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TRANSPARENCY COMMITTEE

Re-assessment of interferon beta and glatiramer acetate in multiple sclerosis

REPORT

July 2010

CONTENTS

BACKGROUND AND INTRODUCTION

HAS' Transparency Committee assesses drugs that have obtained a Marketing Authorisation, when the company marketing them wants them to be included on the list of drugs that may be reimbursed (articles L.162-17 of the French Social Security code and L.5123-2 of the French Public Health code) or on its own initiative.
The Transparency Committee is a scientific body made up of doctors, pharmacists, methodologists and epidemiologists. Its missions are:

- to deliver an opinion to the Ministers for Health and Social Security on whether there is sufficient evidence to justify the reimbursement of medicines by Social Security and/or their use in hospital, notably in view of their actual benefit (AB) and any improvement in actual benefit (IAB) they are likely to contribute compared with treatments already available;
- to contribute to the proper use of medicines by publishing relevant independent scientific information.

These missions are defined in the French Social Security code, particularly in articles R.163-2 to R.163-21, L.161-37, L. 161-39 and L. 161-41.
According to articles L. 162-17, L. 161-37, L.161-39,L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76, R. 161-85 of the Social Security and L. 5123-2 and L. 5123-3 of the Public Health code, the Transparency Committee's opinion states the actual benefit and the improvement in actual benefit contributed by the medicinal product. The assessment is based on a critical analysis of the scientific literature according to the precepts of evidence based medicine and on the opinion of experts, in the indications and at the dosages given in the Marketing Authorisation.

I. Subject of this assessment made by HAS on its own initiative

During the last fifteen years, the options for treating multiple sclerosis (MS) have been extended by the granting of a Marketing Authorisation in this indication to the immunomodulators interferon beta and glatiramer acetate.
Some issues have not yet been resolved, notably the efficacy of these medicines against disease progression and long-term disability, the optimum dose and duration of treatment and the consequences of discontinuing them.

When the first opinions were delivered on the inclusion of these medicines reimbursed by National Health Insurance, the Transparency Committee assessed their efficacy against clinical criteria measured in the short term (≤ 2 years), mainly time to onset or frequency of onset of clinical exacerbations of MS (relapses). The data did not make it possible to assess the long-term impact of these medicines on progression of neurological deficit or patients' disability measured using the Kurtzke Expanded Disability Status Scale (EDSS).

As the inclusion of these medicines on the list for reimbursement is due for renewal, HAS has decided to deliver an opinion on its own initiative on their efficacy and tolerance in the light of recent published data and the dossiers submitted by the companies concerned. This re-assessment mainly concerns the impact of the existing four medicinal products on long-term (> 2 years) disability and tolerance in the indications given in their respective Marketing Authorisations (first demyelinating event, relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS)).

II. General description

A list of the medicinal products included in the assessment is given in Tables 1 and 2. The indications, doses and AB level granted by the Transparency Committee are included in the tables. The AB levels were substantial; the efficacy/adverse effects ratios were considered to be modest.

II.1 Interferon beta (Centralised Procedures)

List I
Exception drug status
Medicine requiring special monitoring during treatment.
Medicine requiring prescription initiation and renewal by neurology specialists only.

ATC classification (2010):

L	Antineoplastic and immunomodulating agents
L03	Immunostimulants
L03A	Cytokines and immunomodulators
L03AB	Interferons

Medicinal product/INN	Adult dose/route of administration	Date of Marketing Authorisation/Indications	IAB
BETAFERON 250 mcg/mL **Interferon beta-1b** **BAYER SANTE**	250 mcg SC/2 days	**<u>30 November 1995</u>** Reduction of frequency and degree of severity of clinical relapses in ambulatory patients (i.e. patients who are able to walk unaided) with relapsing-remitting MS, characterised by at least two attacks of neurological dysfunction over the preceding two year period, followed by complete or incomplete recovery. Patients receiving BETAFERON showed a reduction in frequency (-30%) and severity of clinical relapses, as well as the number of hospitalisations due to disease. Furthermore, there was a prolongation of the relapse-free interval. There is no evidence of an effect of BETAFERON on the duration of exacerbations, on symptoms in-between exacerbations, or on the progression of the disease. The effect of BETAFERON on performance of daily activities or in the social field is not known. BETAFERON has not yet been investigated in patients with progressive multiple sclerosis. There is no evidence of any efficacy against disability. Clinical studies have shown that not all patients respond to BETAFERON. In addition, in some patients clinical relapses have worsened despite treatment. There are no criteria predictive of absence of response or worsening in any individual patient.	**<u>14 February 1996</u>** *(Inclusion for relapsing-remitting MS)* BETAFERON is the first drug to have proved its efficacy in the treatment of relapsing-remitting multiple sclerosis (RRMS). Compared with the current strategy based on immunosuppressants, which are poorly tolerated and whose activity is unproven, the clinical results obtained in terms of reduction in frequency and severity of clinical relapses, despite remaining uncertainties about disease progression and disability, constitute important IAB (**level II**).

