



*National Institute for
Clinical Excellence*

***National Institute for
Clinical Excellence***

11 Strand
London
WC2N 5HR

Web: www.nice.org.uk

***Beta interferon
and glatiramer
acetate for the
treatment of
multiple sclerosis***

Technology Appraisal No. 32

Guidance on the use of beta interferon and glatiramer acetate for the treatment of multiple sclerosis.

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Ordering Information

Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting ref: N0051. A patient version of this document can be obtained by quoting ref: N0053.

A bi-lingual patient leaflet is also available, ref: N0054.

Distribution of Guidelines

This document has been circulated to the following:

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This guidance is written in the following context:

This guidance represents the view of the Institute which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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11 Strand
London
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Beta interferon and glatiramer acetate for the treatment of multiple sclerosis

1. Guidance

- 1.1 On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of multiple sclerosis (MS) in the NHS in England and Wales.
- 1.2 It is likely that patients currently receiving beta interferon or glatiramer acetate for MS, whether as routine therapy or part of a clinical trial, could suffer loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001. This also applies to all participating patients at the conclusion of a clinical trial (irrespective as to whether they had received placebo or active drug) and women whose therapy has been interrupted by pregnancy.
- 1.3 The Department of Health and the National Assembly for Wales are invited to consider the strategy outlined in Section 7.1 with a view to acquiring any or all of the medicines appraised for this guidance in a manner that could be considered to be cost effective.

This section (Section 1) constitutes the Institute's guidance on the use of beta interferon and glatiramer acetate for the treatment of multiple sclerosis. The remainder of the document is structured in the following way:

2 Clinical need	9 Review of guidance
3 The technologies	Appendix A: Appraisal Committee
4 Evidence	Appendix B: Sources of evidence
5 Further research	Appendix C: Information for patients
6 Implications for the NHS	Appendix D: Expanded Disability Status Scale
7 Implementation	Appendix E: Measurement of health benefits
8 Related guidance	

The full document and a summary of evidence are available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0051.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0870 1555 455, rhif cyfeirnod N0052.

- 2.1 MS is a disabling neurological disease. It is estimated that in England and Wales MS affects some 63,000 people. MS usually begins in individuals aged between 20 and 40 years, and occurs in about twice as many women as men. It is characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, resulting in the removal of the insulating myelin sheath covering the nerves. Multiple areas of scar tissue (sclerosis) form along the nerve fibres, slowing or blocking the transmission of signals to and from the brain and spinal cord, so that functions such as movement and sensation may be lost.
- 2.2 There are several forms of MS. Some 80–90% of people start with relapsing remitting MS (RRMS). In this form of the disease, recurrent attacks of loss of neurological function, termed relapses, are separated by periods of complete or incomplete recovery, described as remissions. After about 10 years (without treatment), about half of people with MS begin a continuous downward progression, which may also include acute relapses. This form of MS is known as secondary progressive (SPMS). RRMS accounts for about 45% and SPMS for about 45 % of the total population with MS. In a third type of MS, primary progressive (accounting for about 10% of cases), the disease progresses inexorably from onset. Benign MS is a fourth and relatively rare condition.
- 2.3 Magnetic resonance imaging (MRI) shows that lesions develop in the brain and spinal cord tissues as the disease progresses. Development of MRI lesions may not initially correlate directly with the clinical manifestations of the disease as lesions often occur in 'silent' areas of the brain and spinal cord. However, lesions may precede the onset of overt symptoms of MS, and MRI data have been used as a surrogate marker of disease activity and/or progression.
- 2.4 The course of MS is unpredictable with variations in severity and progression rate. It tends to progress faster in men and people who are older at the time of onset.
- 2.5 The disease has an adverse and often highly debilitating impact on the quality of life of people with MS and their families. Relapses may require admission to hospital, and be associated with a level of disability and incapacity that disrupts working, family and social life. MS, even in its early stages, undermines patients' confidence, restricts their activity and may limit their role in society in many ways including inability to continue employment or to take part in usual family activities. Weakness, chronic fatigue, unsteady gait, speech problems and incontinence can leave people with MS feeling isolated and depressed. Substantial burdens, including emotional and financial burdens, are imposed on primary/informal carers, who are often patients' partners. In the management of MS, emphasis is often placed on the problems of long-term disability. However, the emotional

impact of relapses on patients and carers is also considerable.

2.6 The progression of MS is usually measured using the Expanded Disability Status Scale (EDSS). This scale is measured in half units from 0, which represents no disability, to 10, which denotes death; 7 denotes 'essentially restricted to wheelchair'. An important feature of the EDSS scale, however, is that it is non-linear, and small incremental changes reflect a much greater effect on patients' quality of life and dependency levels the higher they are on the EDSS scale. The full scale is set out in Appendix D.

