THE SCOTTISH OFFICE

Department of Health

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**Enquiries to:**

Mr W Scott (on drug related matters)
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Dear Colleague

## NEW DRUGS FOR MULTIPLE SCLEROSIS

### Summary

1. The paper attached provides information about the possible licensing in the near future of Beta-Interferon. It advises purchasers and providers about the steps they should take to prepare for this.

### Action

2. NHS purchasers and providers in Scotland are asked to develop and plan to implement local arrangements to manage the entry of Beta-Interferon into the NHS, in the light of the possibility of its being licensed in the near future. In particular, they are asked to make arrangements for the prescribing of Beta-Interferon to be initiated and continued through hospitals.

3. However, the Department has recently received a letter, signed by all 25 consultant neurologists in Scotland, stating that in their view "there is not enough evidence to recommend this drug to MS patients in routine clinical practice" and that "we would like to ask our MS patients to participate in placebo-controlled trials examining disability, measured in a valid way". Arrangements are being made to discuss this issue with representatives of the neurologists as quickly as possible.

4. In the meantime, you and copy recipients will need to be aware of the information and provisional prescribing arrangements described in the enclosed Annex.

5. Health Boards are requested to circulate this MEL to all GPs within their area.

Yours sincerely

Robert Kendell

**ROBERT KENDELL**
Chief Medical Officer

**KEVIN WOODS**
Director of Purchasing

Bill Scott

**BILL SCOTT**
Chief Pharmacist

ANNEX A

# NEW DRUGS FOR MULTIPLE SCLEROSIS

## Introduction

1. This MEL provides information about the possible licensing, in the near future, of a Beta-Interferon preparation for multiple sclerosis. It asks purchasing authorities and providers to develop and implement local arrangements to manage the entry of such drugs into the NHS, in consultation with other key interests, especially GPs and patient interest groups; and in particular, to **initiate and continue prescribing of Beta-Interferon through hospitals**. In doing so, they are asked to take account of the checklist of issues in the Annex, and the attached clinical advice from the Standing Medical Advisory Committee in England on the use of Interferon-Beta-1b in relapsing - remitting multiple sclerosis in adults.

## Background/Licensing Status

2. There is a growing interest in the development of Beta-Interferon drugs in the treatment of multiple sclerosis and the European Medicines Evaluation Agency (EMEA) is expected to reach a decision shortly on whether to grant a pan-European licence for one such drug (Interferon Beta 1b preparation). Other new products for the treatment of MS are also being developed, including other Beta interferons, and further licensing decisions may follow in due course. If a licence is granted, the drug will - in line with Ministers' commitment that patients should receive treatment which they clinically need - become available for NHS prescription, subject to any conditions which may be attached to the licence and to clinical decisions about the appropriateness of treatment in individual cases. As with other drugs, prescribing the drug outside licensed indications is not encouraged.

## Clinical Issues

3. Information from clinical trials using Beta-Interferon has only been published about the relapsing-remitting form of multiple sclerosis, where the drug has been shown to reduce the number, and possibly also the severity, of relapses in patients who manifest certain symptoms of the disease. The SMAC clinical advice (attached as Annex B gives further information on the therapeutic indications, and the issues which these present for accurate diagnosis and assessment of patients. No studies have yet been published on the effect of Beta-Interferon in patients with other forms of multiple sclerosis, or its effect on cumulative disability, which is ultimately what matters.

4. Decisions about the treatment of individual patients are, as always, for the clinical judgement of the doctor concerned and no doctor is prohibited from prescribing this treatment. However, in view of the complex clinical considerations, **it is recommended that GPs should be encouraged not to prescribe Beta-Interferon drugs themselves but to refer patients who apparently fulfil the indications for this form of treatment to a hospital neurologist or another consultant with a special interest in neurological disorders for specialist assessment (or reassessment)**. Where treatment with Beta-Interferon is considered appropriate, it is recommended that treatment should be initiated and prescribed by the specialist.

5. As with many new drug treatments, information is not yet available about the long-term clinical effects of Beta-Interferon. These will need to be evaluated over time. In order to maximise opportunities for monitoring and evaluating the effectiveness of treatment, **it will usually be appropriate for clinical responsibility for prescribing Beta-Interferon to remain with the hospital consultant**, at least during the initial post-licensing years.

**Clinical Objectives**

6. Key aims of the above approach are to :-

- target the drug appropriately at patients who are most likely to benefit from treatment;
- develop a consistent approach to patient education and training in the use of the drug;
- provide structured opportunities to monitor and evaluate treatment, including side-effects, and compare its effectiveness between patients;
- help inform decisions about when it is appropriate to withdraw treatment in individual cases.

