**Background**

1. NICE follows an open, structured and widely publicised process for all its technology appraisals. The process was developed following consultation and is the process we are following for the beta interferon/glatiramer review. The details of the process and the dates for all appraisals are published in the technology appraisal section of the NICE web site (http://www.nice.org.uk/).

2. **NOTE:** NICE has **not** issued any guidance to the NHS on the use of either beta interferon or glatiramer in Multiple Sclerosis.

3. The Department of Health (DH) has reminded the NHS in England that existing guidance to the NHS on drug treatments for multiple sclerosis (MS) remains in place pending publication the Institute’s guidance. This guidance is contained in DH documents EL(95)97 and HSC 1999/176 both of which can be accessed from the DH website at www.doh.gov.uk/multiplesclerosisdrugsguidance.

4. The DH guidance asks NHS organisations to develop and implement local arrangements to manage the entry of such drugs into the NHS, in consultation with other key interests, and in particular, to initiate and continue prescribing of beta-interferon through hospitals. HSC 1999/176 asks NHS bodies to continue with these local arrangements until the NICE guidance becomes available.

**What’s happened so far in the NICE appraisal?**

5. The Department of Health (DH) and the National Assembly for Wales (NAW) asked NICE to appraise beta interferon/glatiramer for MS on the **6 August 1999.**

6. NICE wrote to interested parties (manufacturers, national patient/carer groups and professional bodies) on the same day, asking that any submissions they wished to make should be by **1 November 1999.**

7. Following the consultation between the manufacturers and the DH / NAW the Institute agreed an extension to the submission date until **February 2000.**

8. During this time NICE commissioned a review of the published evidence of the clinical and cost effectiveness of these medicines from the Northern and Yorkshire Drug and Therapeutic Centre.

9. In **February 2000** NICE received submissions from the manufacturers, patient/carer groups and the professional bodies involved (the ‘consultees’). Some of these submissions contained both published and unpublished information, and some of this material was classed as ‘commercial in confidence.’

10. The submissions from the manufacturers were assessed and combined with the review of the published literature into an Assessment Report by the Northern and Yorkshire team.

11. The Assessment Report, and the original submissions from patient/carer organisations and the professional groups, together with the manufacturers’ submissions were made available to the Appraisal Committee as an Evaluation report.

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12. The first meeting of the Appraisal Committee (membership published in the technology appraisal section of the NICE web site) for beta interferon / glatiramer in MS was held on the **30 May 2000**. In addition to the written submissions the committee also had ‘experts for the day’ at its meeting. They represented a patient/carer organisation and health professionals with experience in this area. These individuals were nominated by their own organisations. The minutes of this meeting are published in the technology appraisal section of the NICE web site.

13. Following the committee meeting, the Appraisal Committee then prepared its provisional views on the evidence – known as a PAD (Provisional Appraisal Determination). The PAD is only sent for consultation to the groups identified as consultees.

14. NICE asked for comments on the PAD from the consultees. This means that they circulated the PAD to the patient/carer groups, professional groups and the manufacturers involved and also the Department of Health and the National Assembly for Wales.

**Note:** The organisations that represent pharmaceutical and medical device manufacturers had previously informed the Institute that a PAD, (which may differ from the final guidance) could have a significant impact on their share price and on patients’ confidence and asked that it and the remaining appraisal documentation be treated as confidential material. Therefore for appraisals that commenced before February 2001 the appraisal documents are circulated to consultees as strictly confidential material. The beta interferon / glatiramer appraisal is therefore subject to this confidentiality arrangement.

15. The Appraisal Committee met again on the **27 July 2000** to consider its provisional determination in the light of the feedback received from the consultees. The minutes of this meeting are published in the technology appraisal section of the NICE web site. At this meeting the Appraisal Committee made their final determination (Final Appraisal Determination – FAD) and submitted it to NICE.

**Note:** At this point, the appraisal for glatiramer in the treatment of MS was put on hold until the manufacturer received its UK Marketing Authorisation (license for sale in the UK) from the licensing authority.

16. NICE received the FAD and as part of the process of developing the final guidance circulated it to the consultees (including patient/carer groups, professional groups and the manufacturers) for them to decide if they wished to appeal.

17. Eight appeals were received against the draft guidance (FAD) for beta interferon. An independent appeal panel considered the appeals on the **22 and 23 September 2000**.

18. Their decision was published on **8 November 2000**. Parts of the Appeal were rejected and parts were upheld. Full details of the appeal are published on the technology appraisal section of the NICE web site. The press release and full appeal document are published on the NICE web site.