		26 January1999 Indicated for slowing progression of disease and for the reduction of frequency of clinical relapses. The effect of treatment is obtained in patients with or without clinical relapse, and irrespective of the level of disability (patients with mild disease and those unable to walk were not studied). BETAFERON has not yet been studied in patients with immediately progressive multiple sclerosis.	**16 June 1999** *(Extension of indication to SPMS)* BETAFERON is the first medicinal product to have been shown to delay disease progression in secondary progressive multiple sclerosis. This results in major improvement in actual benefit (**level I**).
			24 May 2000 *(Amendment to IAB text in the Prescribing Information)* BETAFERON was the first medicine to have proved its long-term efficacy in the treatment of relapsing-remitting forms of MS. Since then, AVONEX and REBIF have also demonstrated their efficacy in relapsing-remitting MS. **These three interferons have the same level of IAB (level I).**
		19 November 2001 Treatment of patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	**11 September 2002** *Renewal of inclusion (submission of INCOMIN study)* *and change of Marketing Authorisation text for SPMS (evidenced by relapses)* INCOMIN study Conclusion: this is the first published trial comparing two interferons in the treatment of relapsing-remitting MS. Open treatment was ethically justified but reduced the relevance of the study. After administration according to the regimens given in the Marketing Authorisation, a difference was observed in favour of BETAFERON against clinical relapses and disease progression. Data from this study comparing two beta interferons were in favour of a dose effect and/or a frequency of administration effect, but did not confirm the security of one interferon over another. **IAB**: The change in the text of the indication in secondary progressive MS does not change the level of improvement in actual benefit contributed by BETAFERON from that initially established.
		12 July 2004 Treatment of patients with relapsing-remitting multiple sclerosis with at least two clinical relapses during the previous two years.	

		1 June 2006 Treatment of patients with a single demyelinating event with an active inflammatory process, severe enough to warrant treatment with intravenous corticosteroids, where alternative diagnoses are excluded and who are considered to be at high risk of developing clinically definite multiple sclerosis.	**4 October 2006** *(Extension of indication to a single demyelinating event)* In view of the uncertainties related to indirect comparisons, in this extension of indication the Transparency Committee notes that the amount of effect obtained in the BENEFIT study for BETAFERON seems to be similar to that obtained in the CHAMPS study for AVONEX (Transparency Committee opinion dated 8 January 2003). Consequently, the Committee considers that the medicinal product BETAFERON does not provide any improvement in actual benefit compared with the medicinal product AVONEX (**IAB V**).
EXTAVIA 250 mcg/mL **Interferon β1-b** **NOVARTIS PHARMA**	250 mcg SC/2 days	**20 May 2008** Treatment of patients with a single demyelinating event with an active inflammatory process, severe enough to warrant treatment with intravenous corticosteroids, where alternative diagnoses are excluded and who are considered to be at high risk of developing clinically definite multiple sclerosis. Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years. Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	**3 September 2008** This medicinal product does not contribute any improvement in actual benefit in the treatment of multiple sclerosis.
AVONEX 30 µg / 0.5 mL **Interferon beta-1a** **Biogen Idec France**	30 µg IM/week	**13 March 1997** Treatment of patients who are able to walk unassisted and who have been diagnosed with relapsing-remitting multiple sclerosis (MS), defined as at least two neurological events (relapses) during the previous three years without evidence of continuous progression between relapses. AVONEX slows the progression of disability and decreases the frequency of relapses [over a two-year period]. AVONEX has not yet been studied in patients with progressive multiple sclerosis. *(deletion - Marketing Authorisation dated 14 February 2005)* AVONEX should be discontinued in patients who develop progressive MS. Not all patients respond to treatment with AVONEX. No clinical criteria predictive of response to treatment have been identified. *(deletion - Marketing Authorisation dated 14 February 2005)*	**8 June 1997** Compared with the current strategy based on immunosuppressants, which are poorly tolerated and whose activity is unproven, AVONEX not only reduces the frequency of clinical relapses, but is also the first medicinal product to have demonstrated slowing of disease progression. This results in major improvement in actual benefit (level I), while with regard to interferon beta-1b, compared with the same strategy, the uncertainties concerning long-term disease progression led the Transparency Committee to recognise its important improvement in actual benefit (**level II**).