3.1 There are four general approaches to the treatment of MS, which may be undertaken separately or in combination:

- Management of symptoms and disability with speech, physio- and occupational therapy and pharmacological or other therapeutic agents;
- Management of the emotional and social consequences of relapses and disability;
- Treatment of acute relapses with corticosteroids;
- Disease-modifying treatment targeted at reducing the frequency and/or severity of relapses and/or slowing the course of the disease. The beta interferons and glatiramer acetate constitute the only options presently available in this category.

Beta interferons

3.2 There are three beta interferon products: Avonex (manufactured by Biogen) and Rebif (Serono) are interferon beta-1a products licensed only for the treatment of RRMS. Betaferon (Schering) is interferon beta-1b and is licensed for the treatment of both RRMS and SPMS .

3.3 The beta interferons work by reducing the inflammatory process that characterises MS. Such inflammation usually precedes an MS relapse. However, the precise mode of action of these disease-modifying agents on immunological mechanisms remains uncertain.

3.4 The beta interferons commonly cause temporary influenza-like adverse effects (in about 50% of patients), as well as injection site reactions and leucopenia. Less commonly, the use of the beta interferons is associated with symptoms of depression. In addition, these agents, by the nature of their chemical structure, have antigenic effects and therefore may induce the development of antibodies, high titres of which have been observed in some patients. Theoretically, these antibodies may produce allergic reactions or bind to the drug molecule neutralising its effects. The significance of these

antibodies on the effectiveness of the beta interferons is uncertain, as such effects have not been reported in clinical practice.

- 3.5 Based on a survey of health authorities in England and Wales, undertaken in January 2000, an estimated 1,750 people are currently prescribed beta interferons, which equates to 2.8% of all MS patients, or 3.3% of those with RRMS or SPMS. These percentages vary between health authorities.
- 3.6 The current annual cost per patient of the beta interferons in the UK is £7,259 (Betaferon), £9,061 (Avonex) or £9,088/£12,068 (lower dose/higher dose Rebif).

Glatiramer acetate


- 3.7 Glatiramer acetate (Copaxone, TEVA/Aventis) is licensed for the treatment of RRMS.
- 3.8 Glatiramer acetate works by reducing the inflammation around nerves. Such inflammation usually precedes an MS relapse. Glatiramer is an acetate salt of polypeptides formed from the synthesis of four amino acids. It resembles myelin, the basic protein that is found in the sheath surrounding nerves. In structure, therefore, glatiramer is quite distinct from the beta interferons. Its exact mode of action, as with the beta interferons, is unknown, but it is thought also to inhibit antigen presentation to white blood cells and to induce antigen-specific suppressor T cells.
- 3.9 Glatiramer acetate can cause flushing, chest tightness, palpitations, anxiety and breathlessness, and also injection site reactions, but these effects are generally easily managed. In addition, by the nature of its chemical structure, glatiramer acetate has antigenic effects and therefore may induce the development of antibodies in patients. Theoretically these antibodies may produce allergic reactions or bind to the drug molecule neutralising its effects. The significance of these antibodies on the effectiveness of glatiramer is uncertain as such effects have not been reported in clinical practice.
- 3.10 The cost per patient of glatiramer acetate is £6,650 per year.

4

Evidence

Clinical effectiveness: beta interferons

- 4.1 Clinical trials have shown that all three interferon products reduce relapse frequency and severity in patients with RRMS and may also influence duration of relapse. The reduction in frequency amounts to about 30% on average, and is equivalent to approximately one relapse avoided every 2.5 years in people with RRMS. This reduction has been demonstrated for the first 2 years of therapy.


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- 4.2 Disability progression is delayed by treatment, but the effects of treatment on disability in the long term, following cessation of therapy, cannot be predicted reliably on the basis of the short-term evidence from the clinical trials seen by the Committee.
 - 4.3 The proposition that the beta interferons have a positive effect beyond 2 years is supported by open-label studies. These longer-term studies have assessed the effectiveness of beta interferon by comparing observed with expected levels of disease activity. For people who have taken the drug in studies for approximately 4 years, disease activity appears to be lower than might otherwise be expected from studies of the natural history of MS.
 - 4.4 One of the interferon products (Betaferon) has also been shown to reduce relapse frequency and severity in SPMS. In a clinical trial in SPMS of another interferon product there was a difference from placebo in reduction of relapse frequency but this effect did not reach formal statistical significance.

Clinical effectiveness: glatiramer acetate

- 4.5 Clinical trials have shown that glatiramer acetate reduces relapse frequency in patients with RRMS. This reduction amounts to about 30% on average, which is equivalent to approximately one relapse avoided every 2.5 years. This reduction has been adequately demonstrated for the first 2 years of therapy.
- 4.6 Data from an open-label follow-up study of a small number of people (73) with RRMS showed that 75% of them were unchanged or improved in terms of accumulation of disability after 8 years using glatiramer acetate.

