferon preparations have been associated with miscarriages, their use is contraindicated in pregnancy. They should also not be used during lactation.

### **5. Neutralising Antibodies**

In about 20% of patients having beta interferon-1a preparations, and 40% beta interferon-1b, serum neutralising antibodies to the beta interferon have developed. These usually appear after 6-12 months. In some patients they subsequently disappear; in others they persist. Neutralising antibodies have been associated with an apparent loss of efficacy on relapse rate for beta interferon-1b, but not beta interferon-1a preparations. It is unclear whether neutralising antibodies have an effect on progression in disability. Because the relationship between neutralising antibodies and clinical course is not clearly defined, it is recommended that neutralising antibody testing is not used routinely in making decisions to continue or discontinue treatment. It is good practice to store blood samples from treated patients for future assay should new evidence indicate a clearer effect of neutralising antibodies on the clinical course of MS.

### **6. Long Term Effectiveness**

The double-blind, placebo-controlled trials have lasted two to three years. It is not known whether the demonstrated efficacy on relapse rate and disability progression are sustained beyond this time. There are theoretical reasons for proposing that treatment which suppresses relapses and MRI lesions in the earlier stages of relapsing remitting MS may delay the development of serious long term disabilities:

1. Long term natural history studies have shown that relapse frequency in the first two years and disability resulting from relapses within the first 5 years from onset are associated with a worse prognosis for long term disability after 25 years [12,13, G Ebers unpublished observations].
2. MRI lesion load and activity in patients with clinically isolated syndromes, and during the next 10 years when most patients develop relapsing remitting MS, correlates well with clinical evolution over this period, both in terms of further relapses and the development of disability [14, 15]. Suppression of new MRI lesions thus has potential for long term benefits.
3. Immunomodulatory treatment may be more effective when given early because at this stage of the disease the immunopathogenic mechanisms and underlying pathology are less complex. With disease evolution, epitope spreading may result in a more complex repertoire of immunological events that are less accessible to treatment. Over time, increasing amounts of axonal loss occur leading to irreversible disability – at least some of this axonal loss is attributable to immune mediated inflammation [16, 17].

### **7. General Management Advice**

Beta interferon should be initiated by a consultant neurologist with expertise in MS, and follow-up should be closely supervised by a consultant neurologist. Prior to starting treatment, all patients should have a full blood count, liver function tests, urea and electrolytes and protein electrophoresis (the latter is to ensure that the patient does not have a monoclonal gammopathy, since the administration of cytokines, including beta interferon, to patients with a pre-existing monoclonal gammopathy has been associated with the development of the systemic capillary leak syndrome with shock-like symptoms and fatal outcome[18]). Regular follow-up is essential, to monitor and manage adverse effects, and any other problems related

to the disease or its treatment. It is suggested that follow-ups are performed at month one and three, and then three monthly until the end of the first year after which six monthly intervals are sufficient. Full blood count and liver function tests should be obtained at all follow-ups.

MS specialist nurses play an important role in providing information and reassurance to patients on treatment during and between clinic attendances. It is important from the outset to give patients accurate information on the expectations of treatment, including the evidence that efficacy of beta interferons is only partial, moderate and not curative. Patients can also obtain information from the Multiple Sclerosis Society and other patient groups which have jointly produced information leaflets in lay language, as well as a range of leaflets on other symptomatic, psychological and social aspects of living with MS. A freephone helpline is provided by the Multiple Sclerosis Society on 0800 800 8000.

## **8. Future questions**

There remain important areas of uncertainty concerning the use of beta interferon in MS.

8.1 The long term efficacy and risks of treatment This is an issue of major importance given that MS is a disease which typically evolves over decades, whereas the current placebo-controlled, double blind trials that have shown efficacy have been of only two or three years duration. Because of the potential for long term benefits (section C6), treatment should be provided for the patient subgroup defined (section B), but because it will be some years until the long term effects are known, systematic audit of all treated patients is recommended. It will be especially important to know the long term effects of early treatment. The ABN therefore believes that:

- (i) treatment should be prescribed and supervised by a neurologist with expertise in MS
- (ii) the same protocol should be used throughout the UK
- (iii) audit of outcomes should be collected - a national database would be ideal.
- (iv) further research into the long-term benefits of treatment of clinically isolated syndromes is necessary.