19. NICE asked the Appraisal Committee to reconsider the original evidence in the light of the Appeal Panel’s decision. NICE also asked the committee to look at a new economic model submitted, by a manufacturer (Schering), as commercial in confidence material at the appeal hearing.
20. The Appraisal Committee met to reconsider the evidence on 13 December 2000. The committee considered the original evidence in light of the appeal panel’s decisions. In addition they considered the new evidence and heard again from the groups that represent people with MS and their carers. The groups were the MS Society and the MS Research Trust and their representatives included people with MS. The minutes of this meeting are published in the technology appraisal section of the NICE web site.

Note: In the meantime, glatiramer was granted its UK license. The appraisal of this technology has recommenced and the Appraisal Committee considered this technology alongside beta interferon at their meeting on 13 December 2000.

21. During this appraisal the Committee has considered evidence that included economic models supplied by manufacturers and independent researchers. The models are used to inform their judgement on the cost effectiveness of these medicines.

22. At the meeting on December 13 2000 a review of the economic models was presented which raised a number of concerns (refer to the published minutes). The Committee gave careful consideration to each of these concerns and then reflected generally on the evidence relating to cost effectiveness for both medicines. During this discussion, it was noted that the economic models for both medicines had been challenged on methodological grounds and had doubts cast on the reasonableness of the assumptions they had used.

23. Having considered the evidence and comments made by the people with MS and the patient organisations and having reflected on the analysis of the existing and new economic modelling, the Committee considered the merits of preparing an appraisal determination for either beta interferon or glatiramer.

Note: Serious reservations were expressed about the economic models. Given the importance of the advice which the Committee was being asked to provide it was suggested that if the flaws, which had been identified in the models presented so far, were capable (in whole or part) of being rectified, there would be benefit in doing so. If there were no opportunity to undertake any further work on the economic modelling, the Committee would need to prepare an appraisal determination.

24. On the basis of the information in front of it the Committee asked their Chairman to prepare an appraisal determination which reflected that, on the basis of the evidence presented, the Committee did not consider that either the beta interferon or glatiramer had demonstrated that their use in the NHS in England and Wales could be considered to be cost effective. The Chair agreed to do so and indicated that he would advise the Institute of the Committee’s serious reservations over the economic modelling.

25. The evidence relating to the cost effectiveness of these medicines is critically important in this appraisal. Therefore the Institute carefully considered the Appraisal Committee’s concerns and decided to commission further economic modelling on the beta interferon and glatiramer acetate. As soon as this decision had been made NICE informed the consultees and after the pre-agreed time they notified the public on the 22 December 2000.

26. It was known that the commissioning, construction and evaluation of the new modelling would take around 5 months and therefore the timeline for the appraisal process for both medicines was extended. Although the Institute

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accepted this would delay production of the final guidance, it considered that this action was in the best interests of people with MS and those who care for them. It is of the utmost importance that the Institute’s guidance is both evidence-based and seen to be fair by those effected by it.

27. In January 2001 the Institute wrote to the consultees on 3 issues:

I. Consulting on its proposals for the process for commissioning the development of the new economic modelling and identifying where stakeholders could become involved (the draft process document is attached to press release 2001/04 and published on the Institute’s web site – use the search engine within the site and search on ‘multiple sclerosis’)

II. Asking if manufacturers were prepared to release data they may have, including patient specific data from clinical trials likely to be of use to the modellers. Data would be made available through the Institute and treated in accordance with the Institute's standard arrangements for handling data supplied by consultees.

III. Requesting nominations of individuals or organisations that consultees' consider have the capability and experience to undertake the economic modelling.

The Institute asked for responses by the 9 Feb. 2001.

28. The Institute’s Research and Development Committee met in February 2001 to consider the consultation feedback and agree the process and timetable for commissioning the new economic model. Following this meeting the Institute also advertised for health economic modellers.

29. The Institute appointed a consortium based on the Sheffield School of Health and Related Research (ScHARR) and the Department of Mathematics and Statistics at the University of Sheffield working with colleagues from Oxford, City, Newcastle, Nottingham and York Universities to undertake the work.

30. The Institute, the consortium and the consultees met on 30 March 2001. The meeting was constructive and provided an opportunity for a useful exchange of views on the approach being taken by the Institute to the final phase of the appraisal. Work began to construct the new economic model and the Institute asked the manufacturers to provide relevant clinical trial data to the consortium. They considered this request and some data was provided to the consortium.