		Treatment of patients able to walk unassisted, with relapsing-remitting multiple sclerosis (MS), defined as at least two neurological events (relapses) during the previous three years without evidence of regular progression between relapses. AVONEX slows disease progression and reduces frequency of relapses. **7 May 2002** Treatment of patients with a single demyelinating event with an active inflammatory process, severe enough to warrant treatment with intravenous corticosteroids, where alternative diagnoses are excluded and who are determined to be at high risk of developing clinically definite multiple sclerosis. **3 March 2008** Treatment of patients with relapsing-remitting multiple sclerosis (RRMS). In clinical trials, this is characterised by two or more clinical relapses occurring during the previous three years without evidence of regular progression between relapses; AVONEX slows disease progression and reduces frequency of clinical relapses. AVONEX should be discontinued in patients who develop progressive MS.	**8 January 2003** *(Extension of indication to a single demyelinating event)* The results obtained in this extension of indication (a single demyelinating event) confirm the improvement in actual benefit previously established for this medicinal product (major improvement, **level I**).
REBIF **22 µg / 0.5 mL** **44 µg / 0.5 mL** **8.8 µg / 22 µg** **Interferon beta-1a** **MERCK SERONO**	22/44 µg SC 3x/week	**4 May 1998** Treatment of patients who are able to walk unassisted and who have been diagnosed with relapsing-remitting multiple sclerosis (RRMS), defined as at least two neurological events (relapses) during the previous two years. REBIF 22 µg reduces the frequency and severity of relapses over a 2-year period. REBIF has not yet been studied in patients with progressive multiple sclerosis; treatment should be discontinued in patients who develop progressive MS.	**3 June 1998** *(Inclusion of REBIF 22 µg)* Compared with the current strategy based on immunosuppressants, which are poorly tolerated and whose activity is unproven, the reduction in frequency and severity of clinical relapses obtained with BETAFERON (INF-β-1b) led the Transparency Committee to recognise its important improvement in actual benefit (**level II**), while this improvement was major for AVONEX (INF-β-1a) which was the first medicinal product to also demonstrate slowing of disease progression. REBIF is the second INF-β 1-a after AVONEX. The level of clinically efficacy currently demonstrated only in preventing relapses, together with the tri-weekly mode of administration, puts REBIF on the same level as BETAFERON. However, compared with BETAFERON, the Committee recognises a minor potential advantage in terms of efficacy against disease progression in view of the first results obtained in clinical trials, but their relevance needs to be confirmed.

		1 February 1999 Treatment of patients who are able to walk unassisted and who have been diagnosed with relapsing-remitting multiple sclerosis (RRMS), defined as at least two neurological events (relapses) during the previous two years. REBIF® 22 µg reduces the frequency and severity of relapses over a 2-year period *and slows disease progression*."	**7 July 1999** *(Change of wording of the indication)* Recognition of REBIF activity against disease progression is based on a new analysis of the efficacy data in the Marketing Authorisation dossier. This led to the conclusion that the proportion of patients with disease progression, defined as an increase of at least 1 point on the EDSS scale, confirmed at three months, was reduced from 39% (placebo) to 30% (REBIF 22 µg). In patients with relapsing-remitting multiple sclerosis (RRMS), REBIF, as the other beta interferons, has therefore proved its efficacy in slowing disease progression. This reinforces the substantial actual benefit of interferon beta in managing these patients. Unlike AVONEX, which demonstrated slowing of disease progression over a six-month period but in patients with mild to moderate forms of the disease (EDSS score between 1 and 3.5), REBIF, as BETAFERON, has demonstrated similar efficacy but over a shorter period (three months); however, the patients concerned had more severe forms of disease (with disability up to 5 and 5.5 respectively on the EDSS scale). Consequently, in RRMS, **REBIF 22 µg shares the same actual benefit as BETAFERON and AVONEX.**
		29 March 1999 Marketing Authorisation REBIF 44 µg / 0.5mL	**6 August 1999** *(Inclusion of REBIF 44 µg)* REBIF 44 µg shares the improvement in actual benefit (IAB) contributed by AVONEX, BETAFERON and REBIF 22 µg.
		21 November 2001 REBIF is indicated for the treatment of patients with multiple sclerosis characterised by two or more acute exacerbations in the previous two years. Its efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity.	**6 March 2002** *(Extension of indication to SPMS)* In the extension of indication, the improvement in actual benefit (IAB) remains major (level I) and REBIF shares the same IAB as BETAFERON (INF-β-1b).
			11 September 2002 *Submission of follow-up results at 48 weeks from the **EVIDENCE study** (REBIF 44 µg vs AVONEX 30 µg)* After administration according to the regimens given in the Marketing Authorisation, the difference between the two groups in favour of REBIF observed at 24 weeks was confirmed at 48 weeks, and remained stable between 24 and 48 weeks.

			Data from this study comparing two beta-1a interferons was in favour of a dose effect and/or a frequency effect of administration effect but did not confirm the superiority of one interferon over another.
		19 January 2006 Marketing Authorisation starter kit REBIF 8 µg / 22 µg **31 May 2006** Treatment of relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years. Its efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity.	

II.2 Glatiramer acetate (national Marketing Authorisation)

List I
Exception drug status
Medicine requiring special monitoring during treatment.
Medicine requiring prescription initiation and renewal by neurology specialists only.