Clinical effectiveness: general

- 4.7 There is evidence of the value of MRI as a marker of disease activity in MS. The Committee interpreted the MRI findings from published clinical trials as supportive of its conclusions on the clinical effectiveness of these products in MS. In routine clinical practice in England and Wales, MRI scanning has not been used as a direct measure of the progress of MS or of the response to therapeutic intervention in preference to assessment of the clinical symptoms and signs of the disease.
- 4.8 The Committee considered in detail evidence taken directly from patients and two advocacy organisations (see Appendix B). The patient organisations and the patients who attended the Committee meeting spoke of the patients' experience of this distressing disease and of the impact of the beta interferons and glatiramer on relapses and disease



progression. This dialogue provided important insight into the effect of relapses on patients' daily lives and the value that they place on the potential avoidance and reduction in severity of relapses with the use of these drugs, as well as into the more general effects of MS on quality of life and capacity to work. The Committee was also provided with recently published evidence for the effect of MS on cognitive function (for example, difficulties with memory and general alertness), which was in addition to the impact of relapses on quality of life. It was clear from the representations made to the Committee by these individuals and groups that they considered that these medicines had a very positive effect in some people with MS.

Cost effectiveness

- 4.9 During 2000 the Committee reviewed models of the cost effectiveness of the medicines submitted by each manufacturer and two models prepared by independent sources. All the models calculated cost-utilities – costs per quality-adjusted life year (QALY) – but came to widely differing final estimates. These ranged from about £10,000 per QALY (an estimate derived from commercial-in-confidence data supplied by one of the manufacturers) to over \$3 million per QALY (an American research group's findings). These estimates were very sensitive to assumptions made in the modelling process including, in particular, the impact of a relapse on quality of life and the time horizon over which benefits from therapy may be accrued. In addition the Committee recognised that uncertainties in the data or methods used were liable to magnification in the extrapolation of the benefit beyond the duration of clinical trial-based treatment data.
- 4.10 The Committee therefore resolved that in the absence of further economic modelling it would be very difficult to make a recommendation on the cost effectiveness of these medicines with any confidence. The Institute commissioned a new cost-effectiveness analysis that was designed to address the problems associated with existing models. In doing so the Institute sought a maximum of cooperation between the group undertaking the new modelling ('the Consortium') and the consultees. This was designed both to help reconcile views on the model design and to ensure that the consultees were able to supply appropriate data to the Consortium. In the event, additional data for the new analysis were provided by Schering and Biogen. Data were provided but subsequently withdrawn by TEVA. No data were provided by Serono.
- 4.11 The new analysis compared treated patients' experience of both relapse and progression with the natural history of the disease. It examined the effects of using different time horizons and showed that the estimated mean cost per

QALY gained (CQG) from treatment fell as the time horizon was lengthened. Shorter time horizons such as 5 years require less extrapolation from trial data but ignore possible gains resulting from the postponement of later, more debilitating, stages of the disease. On the other hand, lengthening the time horizon successively to 10 and 20 years increases the extrapolation error but includes more of the possible gains from postponement of later more debilitating stages of the disease. The Committee took the view that extrapolation errors for time periods over 20 years, more than double the period for which clinical data for patients on therapy are available, were so great that it could not consider estimates of cost effectiveness beyond 20 years. The Committee therefore considered only the three time horizons of 5, 10 and 20 years.


- 4.12 While the Committee recognised that the extrapolation problem grows significantly as the time horizon increases, it nevertheless considered carefully estimates for each time frame. Estimated mean CQGs for 5- and 10-year time frames were higher (ranging from £380,000 to £780,000 for the 5-year model, and from £190,000 to £425,000 for the 10-year model) than for the 20-year time frame. At 20 years, using the results of the additional modelling, the estimated mean CQG ranged from £40,000 to £90,000 for the four products considered.
- 4.13 In response to both manufacturers' and patient/carer organisations' comments, further analysis of the Consortium model was undertaken. An important component of this further review was the consideration of new observational data from a large survey conducted by the MS Research Trust (MSRT) of people with MS and their carers. This large survey used a questionnaire sent to a group of their members, who volunteered to provide personal details, characteristics of the form of MS (type of disease, number and frequency of relapses, EDSS score, presence of difficulties of cognition), and whether they were taking a beta interferon or glatiramer. The survey elicited quality-of-life information using the EQ-5D instrument (from which utility estimates may be derived). The survey which had been directed at people with whom the Trust had had some contact since its inception in 1993, and to which there were 1555 respondents, covered all MS types, including benign and primary progressive. In a number of responses the type of MS was not stated. Of the respondents, 152 were receiving treatment with one of the products considered in this appraisal at the time of the questionnaire.
- 4.14 The Consortium was asked to advise the Committee on whether the MSRT dataset was suitable for use within the model and if so, to advise on its effects on the model's estimates of CQG. The Consortium confirmed that the MSRT questionnaire results improve the database on

utilities for EDSS states. However, further analysis of these data by the Consortium did not provide conclusive evidence of an effect of treatment on utility that was not already encapsulated in EDSS scores and relapse. The Consortium advised the Committee that they considered that the application of the appropriate population from the MSRT utilities dataset to their original model was valid and that they had now done this.