31. A further meeting with consultees was held on 8 June 2001 and the consultees were given the opportunity to examine the new model in detail.

32. The Appraisal Committee met on the 26 of July 2001 to consider the new economic modelling.

33. After this meeting the Appraisal Committee produced a Provisional Appraisal Determination (PAD). This was sent to the consultees (including patient/carer organistaions, professional bodies and manufacturers) on 4 August 2001.

34. Because of speculation in the media surrounding the content of the PAD, the Chairman on the recommendation of two of the Institute’s Executive Directors, took the decision, in line with Institute policy, to publish the PAD on the nice website (www.nice.org.uk). Note: The Provisional Appraisal Determination is a consultation document, NOT guidance to the NHS. NICE has not issued any guidance on the use of beta interferon or glatarimer.

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36. The Appraisal Committee met again on the 25 September 2001 to consider the comments from the consultees. Part of the comments received from consultees contained further economic modelling data that the committee wished to consider further. The committee asked that the Sheffield School of Health and Related Research (ScHARR) should analyse this data and provide a new economic model. This was agreed and consultees were informed.

37. The Appraisal Committee met on the 25th October 2001 to agree the Final Appraisal Determination (FAD). The Institute issued the FAD to consultees on 30th October 2001 for them to consider if they wished to appeal. Consultees had been previously informed that the Institute would publish the FAD on its website shortly after it was received by consultees.

38. The Institute published the FAD on its website on 2 November 2001.

39. The Final Appraisal Determination was sent to the consultees on Monday 29th October 2001 and was published on the NICE website on Friday 2nd November 2001. The consultees had until 14th November 2001 to lodge an appeal against the guidance if they believed that the Institute:
   - has not acted fairly and in accordance with its procedures
   - has made a decision that is perverse in light of the evidence presented
   - has exceeded its powers

40. The following appellants lodged appeals:
   - Teva Pharmaceuticals and Aventis Pharma Ltd jointly
   - Biogen Ltd and Schering Health Care jointly
   - Serono Pharmaceuticals Ltd
   - The Neurological Alliance
   - The Royal College of Nursing
   - The Multiple Sclerosis Society
   - The Multiple Sclerosis Trust

   All the appellants were represented at the appeal hearing with the exception of the Neurological Alliance. The MS Society communicated the views of the Neurological Alliance on its behalf.

41. The Appeal Panel convened on 26th November 2001 to consider these appeals. The Appeal Panel comprised Professor Sir Michael Rawlins (chair of the Appeal Panel and chair of the Institute), Mrs Mary McClarey and Ms Mercy Jeyasingham (non-executive directors of the Institute’s Board), Mrs Gill Donovan (patient representative) and Dr Peter Brock (industry representative).

What stage is the process at?

42. On Friday 25th January 2002 the Institute announced that the appeals against the guidance had not been upheld.

43. As stated in the Institute’s guidance for appellants, the Board may amend the Guidance to the NHS in the light of the Appeal Panel’s advice. The Guidance will then be issued to the NHS.

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What happens next?

44. The decision of the Appeal Panel means that the conclusions set out in the Final Appraisal Determination will form the basis of the Institute’s guidance to the NHS in England and Wales. **NICE will issue its guidance on Monday 4th February 2002.**

45. The Institute’s provisional determination in August 2001, suggested that the Department of Health, the National Assembly for Wales, and manufacturers should consider how they could enable any or all of these drugs, to be secured for patients in a cost effective manner.

We are pleased that the Department of Health acted on the Institute’s advice and have entered into discussions with manufacturers. Since the Institute has not been party to these discussions we are unable to comment on them further. The department of health website is [www.doh.gov.uk](http://www.doh.gov.uk)

Consultees in this appraisal are:

- Association of British Neurologists
- Biogen Ltd
- Department of Health
- Faculty of Pharmaceutical Medicine
- MS Research Group of the Association of British Neurologists
- MS Research Trust
- National Assembly for Wales
- Neurological Alliance
- Royal College of General Practitioners
- Royal College of Physicians
- Royal Pharmaceutical Society
- Schering Health Care Ltd
- Serono Pharmaceuticals Ltd.
- Teva Pharmaceuticals Ltd.
- The Chartered Society of Physiotherapy
- The Multiple Sclerosis Society of Great Britain and Northern Ireland
- The National Hospital for Neurology and Neurosurgery

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