ATC classification (2010):

L	Antineoplastic and immunomodulating agents
03	Immunostimulants
A	Cytokines and immunomodulators
X	Other cytokines and immunomodulators
13	glatiramer acetate

Medicinal product/INN	Adult dose/route of administration	Date of Marketing Authorisation/Indications	IAB
COPAXONE 20 mg/mL **Glatiramer acetate** **SANOFI-AVENTIS**	20 mg SC/ day	**<u>25 January 2002</u>** Glatiramer acetate is indicated for the reduction in frequency of relapses in ambulatory patients (i.e. who can walk unaided) with relapsing-remitting multiple sclerosis (RRMS) characterised by at least two attacks of neurological dysfunction over the preceding two-year period. Glatiramer acetate has not demonstrated any beneficial effect on disease progression. Glatiramer acetate is not indicated for the treatment of primary or secondary progressive MS.	**<u>20 November 2002</u>** In view of its good tolerance profile and despite the absence of evidence for slowing of disease progression, Copaxone **shares the IAB of interferons (level I)** in the treatment of patients with relapsing-remitting MS.
		<u>26 March 2004</u> Copaxone 20 mg/mL, solution for injection in pre-filled syringe	**<u>19 May 2004</u>** This new presentation does not contribute any improvement in actual benefit compared with the presentation as powder and solvent for solution for injection which is already included on the reimbursement list.

LITERATURE SEARCH

I. Analysis of data in the literature

I.1 Databases searched

- Medline (National Library of Medicine, United States);
- Embase (Elsevier, Netherlands);
- Pascal (French National Institute for Scientific and Technical Information).

I.2 Review collections and organisations

- Cochrane Library (United Kingdom)
- National Guideline Clearinghouse (Agency for Healthcare Research and Quality, United States);
- HTA Database (International Network of Agencies for Health Technology Assessment - INAHTA);
- A.F.Lemanissier Medical Library (France);
- CISMef (Catalog and Index of French Language Health Resources on the Internet) practice guidelines (France);
- CMA Infobase - Clinical Practice Guidelines (Canada);
- National Library for Health - Guidelines Finder (United Kingdom).

I.3 Other sources

- Websites of relevant organisations, institutions and professional societies;
- Reference lists of articles and documents studied.

II. Search strategy and results

The search strategy was created using either thesaurus terms (MeSH headings) or terms from the title or summary (free text), for each subject. They were combined in as many steps as necessary using the operators "AND", "OR" and "NOT". They were also combined with descriptive terms for the type of study.

Table 4 (Annex I) illustrates the search strategy and the results in terms of number of references obtained by type of study and by subject over a given period.

This literature search was continued up to the end of January 2010.

III. Dossiers submitted by companies

Companies were contacted to provide HAS with recent information on the medicines to enable their re-asessment. Data satisfying the selection criteria and items included in the analysis are listed below.

IV. Data provided by AFSSAPS

AFSSAPS' Pharmacovigilance Department was asked about any adverse events that had occurred and been declared during treatment.

CLINICAL DATA ON EFFICACY

Efficacy data were analysed by indication. The analysis was based on the most recent European guidelines on evaluating beta interferons (INF-β) and glatiramer acetate in MS.
New data extracted from the dossiers submitted by companies and/or the literature search were incorporated into the document. A critical review of the data was performed, so that only meta-analyses, well-designed systematic reviews and studies of a high level of evidence were retained. Only studies using clinical outcome measures were included.
Assessment of the impact of these drugs on long-term disability (> 2/3 years) concerned follow-up of patients who had taken part in randomised placebo-controlled trials and in observational studies evaluating disease progression under immunomodulator therapy (interferon beta or glatiramer acetate).

I. PLACEBO-CONTROLLED STUDIES WITH OPEN FOLLOW-UP

I.1 First neurological event consistent with MS

I.1.1 Systematic review of randomised placebo-controlled trials

Clerico M, Faggiano F, Rice GPA, Tintoré Sbiana M, Durelli L. The Cochrane Library 2009, Issue 2. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis (Review) 2008

The literature search for this Cochrane review concerned the Cochrane MS Group Trials Register (June 2007), the Cochrane Central Register of Controlled Trials (COCHRANE LIBRARY Issue 3 2007), MEDLINE (January 1966 - June 2007), EMBASE (January 1974 - June 2007) and reference lists from the published articles. Manufacturers and researchers in the field were contacted.

There were three randomised controlled trials evaluating interferon beta-1a (CHAMPS[1], ETOMS[2]) and interferon beta-1b (BENEFIT[3]) in 1160 patients with a first demyelinating event (639 INF-β, 521 placebo). The available data were limited to one year of follow-up for the CHAMPS trial (39% of patients were not followed up at two years because they dropped out of the trial prematurely after the intermediate analysis).
Meta-analyses of the data showed that the proportion of patients with clinically definite multiple sclerosis (CDMS) was lower in patients treated with interferon than in patients treated with placebo.

At one year, the risk of conversion was 19% in patients receiving interferon and 30% in those receiving placebo (odds ratio (OR) 0.53, 95% CI 0.40 to 0.71); at two years (ETOMS, BENEFIT) the risk was 29% for interferon and 45% for placebo (OR 0.52, 95% CI 0.38 to 0.70).
Early treatment with interferon beta delays conversion to clinically definite multiple sclerosis (onset of a further relapse) at two years (ETOMS, BENEFIT).