- 4.15 Benefit, measured in terms of disease progression, accrues whilst a patient is on treatment. When treatment stops (by 10 years for most patients), the model assumes that disease progression continues at a rate consistent with the natural history of the condition. Additionally, the model assumes that the treated group maintain benefit after cessation of treatment whilst incurring no additional treatment costs. Therefore, incorporating in the model the MSRT utilities data-set, the estimated CQG at 20 years (the time frame of the model) is between £35,000 and £104,000. However, as there is no evidence on the long-term progression of patients after cessation of therapy, it remains possible that the additional benefit on therapy is not maintained when treatment stops. In this case, the CQG will increase. For example, if all benefit ceases after treatment stops at 10 years, the estimated CQG after 20 years would be between £120,000 and £339,000.
- 4.16 In response to requests from some consultees, the Committee also examined the modelling of approaches in which therapy would begin at progressively higher levels of EDSS. While these approaches lowered the estimated mean CQG substantially, the Committee concluded that this result was a product of the assumption in the model relating to disease progression off treatment at later time periods.

Consideration

- 4.17 Given the nature of the disease, considering the effects of treatment beyond the end of therapy is appropriate. Without data that measure such effects modelling is required. The results will reflect the underlying uncertainty of the assumptions that underpin the model. The Committee was encouraged, by consultees, to consider time horizons of 20 years and beyond in this condition although the maximum extent of published observations of disease progression in treated patients in MS is 8 years.
- 4.18 The new economic modelling incorporated two key assumptions: (a) continuing benefit on treatment and (b) on discontinuation of treatment, a return to a rate of progression equivalent to the natural history of the disease. Both of these assumptions become increasingly unreliable as the time horizon is increased.

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- 4.19 The results of modelling approaches in which therapy would begin at progressively higher levels of EDSS are products of the assumption in the model relating to disease progression off treatment at later time periods and therefore do not constitute a suitable basis for formulating guidance.
- 4.20 The CQG estimates in paragraph 4.15 will be reduced by the inclusion of the effects on personal social service costs. In considering comments from consultees, the Committee took the view that the improvement in the estimates of CQG, even if such effects were assumed to be as much as 15%, would not materially affect their conclusion.
- 4.21 In its deliberations on cost effectiveness the Committee was mindful of the various criticisms of QALYs in general and their use in this specific context. Some of these issues are addressed in Appendix E.
- 4.22 The Committee, in its appraisals of health technologies, is required to consider the broad balance between benefits and costs. In doing so, it must consider not only the cost effectiveness of the particular technology under consideration, but where that cost effectiveness stands relative to treatments for other conditions. The Committee found no measures other than QALYs that could better assist in its responsibility to make a judgement about the 'balance of costs and benefits'. The estimates in paragraph 4.15 constitute the best available evidence.
- 4.23 Long-term extrapolation of treatment benefit after cessation of therapy is not supported by evidence. The Committee therefore decided that its conclusion on the cost effectiveness of these products must take account of the uncertainty associated with an assumption that treatment benefit is maintained for 10 years or more after cessation of therapy. On the balance of costs and benefits, the beta interferons and glatiramer acetate are not cost effective. In reaching this conclusion, the Committee had in mind the cost-effectiveness ratios of the technologies which the Institute has previously recommended for use in the NHS in England and Wales.
- 4.24 In arriving at this conclusion, the Appraisal Committee took account of the Directions to the Institute laid out by the Secretary of State for Health. Those Directions require the Institute to take into account inter alia the degree of clinical need of people with the condition, the broad balance of benefits and costs and the efficient use of NHS resources. The Institute did not receive guidance from the Secretary of State or the National Assembly for Wales on the resources that may be available for these medicines.

4.25 The Committee considered the view that there was no valid basis for distinguishing guidance between patients currently receiving treatment with one of these medicines and other patients. This would have the implication that patients currently being prescribed a beta interferon or glatiramer should have no greater access to therapy than others. The Committee felt that this view must be balanced against other considerations such as the existing, at least implicit, patient-doctor agreement to continue therapy once started and the potential loss of well being that might follow from unanticipated treatment changes. The Committee concluded that these were relevant factors, which patients currently receiving beta interferon or glatiramer acetate for MS and their consultants might bear in mind when considering this guidance. Consultants and their patients might reasonably conclude that therapy should not be withdrawn as a result of this guidance but that they should continue treatment until individual patients and their consultants consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001.