8.2 The relationship between MRI and clinical measures of outcome. This issue has been highlighted by a difference in magnitude of the effect of treatment on MRI (marked) and clinical outcome (moderate). Whereas there are robust correlations between MRI lesions (as seen on standard T2-weighted or gadolinium enhanced T1-weighted images) and clinical activity markers in clinically isolated syndromes and early relapsing remitting MS, these become weaker with disease evolution and are sometimes absent altogether in the progressive forms of MS [19]. T2 and gadolinium enhancing lesions are associated with relapses [20] and enhancing lesions are characterized pathologically by acute inflammation with demyelination [21]. There are, however, other pathological events which become more prominent with increasing disease duration and disability. These include axonal loss and normal appearing white matter changes, both of which can be monitored using MR techniques such as MR spectroscopy, atrophy measures and magnetization transfer imaging. The evolution of a more diffuse neurodegenerative process appears to be an important mechanism for progressive MS and would account for the weakening relationship between T2/gadolinium markers and disability. It is

however possible that the extent of early inflammation influences the degree of late neurodegeneration [16, 17, 19]. A critical area for future research is to elucidate the longitudinal relationships between the inflammatory and neurodegenerative processes.

- 8.3 Whether or not there are subgroups other than those currently defined (section B) in whom treatment would be most effective. Treatment response appears to be heterogeneous in clinical practice. There may be subgroups in whom the benefits are particularly large. It might be argued that treatment with beta interferon is most suitable for those with a particularly active clinical course e.g. those with relapsing remitting MS who are having frequent, disabling relapses and who are accumulating residual deficit following relapses. However, past clinical features are not necessarily reliable predictors of the future clinical course, or of the response to treatment. The present guidelines are considered by the ABN to define the subgroup in whom treatment is most appropriate based on current evidence. Further research is needed to find more reliable treatment outcome predictors for individual patients.
- 8.4 The effect of neutralising antibodies on the clinical course. It would be appropriate to incorporate monitoring of neutralising antibody status within a systematic audit of patients proposed in section 8.1, to define their relevance.
- 8.5 Cost effectiveness. The treatments are expensive, and any future reductions in costs from manufacturers would be most welcome. The ABN considers that current assessments of cost effectiveness are insufficiently robust to preclude these therapies being provided to the patient subgroup (section B) in whom clinical benefits have been established. In particular, the potential for longer term benefits from the treatments make assumptions from cost-effectiveness models based on studies of short duration hazardous.

## **(D) BACKGROUND INFORMATION: GLATIRAMER ACETATE**

### **1. Introduction**

Glatiramer acetate (Copolymer-1; Copaxone) has been studied in a single, phase 3, two-year, double-blind, placebo controlled trial of patients with relapsing-remitting multiple sclerosis (MS) [22] and in a number of smaller [23, 24] or shorter duration [25] studies. The phase 3 two-year study provides the main basis for the present assessment of glatiramer acetate in MS. Glatiramer acetate is composed of four amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. As currently available, it is administered subcutaneously. It was developed as a drug which would suppress experimental allergic encephalomyelitis in guinea pigs. Its mechanism of action in MS is not known.

### **2. Evidence of efficacy**

#### 2.1 Relapsing-remitting MS.

A phase three, double blind, placebo controlled trial over two years was performed in 126 patients on placebo and 125 on glatiramer acetate [22]. The treatment dosage was 20 mg by daily subcutaneous injections. The entry criteria were clinically definite relapsing-remitting MS, ages 18-45 years, continued ability to walk unaided with an EDSS score between 0 and 5.0, and a history of at least two documented relapses in the two years prior to study entry, with onset of the first relapse at least one year prior to randomisation.

Over the two year period of the study, there was a 29% reduction in relapse rate in the glatiramer acetate group compared to the placebo. There was no significant difference between

the treatment arms in the proportion of patients who experienced a sustained increase in neurological impairment or disability (defined as an increase of one or more EDSS steps maintained for at least 3 months).

A small placebo-controlled, double blind, two year study involving 48 relapsing remitting MS patients performed in the 1980s also reported a reduction in relapse rate associated with glatiramer acetate treatment [23].

## 2.2 Primary and secondary progressive multiple sclerosis.

Placebo controlled studies on these subgroups evaluated separately have not yet been published. A phase 3, placebo-controlled, double blind study of glatiramer acetate in primary-progressive MS is currently in progress. A placebo-controlled study, involving 106 patients with chronic progressive MS, described a trend towards benefit with glatiramer acetate treatment, which was not statistically significant [24].