The most commonly reported adverse events were flu-like syndrome (CHAMPS 54% INF-β vs 26% placebo, BENEFIT 44% vs 18%) and injection-site reactions (ETOMS 60% vs 12%, BENEFIT 48.3% vs 8.5%).

[1] Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW and the CHAMPS Study Group. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N Engl J Med 2000;343:898-904.

[2] Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001;357(9268):1576-82.

[3] Kappos L. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;67:1-8.

I.1.2 Open follow-up of patients receiving active treatment (extension of controlled trials)

Extension of the CHAMPS trial[4]

Fifty-three percent (53%) of the patients randomised in the CHAMPS study (203/383) were followed while being treated with AVONEX 30 µg IM/week. For patients originally treated with placebo, active treatment was started at the time they were diagnosed with clinically definite MS (CDMS) or at the time of their last visit. Twenty-six percent (26%) of the patients included in follow-up developed CDMS, 66% completed the CHAMPS study and did not develop CDMS and 6% did not complete the study. 76% were receiving INF-β-1a, 17% were not receiving any treatment and 7% were receiving another form of treatment. 65% of patients had an EDSS score ≤ 1.5.
At five years, the cumulative probability of development of CDMS was 36% in the group originally treated with interferon (n=100) and 49% in the group previously treated with placebo (n=103), hazard ratio (HR) 0.65, 95% CI 0.43 to 0.97. The annualised relapse rate[5,6] was 0.17 versus 0.32. Mean EDSS score was ≥ 3 in 11% and 14% of patients respectively.

Extension of the BENEFIT study[7,8]

Four hundred and eighteen (418) of the 487 patients randomised in the BENEFIT study were followed during the open phase. Three hundred and seventy-eight (378) patients received treatment with BETAFERON 250 µg SC /2 day, i.e. 261 patients originally treated with interferon (early treatment, ET) and 157 patients originally treated with placebo (delayed treatment, DT). Mean baseline EDSS score was 1.5. At 3 years, 343 patients were still being treated. Median treatment duration in the group originally receiving placebo was 12 months. The proportion of patients developing clinically definite multiple sclerosis (CDMS) was 37% (99 patients) in the ET group and 51% (85 patients) in the DT group. Disease progression (increase of at least 1 point in EDSS) was recorded in 14% of patients in the ET group and in 23% of patients in the DT group (relative risk (RR) 0.6, 95% CI 0.39 to 0.92).

Five-year follow-up was completed by 358 patients (ET n=235; DT n=123). Median treatment duration in the group originally receiving placebo was 2 years 11 months. Risk of development of CDMS was 46% in patients in the ET group and 57% in patients in the DT group (HR 0.63, 95% CI 0.48 to 0.83). Disease progression (increase of at least 1 point in EDSS) was recorded in 21% of patients in the ET group and in 23% of patients in the DT group.

I.2 Relapsing-remitting multiple sclerosis

I.2.1 Interferons

a. Systematic review of placebo-controlled studies

Interferon in relapsing-remitting multiple sclerosis. Rice GPA, Incorvaia B, Munari LM, Ebers G, Polman C, D'Amico R, Parmelli E, Filippini G. Cochrane Database of Systematic Reviews, Issue 2, 2009.

The literature search for the Cochrane review included the Cochrane MS Group Trials Register (April 2007), MEDLINE (January 1966 - April 2007), EMBASE (January 1985 - April 2007) and reference lists of articles. Manufacturers and researchers in the field were also contacted. Reports from

[4] Kinkel RP & the CHAMPIONS Study Group. Interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;66 (5): 678-84.

[5] Quotient of the total number of relapses by the total number of days' participation multiplied by 365 days.

[6] Onset or recurrence of neurological symptoms, in the absence of fever or infection, persisting for at least 24 hours, accompanied by neurological signs on neurological examination.

[7] Kappos L. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 2007;370:389-97.

[8] Kappos L. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurology 2009;8(11):987-97.

congresses of neurology societies and learned societies specialising in MS in Europe and in the United States between 1999 and 2007 were searched manually.

The review included eight double-blind randomised placebo-controlled trials (1301 patients with RRMS according to the Poser 1983 criteria) - Knobler 1993, IFNB MS Group 1993, Durelli 1994, MSCRG 1996,, PRISMS Lancet 1998, Myhr 1999, OWIMS 1999, Polman 2003. Seventy-one percent (71%) of patients (INFB MS Group 1993, MSCRG 1996, PRISMS 1998) contributed to the results concerning relapse (RR 0.80, 95% CI 0.73 to 0.88) and disease progression - increase of at least one point in EDSS score at two successive assessments at least three months apart (6 months for AVONEX) - (RR 0.69, 95% CI 0.55 to 0.87) over the two-year treatment period.