4.26 Other than disease-modifying treatments, management strategies for MS are aimed at ameliorating symptoms, in order to allow the patient to maintain an optimal quality of life, as presently there is no cure for the disease. The Committee is aware that the Institute has commissioned a clinical guideline on the management of MS. It is also aware that this guideline will examine and make recommendations on the range of interventions available for people with this disease.

5

Further research

5.1 Trusts and health authorities are encouraged to collect data on all people with MS who continue on beta interferon or glatiramer as indicated in paragraph 1.2. The data collected could usefully include details of the patient and the reason they are receiving treatment. It would be helpful also to record the preparation used, the patient's relapse frequency and disease progression while on treatment, the development of adverse effects and neutralising antibodies, compliance with the therapy, the reasons for discontinuing therapy and the subsequent rate of progression of the disease.

6

Implications for the NHS

6.1 On the basis of the recommendations in Section 1, but subject to any developments resulting from the implementation advice in Section 7.1 below, it is not expected that this guidance will result in a material change in current expenditure on these medicines.

7

Implementation

- 7.1 The Committee considered that the Department of Health, the National Assembly for Wales and manufacturers, might usefully consider what actions could be taken, jointly, to enable any of the four medicines appraised for this guidance to be secured for patients in the NHS in England and Wales, in a manner which could be considered to be cost effective. Unless further evidence emerges which reveals a significant improvement in their clinical effectiveness, the cost-effectiveness of these medicines can only be improved if there is a significant reduction in the total cost of their acquisition by the NHS in England and Wales. The uncertainty surrounding the definition of which patients benefit and to what extent, together with the ability of the NHS to identify a total potential patient population for which these medicines might most beneficially be purchased, are factors which could be considered relevant in any discussions between the Department of Health and the National Assembly for Wales and manufacturers on ways in which these medicines could be acquired cost effectively. The Committee noted that the results of the additional economic modelling commissioned by the Institute revealed that interferon beta-1b (Betaferon, Schering) is, currently, the most cost effective of the four products appraised for this guidance.
- 7.2 Further guidance on audit of the care provided to people with MS is forthcoming with the publication by the Institute of a clinical guideline on the management of MS.

8

Related guidance

- 8.1 The Institute has been commissioned to produce a full clinical guideline on the management of MS. The planned publication date of this guidance is January 2003.

9

Review of guidance

- 9.1 This guidance will be reviewed in November 2004.
- 9.2 Should any significant new evidence of clinical effectiveness or a re-evaluation of published or unpublished clinical data become available, or if there were to be a substantial change in unit costs or other actions, which led to a significant change in the cost effectiveness of the beta interferons or glatiramer, this new information will be considered by the Institute. A judgement will be made at that time as to whether such evidence should result in an earlier review of this guidance.

Andrew Dillon
Chief Executive

January 2002

APPENDIX A

Appraisal committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst

Dean, School of Health Related Research
Sheffield University

Professor David Barnett (Chairman)

Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry

Professor of Morbid Anatomy
St Bartholomew's and Royal London
School of Medicine

Dr Sheila Bird

MRC Biostatistics Unit
Cambridge

Dr Karl Claxton

Lecturer in Economics
University of York

Professor Duncan Colin-Jones

Professor of Gastroenterology
University of Southampton

Professor Sarah Cowley

Professor of Community Practice
Development
Kings College, London

Dr Nicky Cullum

Reader in Health Studies
University of York

Mr Chris Evennett

Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest

Clinical Director and Consultant
Nephrologist
Richard Bright Renal Unit and
Chairman of the UK Renal Registry

Ms Jean Gaffin

Formerly Executive Director
National Council for Hospice and
Specialist Palliative Care Service

Mrs Sue Gallagher

Chief Executive
Merton, Sutton and Wandsworth
Health Authority

Dr Trevor Gibbs

Head, Global Clinical Safety &
Pharmacovigilance
GlaxoSmithKline

Mr John Goulston

Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home

Professor of Diabetes Medicine
University of Newcastle

Dr Terry John

General Practitioner
The Firs, London

Dr Diane Ketley

Research into Practice Programme
Leader
NHS Modernisation Agency

Dr Mayur Lakhani

General Practitioner, Highgate Surgery
Leicester and Lecturer, University of
Leicester

Mr M Mughal

Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge

Chief Executive
Changing Faces

Professor Philip Routledge

Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens

(Vice-Chairman)
Professor of Public Health
University of Birmingham

Dr Cathryn Thomas

General Practitioner, Senior Lecturer
Department of Primary Care and
General Practice
University of Birmingham