### **3. MRI Outcomes**

The main clinical trial was not accompanied by MRI data. Therefore, a separate 9 month, double-blind, placebo controlled, trial in 239 relapsing remitting MS patients using monthly MRI scans to evaluate efficacy has been performed. There was a reduction in the number of enhancing lesions in the glatiramer acetate arm of approximately 35% [25]. A 33% reduction in relapse rate in the glatiramer acetate arm was also reported in this study.

### **4. Adverse effects**

The treatment is generally well tolerated. It is given subcutaneously and may be associated with injection site changes, including erythema, pruritis, pain and induration. Some patients experience a systemic reaction, including symptoms of flushing, chest pain, dyspnoea, and palpitations. This was seen at least once in 19/125 (15%) of glatiramer acetate treated patients in the large relapsing-remitting trial, but occurred only once in 10 of these [22].

Although no untoward long-term effects have yet appeared, it should be borne in mind that the widespread use of glatiramer acetate has been limited until recent years. It was licensed in the United States in 1997 and in the UK in 2000. Patients chronically injected with glatiramer acetate commonly develop binding antibodies at three to six months which later decline [26]. There is no evidence to date that antibody development modifies the response to treatment.

### **5. Long term effects**

The main trial in relapsing remitting MS lasted two years, although there was extended follow-up in most patients into a third year [26]. It is not known whether the demonstrated efficacy on relapse rate is sustained beyond this time - longer term follow up is limited to relatively small numbers of patients. Nor is it yet possible to exclude the emergence of additional adverse effects with longer periods of continuous treatment.

### **6. Comparison of beta interferon and glatiramer acetate**

The magnitude of the effect of both therapies on relapse rate in relapsing remitting MS appears comparable, although there have been no definitive studies directly comparing the effects of beta interferon and glatiramer acetate. Overall, beta interferon preparations have been evaluated

in a larger number of clinical trials involving a greater number of patients. The two should not be used in combination as there are no reliable data on its safety or effect.

### **7. General Management Advice**

As for beta interferon, glatiramer acetate should be initiated only by a consultant neurologist, and follow-up should be closely supervised by a consultant neurologist. It is not necessary to monitor routine blood tests or neutralizing antibodies.

### **8. Future questions**

The issues raised concerning beta interferon in section C 8.1-8.3 and 8.5 apply equally to glatiramer acetate. We therefore recommend that treatment is prescribed, supervised and audited as outlined in section C 8.1.

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## **(F) DEFINITIONS OF CLINICAL FEATURES & SUBGROUPS**

*Relapses* (also may be called attacks or exacerbations) These are episodes of acute or subacute neurological symptoms, which last a minimum of 24 hours, but usually for a longer period (typically several weeks). The patient’s first attack has the same status.

*Relapsing remitting MS* A patient who has a history of recurrent relapses of neurological dysfunction (minimum of two), with complete or partial remission from at least some of the relapses, and with a stable neurological condition between relapses.

*Secondary progressive MS* A patient who has had a previous phase of relapsing remitting disease which has been followed by a period of steadily increasing neurological deficit over a period of at least 6 months. There may or may not be acute relapses superimposed on the phase of secondary progression. Patients who have a single relapse followed later by a slowly progressive phase may also be regarded as having secondary progressive multiple sclerosis.

*Primary progressive MS* A patient in whom there is a gradual onset of symptoms, with a subsequent development of increasing disability, but without a history of relapses or remissions.

*Clinically isolated syndrome.* The patient with a single acute clinical event (relapse) affecting the central nervous system and with features characteristic of demyelination e.g. unilateral

optic neuritis, brain stem or spinal cord syndromes. Other (non demyelinating) causes have been excluded by appropriate investigations.

#### **(G) FUTURE GUIDELINES**

Further guidelines on the use of beta interferon and glatiramer acetate will be prepared in response to relevant new data from trials or other sources and circulated to members as soon as they have been agreed by Council.

#### **(H) DISCLOSURE**

The Association of British Neurologists has received financial support from the pharmaceutical industry including the manufacturers of beta interferon and glatiramer acetate. No such support was used in the process of drawing up these guidelines either by the ABN or by individual members of the guidelines group.

The members of the ABN MS guidelines advisory group (with disclosures added) are:

#### **Professor David Chadwick (Chairman)**

The Chairman has no conflict of interest.

#### **Professor Alastair Compston, Professor David Miller, Dr John Zajicek**

As specialist members of the panel, they have received some grant support from the relevant pharmaceutical companies and have provided expert advice to them.

#### **Dr Jeremy Dick, Professor Christopher Martyn, Dr Fred Schon**

They have received support for travel expenses to international meetings.

Their units have received other educational support from the industry.