If premature dropouts from the treatment group are classed as disease progressions (43% MSCRG study, 13% INFB MS Group study, 6.4% PRISM study), the statisticalsignificance of these effects is lost: relapse RR 1.11, 95% CI 0.73 to 1.68; disease progression RR 1.31, 95% CI 0.60 to 2.89.

Advances in magnetic resonance imaging (MRI) technology over the last decade and differences in data reported between trials meant that it was not possible to perform a quantitative analysis of the MRI results.

The most commonly reported adverse events were flu-like syndrome (48% vs 28% for the placebo group); injection site reaction, particularly after subcutaneous administration (62% vs 14%); isolated symptom (fever, joint pain or muscle pain); tiredness; and headache.

b. Follow-up of patients receiving active treatment

Five hundred and six (506) of the 560 patients (506/560) in the PRISMS study (**REBIF** 22 and 44 µg SC 3x/week versus placebo in RRMS patients) were assessed[9,10] at four years; 172/187 patients randomised to the placebo group were further randomised into two groups, i.e. REBIF 22 µg (n=85) and REBIF 44 µg (n=87) 3x/week. Patients receiving active treatment continued with it, i.e. REBIF 22 µg (n=167) or REBIF 44 µg (n=167). Mean baseline EDSS scores were between 2.7 and 3. Twenty-one percent (21%) of patients originally receiving placebo and 11% of patients originally receiving active treatment discontinued treatment. Relative proportions of patients with no disease progression were 51% (22 µg), 56% (44 µg) and 46% (placebo/REBIF). Proportion of patients who had not relapsed at four years were 14.4% (22 µg), 19.0% (44 µg) and 6.7% (placebo/REBIF).

Three hundred and eighty-two (382) patients (68% of patients in the study) continued treatment during the open phase[11], i.e. REBIF 22 µg SC 3x/week (n=123), REBIF 44 µg SC 3x/week (n=136), placebo/REBIF 22 µg (n=60), Placebo/REBIF 44 µg (n=63). Only 275 patients (49%) were still receiving treatment at eight years.

Four hundred and ninety-three (493) of the 802 RRMS patients included in the dose-comparison study evaluating **AVONEX** 30 µg versus 60 µg IM/week at 36 months of treatment (61%) took part in a second double-blind treatment period for a further 12 months.[12] Twenty-seven (27) patients had progressive MS. Mean baseline EDSS scores in the two groups were 3.4 and 3.5. Of these patients, 31/246 patients treated with INF-β-1a 30 µg (13%) and 16/247 patients treated with INF-β-1a 60 µg (6%) stopped treatment prematurely. At 48 months, 30% of patients had an EDSS score ≥ 4 and 22% an EDSS score ≥ 6 in both treatment groups.

A hundred and sixty (160) (53%) of the 301 patients in a phase III trial evaluating **AVONEX** 30 µg IM/week versus placebo (MSCRG 1996) were assessed after eight years of follow-up (AVONEX

[9] The PRISMS Study group & the University of British Columbia MS/MRI analysis group. PRISMS-4: Long term efficacy of interferon beta-1a in relapsing MS. Neurology 2001;56:1628-36.

[10] Oger J., Francis G., Chang P. Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: The PRISMS study. J Neurol Sci 2005;237:45-52.

[11] Kappos L. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology 2006;67:944-953.

[12] Clanet M, Kappos L, Hartung HP, Hohlfeld R and The European IFNβ-1a Dose-Comparison Study Investigators. Interferon β-1a in relapsing multiple sclerosis: four-year extension of the European IFNβ-1a Dose-Comparison Study. Multiple Sclerosis 2004;10:139-144.

n=79, placebo n=81).[13] During follow-up, 97% of patients in the INF-β-1a group and 64% of patients in the placebo group received INF-β-1a, 25% and 31% respectively received INF-β-1b; 13.8% of the patients originally receiving placebo did not receive immunomodulator therapy.
At eight years, 42% of patients originally receiving placebo and 29% of patients originally receiving INF-β-1a had an EDSS score ≥ 6. No information was provided on frequency of relapses.

Data from 260 patients were collected during a retrospective study[14] carried out 16 years after the end of the IFNB MS Group 2-year randomised controlled trial (n=372) evaluating **BETAFERON** 50 µg and 250 µg /2 days versus placebo. No details were given of the different treatments received, clinical events or treatment dropouts. 7.2% and 4.8% of patients originally treated with BETAFERON and 16.3% of patients originally receiving placebo died.

c. Comparative trials: interferon versus interferon

The Transparency Committee opinion of 11 September 2002 concerning data of the **INCOMIN** trial[15] (BETAFERON 250 µg /2 days vs AVONEX 30 µg IM/week) concluded:

"This is the first published trial comparing two interferons in the treatment of relapsing-remitting MS. Open treatment was ethically justified but reduced the relevance of the study.
After administration according to the regimens given in the Marketing Authorisation, a difference was observed in favour of BETAFERON against clinical relapses and disease progression.
Data from this study comparing two beta interferons were in favour of a dose effect and/or a frequency of administration effect, but did not confirm the superiority of one interferon over another."