7. Although it is recommended that GPs should not be encouraged to prescribe Beta-Interferon in accordance with the above guidance, they will retain a key role in:-

- determining whether to refer patients seeking treatment with the drug for specialist assessment (a flow chart based on SMAC's advice to assist in decisions on referral is attached as Annex C);
- other aspects of care for MS patients, including arrangements for continuing care, and prescribing other necessary medication.

**Managing the Introduction of Beta-Interferon**

8. Health Boards and providers are asked, as part of their existing arrangements for managing the introduction of new drugs, to work with other local interests - notably GPs, neurologists and patient interest groups - to develop and implement a prescribing approach for Beta-Interferon through hospitals, as outlined above. It will be important for GPs and hospitals to liaise closely over the management of referrals in order to ensure that the additional workload causes minimum disruption to existing services. The checklist in the Annex sets out suggested issues to be addressed.

**Resource Implications and Funding**

9. Further consideration is being given to the funding consequences of the introduction of Beta-Interferon for 1996-97 and beyond. In the meantime, it will be necessary to assess current resource implications locally. In particular, providers will need to consider workload and manpower implications - eg for hospital neurologists and out-patient departments, especially where a neurology department provides services for MS patients from a wide area,

such as in the north of Scotland. It is likely that patients who apparently fulfil the indications for treatment with Beta-Interferon will wish to have an early opportunity for assessment and diagnosis. Providers are asked to give sympathetic consideration to this issue, taking account of other local priorities. As funding for Beta-Interferon will fall on Hospital and Community Health (including GP Fund Holders) budgets, the impact on the Family Health Services drug bill is likely to be small, though we shall be monitoring this carefully.

**Pharmaceutical Arrangements**

10. If clinically indicated the neurologist with clinical responsibility for the patient will prescribe Beta-Interferon. The arrangements for prescribing and dispensing should take into consideration issues of patient convenience and the need to maintain the "cold chain". The use of Health Board Prescriptions (HBP) provides a mechanism which will allow the patient to receive Beta-Interferon from their own community pharmacy or dispensing doctor. Beta-Interferon prescribed by this mechanism is zero rated for VAT; the cost of the drug and dispensing fees will fall to the hospital service.

**Beta-Interferon: Prescribing Issues**

Purchasers and providers will need to consider the following:-

**Health Boards**

- How many MS patients are estimated to be within the Health Board area? Of these, how many are estimated to be in the relapsing-remitting phase? (It is estimated that there are between 150 and 190 MS sufferers per 100,000 population in Scotland with a relatively higher prevalence in northern areas. About 45% of sufferers are estimated to be in the relapsing-remitting phase.)

- What is the estimated annual incidence of new relapsing-remitting MS cases in the Health Board area?

- Are professional/managerial advisory and decision-making bodies for the introduction of new drugs including Beta-Interferon in their considerations?

- Are all key interests involved in discussions on proposals - eg hospitals, consultant neurologists, GPs, patient interest groups and other relevant representative bodies?

- What are the implications of the introduction of Beta-Interferon on future contracting arrangements (for 1996/97 and future years)?

- Will local information be available for patients, GPs and others on the availability and applicability of treatment?

- How will experience of treatment be evaluated and disseminated?

**Providers**

- What is the likely impact on resources of:

  - initial assessment and reassessment of patients for treatment?

  - continued prescribing and evaluation of treatment?

In particular, what is the likely impact on:

a. waiting times?
b. consultant availability?
c. MRI services?
d. nursing and other support?
e. hospital drugs budgets?

- What are the arrangements for dispensing and supplying the drug to patients, particularly bearing in mind issues of patient convenience (eg from hospital pharmacies, community pharmacies, home-health care arrangements, or other)?

- What are the arrangements for patient education in administering treatment, and other matters related to the use of the drug (eg suitable storage arrangements)?

- What are the arrangements for auditing treatment?

# CLINICAL ADVICE FROM THE STANDING MEDICAL ADVISORY COMMITTEE ON THE USE OF INTERFERON-BETA-1b IN RELAPSING-REMITTING MULTIPLE SCLEROSIS IN ADULTS

**Prepared in consultation with the Association of British Neurologists, the Joint Consultants Committee, the Royal College of General Practitioners, the General Medical Services Committee and following discussions with the Multiple Sclerosis Society.**

SUMMARY

Interferon-beta-1b may be licensed for the treatment of certain patients with multiple sclerosis. A clinical trial conducted over a 2-year period has provided evidence that interferon-beta-1b has a modest effect on the frequency and severity of relapse, but has not been shown to affect the duration of each individual relapse or affect established disability or the progress of disability. It is suggested that treatment should only be initiated after assessment by a neurologist. It is not indicated in patients with the progressive forms of the disease or severely disabled patients. Its effect on the quality of life has not been determined. Its use may be considered in ambulant patients with relapsing/remitting disease who have had at least two disabling relapses in the previous two years. Nevertheless, there remains a substantial debate about the clinical interpretation of the published data from the trial.