APPENDIX B

Sources of evidence

1. The following documentation and opinion were made available to the Committee
 - a. **Assessment Report:**
Prepared by the Northern and Yorkshire Regional Drug & Therapeutics Centre (*Assessment of Interferon-Beta and Glatiramer for the Treatment of Multiple Sclerosis*, April 2000).
 - b. **Additional economic modelling:**
SchARR Consortium Final Report to the National Institute for Clinical Excellence (*Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis*), Centre for Bayesian Statistics in Health Economics, School of Health and Related Research (SchARR), University of Sheffield.
 - c. **Manufacturer/sponsor submissions:**
 - Aventis Pharma Limited
 - Biogen Limited
 - Schering Health Care Limited
 - Serono Pharmaceuticals Limited
 - Teva Pharmaceuticals Limited
 - d. **Professional/specialist group submissions:**
 - Association of British Neurologists
 - Chartered Society of Physiotherapy
 - Royal College of Nursing
 - Royal College of Physicians
 - Royal College of General Practitioners
 - e. **Patient group submissions:**
 - Multiple Sclerosis Research Trust
 - Multiple Sclerosis Society
 - Neurological Alliance
 - f. **External expert and patient advocate submissions:**
 - Mr Peter Cardy, Chief Executive and others representing the Multiple Sclerosis Society
 - Professor Alastair Compston, University Department of Neurology, Addenbrooke's NHS Trust
 - Ms Christine Jones and others representing the Multiple Sclerosis Research Trust
 - Professor Alan Thompson, Garfield Weston Professor of Clinical Rehabilitation, The National Hospital for Neurology and Rehabilitation and Medical Advisor to the Multiple Sclerosis Society
 - Dr John Zajicek, Consultant Neurologist and Honorary Senior Lecturer, Plymouth Postgraduate Medical School

APPENDIX C

Beta interferon and glatiramer acetate for the treatment of multiple sclerosis – information for patients

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0053 for the English patient leaflet and N0054 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, and clinical and surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal involves the manufacturers of the drug or device, professional organisations and the groups who represent patients and their carers.

NICE was asked to look at the evidence on beta interferon and glatiramer acetate and provide guidance that would help the NHS in England and Wales decide where they should be used in the treatment of multiple sclerosis.

What is multiple sclerosis?

Multiple sclerosis (which is very often referred to as 'MS') is a disorder of the central nervous system.

Messages from the brain and spinal cord are sent to the rest of the body by electrical impulses carried along nerve fibres. The nerve fibres in the brain and spinal cord are surrounded by a protective sheath made of a substance called myelin, which acts like the insulating layer of an electrical cable. In people with MS the myelin sheath is damaged and scar tissue is formed (sclerosis). This means that the signals to and from the brain and spinal cord do not get through properly and functions such as movement or sensation may be lost. MS can cause lots of different symptoms and a person's symptoms will depend on which signals are affected.

There are four types of MS.

- *Benign MS.* People with benign MS have a few mild attacks and then recover completely. They do not get worse over time or have any permanent disability.
- *Relapsing-remitting MS.* People with relapsing remitting MS have attacks followed by some time in 'remission', which means that they have fewer or no symptoms. When an attack occurs after some time of remission, it is called a relapse.

During a relapse, previous symptoms may return or new ones may appear. As many as 90 out of 100 people with MS start with relapsing-remitting MS, and about 45 out of 100 people with MS have this form.

- *Secondary progressive MS.* This type of MS starts in the same way as relapsing-remitting MS but then the remissions stop and the disease progresses, with gradually worsening symptoms and increasing disability. About 45 out of 100 people with MS have this form of MS.
- *Primary progressive MS.* People with primary progressive MS do not have periods of remission and relapse. Instead, from the start they have steadily worsening symptoms and progressive disability. About 10 out of 100 people with MS have this form of MS.

MS is usually diagnosed in people aged between 20 and 40. It is not known what causes the disease. It is estimated that in England and Wales MS affects around 63,000 people.

There are four general approaches to helping people with MS:

- treatment of symptoms and disability with speech therapy, physiotherapy and occupational therapy and with medicines or other therapeutic agents
- treatment of the emotional and social consequences of relapses and disability
- treatment of acute relapses with corticosteroids
- prescribing medicines that aim to reduce the frequency and/or severity of relapses and/or slow the course of the disease – at the moment, the beta interferons and glatiramer acetate are the only options available in this category.

Sometimes just one approach is used, and sometimes combinations of approaches are used.

What are beta interferon and glatiramer acetate?

In MS, the damage to the myelin sheath of the nerve fibres is caused by repeated episodes of inflammation in the brain and spinal cord. An episode of inflammation often happens before a relapse. Beta interferon and glatiramer acetate work by reducing the inflammation, although it is not known exactly how they do this.