The opinion of the Transparency Committee on 11 September 2002 concerning the results of follow-up at 48 weeks of the **EVIDENCE trial**[16] (REBIF 44 µg SC 3x/week vs AVONEX 30 µg IM/week) concluded:

After administration according to the regimens given in the Marketing Authorisation, the difference between the two groups in favour of REBIF observed at 24 weeks was confirmed at 48 weeks, and remained stable between 24 and 48 weeks. Data from this study comparing REBIF and AVONEX were in favour of a dose effect and/or a frequency effect of administration effect but did not confirm the superiority of one interferon over another.

The study was extended[17,18]. Two hundred and twenty-three (223) (73%) of the patients originally treated with INF-β-1a IM voluntarily changed their treatment and were treated with INF-β-1a SC. These patients, together with 272 patients (90%) initially treated with INF-β-1a SC, were followed up for a further 32 weeks. It is not possible to interpret the results in terms of difference between the two groups of patients.

[13] Rudick RA et al. Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients. Multiple Sclerosis 2005;11:626-34.

[14] Ebers G C, Reder A T, Traboulsee A, Li D et al. Long term follow-up of the original interferon-β1b trial in multiple sclerosis: design and lessons from a 16-year observational study. Clinical Therapeutics 2009;31(8):1724-36.

[15] Durelli L, Verdun E, Barbero P et al. and the Independent Comparison of Interferon (INCOMIN) Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a two year prospective randomized multicentre study (INCOMIN). Lancet 2002;359:1453-60.

[16] Panitch H, Goodin DS, Francis G et al. for the EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon β-1a treatment regimens in MS: The EVIDENCE trial. Neurology 2002;59:1496-506.

[17] Panitch H, Goodin D, Francis G, Chang P, Coyle P, O'Connor P, Li D & Weishenker B. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci 2005;239:67-74.

[18] Schwid S, Thorpe J, Sharief M, Sandberg-Wollheim M, Rammohan K, Wendt J, Panitch H et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis. Arch. Neurol. 2005;62:785-92.

A Danish open randomised multicentre study[19] compared BETAFERON 250 µg SC/2 days (n=158) and REBIF 22 µg SC/week (n=143). At two years, there was no difference in annualised relapse rate or time to onset of a further relapse between the two treatments.

I.2.2 Glatiramer acetate

a. Systematic review of placebo-controlled studies

Therapy with glatiramer acetate for multiple sclerosis. Murani L, Lovati R, Boiko A. Cochrane Database of Systematic Reviews, Issue 2, 2009.

The literature databases searched were the Cochrane MS Group Trials Register (December 2004), Cochrane Library Issue 4, 2004, Medline (January 1966 to December 2004) and Embase (January 1988 to December 2004). Reports from congresses of neurology societies and learned societies specialising in MS in Europe and in the United States between 1990 and 2004 were searched manually.

The review was based on the results of four double-blind randomised placebo-controlled trials published between 1987 and 2001 (646 patients, 320 patients treated with glatiramer acetate), i.e. Bornstein 1987 and 1991 (progressive MS), Johnson 1995[20] and Comi 2001[21]. Patients were treated for 24, 35 and 9 months respectively.

The review concluded that there was no benefit from glatiramer acetate therapy on disease progression (increase in EDSS score of at least one point for at least three months) and that treatment did not significantly affect the risk of relapse.

The relative risk of at least one relapse was 0.77 (95% CI 0.61 to 0.99) at one year (Bornstein 87, Comi 2001). At two years (Bornstein 87, Johnson 95), this risk was 0.87 (95% CI 0.74 to 1.02) and mean difference in number of relapses was -0.51 (95% CI -0.81 to -0.22). The risk of disease progression was 0.77 (95% CI 0.51 to 1.14) in patients with RRMS and 0.69 (95% CI 0.33 to 1.46) in progressive MS (Bornstein 91).

b. Follow-up of patients receiving active treatment

The Johnson study[22] (1995) was a 24-month double blind randomised placebo-controlled trial carried out in the United States. Two hundred and fifty-one (251) RRMS patients were randomised to Copaxone (n=125) or placebo (n=126). Mean relapse rate, the primary outcome measure, was 1.29 in the Copaxone group versus 1.68 in the placebo group (-0.38, 95% CI -0.68 to -0.08). The annualised relapse rate was 0.59 versus 0.84. Percentages of patients without disease progression were 78.4% versus 75.4 % (RR 0.88, 95% CI 0.56 to 1.38).

Two hundred and eight (208) of the 215 patients[23,24] who completed the treatment period took part in an open follow-up period treated with Copaxone: patients originally randomised to the Copaxone

[19] Koch-Henriksen N. et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology 2006;66:1056-60.

[20] Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-76.

[21] Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Annals of neurology. 2001;49(3):290-7.

[22] Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-76.