## INTRODUCTION

1. It is possible that one or more beta-interferons will be licensed for the treatment of certain groups of patients with multiple sclerosis in the near future. This document is designed to provide guidance to neurologists and other health professionals involved in the treatment and care of people with multiple sclerosis. The present advice refers only to treatment with interferon-beta-1b. It will be updated as further information becomes available.

## BACKGROUND

2. It is widely accepted that the damage to the nervous system in multiple sclerosis is mediated immunologically. Beta-interferon has immuno-modulatory effects and has recently been the subject of a major clinical trial in multiple sclerosis.

3. This trial was of a genetically-engineered form of beta-interferon (interferon-beta-1b) and was published in 1993 (The IFNB Multiple Sclerosis Study Group, 1993). The trial followed a dose finding study in which 30 patients with relapsing remitting multiple sclerosis were randomised to receive 16, 8, 4, 0.8 MIU given by subcutaneous injection three times weekly. The 16 MIU dose was not tolerated, but the lower doses were. The subsequent large scale study was placebo-controlled and double-blind. 372 individuals had relapsing-remitting disease at the time of recruitment and who were able to walk 100 metres without aid or rest. The patients were randomised to receive 8 MIU or 1.6 MIU of beta-interferon or placebo by subcutaneous injection on alternate days. After 2 years there was a reduction in the relapse rate - the primary outcome event - from 1.27 per year in the placebo group to 0.84 per year in the group treated with the high dose (8 MIU) regime, i.e. a reduction of about a third.

4. A secondary outcome measure was severity of relapse as measured on the Scripps Neurological Rating Scale. Severity of relapse was classified into mild, moderate or severe. The annualised rate of moderate and severe exacerbations in the high dose (8 MIU) group (0.23) was half that of the placebo group (0.45). The published results must be interpreted with caution for two reasons. First, data from an unknown number of patients were excluded because they had not been examined at the height of the relapse. Secondly, the Scripps Neurological Rating Scale is not widely used and , as with other assessment scales, there are only limited data available on its validity and reliability.

5. Another secondary outcome was derived from magnetic resonance imaging of the brain (Paty et al, 1993). After 2 years the total mean area of abnormality on a T2 weighted scan had increased by 20% in the placebo group, but was unchanged in the high dose (8 MIU) group. A subgroup of patients in the high dose group was scanned at 6-weekly intervals and showed a median reduction of 83% in the annual rate of active lesions compared with the placebo group. However, there was *no measurable effect on established disability or on the progress of disability*.

6. Data for periods of treatment up to five years have been published (The IFNB Multiple Sclerosis Study Group, 1995), but the data after two years are difficult to interpret because patients remaining in the trial after that time were self-selecting. Bias is therefore inevitable.

7. A second major study (on interferon-beta-1a) has recently been reported at scientific meetings, but not yet published in peer-reviewed form.

## THERAPEUTIC INDICATIONS

8. On the basis of the evidence available so far, interferon-beta-1b should only be considered for the reduction of frequency of clinical relapses in ambulant patients with clinically definite multiple sclerosis, who are in the relapsing-remitting phase of the disease and who have had at least two disabling attacks of neurological dysfunction in the previous two years, followed by recovery, which may or may not have been complete.

9. There is no indication for the use of interferon-beta-1b
either
in patients whose illness started with relapses and remissions who subsequently developed steady progression of disability lasting at least six months (secondary progressive multiple sclerosis) even if relapses are still occurring
or
if the disease has followed a progressive course from onset without clear-cut relapses or remissions (primary progressive multiple sclerosis),
or
in severely disabled patients, for example those who are wheelchair bound or demented.

10. Further clinical trials designed to detect an effect on disability in both relapsing-remitting and progressive disease have already started or are being planned.

## INITIATING TREATMENT

11. Because there is a significant error rate in the diagnosis of multiple sclerosis defined according to standard criteria such as those of Poser et al (1983), and because there will often be ambiguity as to whether a patient does have relapsing-remitting disease, *it is recommended that patients who apparently fulfil the indications for treatment should be referred to a neurologist for a decision on whether treatment is indicated.*

## LABORATORY TESTS

12. The following laboratory tests are recommended prior to initiating therapy with interferon-beta-1b and at three monthly intervals thereafter: haemoglobin, complete and differential white cell count, platelet count, liver function tests.

## DOSAGE, METHOD OF ADMINISTRATION, AND STORAGE

13. The recommended dose of interferon-beta-1b is 8 MIU contained in 1 ml of reconstituted solution to be injected subcutaneously every other day. As it is thermolabile it is recommended that interferon-beta-1b is stored in a refrigerator.

## MONITORING TREATMENT

14. The frequency with which patients on interferon-beta-1b should be reviewed by the neurologist will vary according to the condition of the individual patient. Patients will probably need to be seen several times in the first few weeks. Thereafter they should be reviewed at 6 to 12 monthly intervals and the accompanying audit form completed each time.