There are three beta interferon products available. Two are of a type called interferon beta-1a (Avonex and Rebif) and one is the type interferon beta-1b (Betaferon). Glatiramer acetate (Copaxone) is completely different in structure from beta interferon.

Neither beta interferon nor glatiramer acetate is a cure for MS – that is, they do not repair the damage to the myelin sheath or stop symptoms occurring. But they can have an effect on relapses, as well

as slowing the progression of disability. Clinical studies have shown that, on average, people with relapsing-remitting MS who take beta interferon or glatiramer acetate will have one fewer relapse every 2 and a half years than they would have had if they had not taken the drug.

What has NICE recommended about the use of these products?

NICE has very carefully considered the evidence about the effectiveness of these drugs in people with MS and how much they cost. As well as looking at the results available from clinical trials, it has heard evidence from health professionals, including neurologists, and from patients, their carers and the organisations that represent them.

MS is a disease that affects people over a very long period (often 20 years or more), but at the moment there is no evidence available about the effects of beta interferon or glatiramer acetate on the disease in the long term. Because of this, NICE had to look at 'models' of the cost effectiveness of the drugs. These models make estimates of how the drugs might work in the long term. The further ahead a model looks, the harder it is to be sure about what it tells us.

During 2000, NICE considered several models of the cost effectiveness of beta interferon and glatiramer acetate. There were problems with these models and so the Institute decided to commission a new model.

After considering all of the evidence, including the views and experiences of patients, NICE has issued the following advice to the NHS in England and Wales.

- A recommendation to use these medicines cannot, presently, be justified, taking both benefits and costs into account.
- People who are currently taking beta interferon or glatiramer acetate to treat MS could suffer loss of well being if their treatment was stopped when they did not expect it. Because of this, all NHS patients who are on therapy at the date of publication of this Guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop, bearing in mind the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001. This advice about continuing treatment also applies to all participating patients at the end of a clinical trial (regardless of whether they were receiving placebo or active drug) and to women whose therapy has been interrupted by pregnancy.
- The Department of Health and the National Assembly for Wales, along with the manufacturers of the beta interferon products and glatiramer acetate, have been to consider what action could be taken so that the NHS could obtain these drugs in a way that would be cost effective.

What should I do?

If you, or someone you care for, has MS then you can discuss this advice with your doctor or nurse at your next appointment.

Will NICE review its guidance?

Yes. The guidance will be reviewed in November 2004. In the meantime, NICE will look at any new evidence of that might substantially change the estimates of cost effectiveness of beta interferon or glatiramer acetate – for example, new evidence on clinical effectiveness or new information on costs. It will then decide whether the new evidence should result in a review of its guidance before November 2004.

Further information

Further information on NICE and the full guidance issued to the NHS are available on the NICE website (www.nice.org.uk).


The guidance can also be requested by telephoning 0870 1555 455 and quoting reference number N0051.

If you have access to the internet and would like to find out more about MS, visit the NHS Direct website at www.nhsdirect.nhs.uk.

APPENDIX D

Expanded Disability Status Scale

- 0.0 Normal neurological exam (all grade 0 in Functional Systems [FS]; Cerebral grade 1 acceptable).
- 1.0 No disability, minimal signs in one FS (i.e. grade 1 excluding Cerebral grade 1).
- 1.5 No disability minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).
- 2.0 Minimal disability in one FS (one FS grade 2, others 0 or 1).
- 2.5 Minimal disability in two FS (two FS grade 2, others 0 or 1).
- 3.0 Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.
- 3.5 Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
- 4.0 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 metres.
- 4.5 Fully ambulatory without aid, up and about much of the day, able to work a fully day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability, usually consisting of one FS grade 4 (others 0 to 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.
- 5.0 Ambulatory without aid or rest for about 200 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 to 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- 5.5 Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for steps 4.0).

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- 6.0 Intermittent or unilateral constant assistance (cane, crutch or braces) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
 - 6.5 Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
 - 7.0 Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).
 - 8.0 Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; maintains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems).
 - 8.5 Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self care functions. (Usual FS equivalents are combinations, generally 4+ in several systems).
 - 9.0 Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+).
 - 9.5 Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+).
 - 10.0 Death due to MS.

APPENDIX E

Measurement of health benefits

This Appendix, taken with modifications from the Evaluation Report to the Appraisals Committee, provides some background information on the way in which health benefits are calculated. It does not form part of the guidance proper.

A1 Measuring benefits

A1.1 Measures of the benefit of treatment used in cost-effectiveness analyses can be based on 'natural' units, for example years of life gained, or on value-based measures, for example Quality Adjusted Life Years (QALYs). The number of QALYs gained by using a particular treatment is a measure of its benefit in terms of improvements in the quality of life of patients (including physical performance, pain, distress and psychological improvements as well as changes in survival) summed over a period of time. It therefore incorporates the value of changes in both morbidity and mortality, where these exist.

A1.2 In the particular case of MS, although there are natural units which capture specific aspects of the impact of MS, such as relapses avoided and delaying progression to wheelchair dependency, there is none which captures both the impact on relapses and the full impact of progression. These measures therefore ignore some of the established benefits of the beta interferons.

A1.3 Although imperfect as 'natural' units to capture gains from delayed progression, the EDSS does provide a means to create a value-based measure of benefit. All of the studies that attempt to encompass the full effect of delayed progression have used changes in EDSS converted to changes in QALYs. This requires an estimate of utilities (adjustments for level of quality of life) applied to each of the EDSS levels, and based not on the disability itself but to include all the associated morbidity.

A1.4 An alternative measure is provided in the literature and in the submissions in the form of a measure based on the EDSS called variously Area Under the Curve, integrated area under the EDSS time curve or disability burden unit. This is calculated by multiplying the EDSS score by the time during which that score is observed, and summing over time. This measure is therefore very similar to the QALY, the difference being that EDSS scores are given an equal weight rather than a weight based on the relative utility of different health states.

A1.5 This summed EDSS measure has a number of disadvantages. The numbers used in the EDSS itself are not cardinal numbers either by construction or by behaviour. (A "cardinal" number can be added, subtracted, multiplied or divided, and the result has ready meaning.) The EDSS score is, by contrast, "ordinal", which means that a higher score represents greater disability. But it does not imply, for example, that an EDSS score of 8 (restricted to bed or chair or perambulated in a wheelchair) is twice as disabled a state as an EDSS score of 4 (fully ambulatory and able to walk up to 500 metres without aid or rest). This means that the summed EDSS measure is also not cardinal. Its units are arbitrary, meaning that a cost per summed EDSS score avoided is equally arbitrary. The utility scores used in calculating QALYs weight the underlying EDSS scores in ways designed to produce cardinal numbers having identifiable units. The summed EDSS score therefore shares any problems that the QALY has and has a number of others besides.

A2 The use of QALYs in MS

A.2.1 Although all of the submissions to the Committee from the manufacturers report QALYs and cost-effectiveness ratios derived from them, some also make a number of criticisms of the approach. These include some unexplained "assertions", but the following statements warrant further comment:

A.2.2 *QALYS discriminate against people with MS.*

This appears to be based on two premises. The first is a mistaken belief that QALY measurement does not count transient improvements in quality of life; that is emphatically not the case. The second is a related argument that people with disabilities do not have the same potential to gain QALYs because of their lower underlying quality of life. However, this argument only applies, and then in theory only, to therapies that are life-saving. It does not apply to interventions that improve quality of life – on the contrary, lower quality of life suggests a greater capacity to gain QALYs. Since the impact of therapies for MS is dominated by improvements in quality of life, this criticism does not apply.

A.2.3 *QALYs do not discriminate in favour of people with MS.*

The QALY approach is egalitarian in considering any particular gain in quantity or quality of life as being of equal value regardless of the age, sex or other characteristics of the recipients. The suggestion is that QALYs should be adjusted so that they are greater for

those of working age. In other words, it proposes that one should discriminate against young and old people, because they do not work or have dependants. Whilst there is some evidence that there are those who would support such discrimination, it is unclear how far it should be taken. A logical implication of the argument in favour of such discrimination is that QALYs should be weighted against individuals of working age who do not have dependants or who are unable to work. It might even imply employment of an individual weight based on the number of dependants and the size of income from employment.

A.2.4 *QALY gains are estimated using a population based estimate of utility values, which are inferior to those based on patient preferences.*

The evidence provided by Parkin *et al* (*J of Neurology, Neurosurgery and Psychiatry*, 2000; 68: 144-49) suggested that despite differences in utility values for health states, estimates of QALY gains were not affected by the use of patient rather than population utilities. Moreover, there is an argument that societal-based estimates used consistently for all evaluations are more appropriate because they reflect wider values that are comparable over different therapies.

A.2.5 *QALY gains include average relapses and therefore do not take account of severe relapses.*

This is not correct, since the calculation of an average includes both more severe and milder relapses as well as those of average severity. A larger sample of people with MS, thus containing more relapses than that which has been studied to date, might include a greater number of severe relapses and might plausibly raise the average severity. However, it may also include a smaller proportion of severe relapses and so lower average severity. There is no evidence either way.

A.2.6 *The loss of utility due to relapses may be an underestimate because it is assessed after the event.*

This may be true; there are methodological difficulties with obtaining quality of life data during relapses that are serious enough to require hospitalisation, which mean that it is difficult to test. However, there is no evidence that the values are too high, or too low.