## DURATION OF TREATMENT

15. At the present time it is not known for how long the patient should be treated, since evidence of efficacy beyond two years is incomplete. A decision for treatment beyond this time should be made on an individual basis by the neurologist. It is suggested that treatment with interferon-beta-1b be stopped if there are unacceptable side effects or if there is steady progression of disability for 6 months or 3 or more courses of corticosteroids are required during a one year period.

## TREATMENT OF RELAPSES

16. Relapses of sufficient severity to warrant therapeutic intervention should be treated by the customary steroid regimes.

## CONTRAINDICATIONS

17. Interferon-beta-1b is contraindicated in the following conditions:

- patients who are pregnant or likely to become pregnant
- patients with a history of hypersensitivity to natural or recombinant interferon-beta or human albumin
- patients with a history of severe depressive illness and/or suicidal ideation
- patients with decompensated liver disease
- patients with epilepsy not adequately controlled by treatment
- patients already receiving an immunosuppressive agent other than corticosteroids

## UNDESIRABLE EFFECTS

18. Injection site reactions occur frequently after administration of interferon-beta-1b. These include inflammation, pain, hypersensitivity and necrosis. The incidence of injection site reactions usually decreases over time.

19. Flu-like symptoms (fever, chills, myalgia, malaise, or sweating) are frequently reported by patients on interferon-beta-1b. Patients may be helped by non-steroidal anti-inflammatory drugs or, if the latter are contra-indicated, paracetamol. The incidence of these symptoms usually decreases over time, but they may persist and necessitate termination of treatment.

20. Menstrual disorders may occur in premenopausal patients.

21. Psychological and neurological adverse events including depression, anxiety, emotional lability, depersonalization, convulsions, suicide attempts, and confusion have been observed.

22. In the pivotal trial, 45% of the patients developed serum interferon-beta-1b neutralising activity on at least one occasion. One third had neutralising activity confirmed by at least two consecutive positive titres. The development of neutralising activity was associated with a reduction in clinical efficacy, becoming evident at 18-24 months.

23. Experience with interferon-beta-1b in patients with multiple sclerosis is still limited, consequently infrequent adverse events may not yet have been observed. No information is available about side effects after long term (>5 years) continuous use.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

24. No formal drug interaction studies have been carried out with interferon-beta-1b.

25. The effect of alternate day administration of interferon-beta-1b 8 MIU on drug metabolism in multiple sclerosis patients is unknown. Corticosteroid treatment for relapses for periods of up to 28 days has been well tolerated in patients receiving interferon-beta-1b.

INFLUENCE ON LABORATORY TESTS/FINDINGS

26. At the recommended dose, leucopenia (lymphopenia, neutropenia), or elevated alanine transaminase may be seen. Low calcium, high uric acid, or elevated aspartate transaminase have also been associated with interferon-beta-1b administration.

PREGNANCY AND LACTATION

27. It is not known whether interferon-beta-1b can harm the fetus when administered to a pregnant woman or can affect human reproductive capacity. Spontaneous abortions have been reported in subjects with multiple sclerosis in controlled clinical trials. Interferon-beta-1b is contraindicated during pregnancy and women of childbearing potential should take appropriate contraceptive measures and should be warned of potential hazards. If the patient plans to become pregnant while taking interferon-beta-1b, therapy should be discontinued.

28. It is not known whether interferon-beta-1b is excreted in human milk. Because the risk of serious adverse reactions to interferon-beta-1b in breast fed infants is unknown, a decision should be made whether breast feeding or the drug should be discontinued.

## CHILDREN AND ADOLESCENTS

29. The efficacy and safety of interferon-beta-1b have not been investigated in children and adolescents of less than 18 years of age.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

30. None known.

REFERENCES

The IFNB Multiple Sclerosis Study Group. Interferon-beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655-661.

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Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Annals of Neurology 1983; 13: 227-231.

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**This advice will remain effective for 2 years unless superseded by new advice prepared in the light of new information.**

## AUDIT OF THE USE OF INTERFERON-BETA-1b

To monitor the effectiveness of interferon-beta-1b in the management of relapsing-remitting multiple sclerosis, it is recommended that the neurologist completes the following proforma 6-12 monthly for each patient:

Name: Date of birth:

Date of starting treatment:

Today's date:

Number of relapses since last visit:

Still on treatment? Yes/No

If no, because:-

a) continuing deterioration

b) non-compliance

c) side-effects

- nature of side-effects

d) other

*In view of the potential importance of neutralising activity in determining how long treatment should continue, it is recommended that serum is stored on each occasion for analysis when the assay becomes available in this country.*

## Interferon-beta-1b: to refer or not? - an *aide memoire* for GPs