[23] Johnson KP, Brooks BR, Ford CC, Goodman A, Guarnaccia J, Lisak RP, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. The Copolymer 1 Multiple Sclerosis Study Group. Multiple sclerosis 2000;6(4):255-66.

group (ET) n=101, patients originally randomised to the placebo group (DT) n=107. At six years, 26 ET patients and 21 DT patients had not relapsed. Thirty-one percent (31%) of ET patients and 43% of DT patients had an increase of at least one point in EDSS score.

At eight years[25], 72 ET patients (58%) and 70 DT patients (56%) were still being treated with Copaxone® and being followed in the study. Twenty percent (20%) and 18% respectively of patients had not relapsed.

Data for 232 patients who had been exposed to active treatment during the double-blind period or the open follow-up period were analysed[26] at ten years (19 patients originally treated with placebo refused to participate). Twenty-four percent (24%) (40/169), 11% (24/221) and 3% (6/231) of these patients had a score of respectively 4, 6 and 8. The EDSS score increased by at least one point in 42% of patients. One hundred and eight (108) (46.5%) of these patients were still being treated.

The Comi study (2001) was a double-blind randomised placebo-controlled trial carried out in Europe and in Canada to evaluate the effect of Copaxone® therapy on lesions, monitored by magnetic resonance imaging (MRI). Two hundred and thirty-nine (239) RRMS patients were randomised and treated for nine months, i.e. Copaxone® (n=119) and placebo (n=120). There was a reduction in the number of gadolinium-enhancing lesions on T1-weighted sequences, the primary outcome measure, compared with placebo, i.e. -10.8 (95% CI -18.0 to -3.7).

One hundred and forty-two (142) (63.4%) of the 224 patients originally included in the open follow-up period[27] for patients in the Comi study were assessed after a mean of 5.8 years' treatment with Copaxone. At the end of follow-up, 94 patients (42%) were still being treated with Copaxone®, 21 (9%) were receiving another disease-modifying therapy and 27 (12%) were not receiving any disease-modifying therapy. Mean time between two relapses was 3.5, 1.3 and 2.9 years respectively. 18.8% of patients originally treated with placebo required assistance with walking (EDSS ≥ 6) versus 7% in patients originally treated with Copaxone. Nearly 40% of patients were not assessed.

c. Comparative studies - Glatiramer acetate versus interferon

The **REGARD trial**[28,29], a randomised open trial with blinded clinical assessment of 764 RRMS patients who had had at least one relapse during the year preceding inclusion and who were treated with interferon β-1a SC (44 µg 3/week) versus glatiramer acetate (20 mg SC/day) for two years, found no difference in time to onset of further relapse, the primary outcome measure, i.e. 16.3 months versus 14.2 months (HR= 0.94, 95% CI 0.74 to 1.21).

The **BECOME study,**[30] a randomised single centre trial assessed the cumulative number of lesions (enhancing lesions for T1 and new lesions for T2) in 75 patients, based on an optimised MRI protocol (3-tesla MRI with a triple dose of gadolinium). There was no difference between the glatiramer acetate group and the interferon β-1b group at two years.

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[24] Johnson KP, Brooks BR, Ford CC, Goodman AD, Lisak RP, Myers LW, et al. Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. Multiple sclerosis 2003;9(6):585-91.

[25] Johnson KP, Ford CC, Lisak RP, Wolinsky JS. Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-year data. Acta neurologica Scandinavica 2005;111(1):42-7.

[26] Ford CC, Johnson KP, Lisak RP, Panitch HS, Shifronis G, Wolinsky JS. A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients. Multiple sclerosis 2006;12(3):309-20.

[27] Rovaris M, Comi G, Rocca MA, Valsasina P, Ladkani D, Pieri E, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. Multiple sclerosis 2007;13(4):502-8.

[28] Mikol D, Barkhof F, Chang P, Coyle P, Jeffery D, Musch B, et al. The REGARD trial: a randomised assessor-blinded trial comparing interferon beta-la and glatiramer acetate in relapsing-remitting multiple sclerosis. Multiple Sclerosis 2007;13:S269.

[29] Mikol D, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study: a multicentre, randomised, parallel, open-label trial. The Lancet Neurology 2008; volume 7, Issue 10:903-14.

[30] Cadavid D, Wolansky LJ, Skurnick J et al. Efficacy of treatment of MS with IFN β-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology 2009;72:1976-83.

The open, randomised **BEYOND trial**[31] compared the efficacy and tolerance of interferon β-1b 250 µg and 500 µg 1x/2 days and a dose of glatiramer acetate 20 mg SC 1x/day in RRMS patients. 2244 patients were randomised (2:2:1). There was no difference between treatments in risk of further relapse at two years, the primary efficacy outcome measure. There was no difference in disease progression.

I.3 Secondary progressive multiple sclerosis

The literature search identified five randomised placebo-controlled trials evaluating interferons in secondary progressive MS.

The Kappos European trial,[32] a double-blind randomised trial carried out in 718 patients with SPMS and an EDSS score between 3 and 6.5, compared INF-β-1b 250 µg SC/2 days (n=360) with placebo (n=358). Mean baseline EDSS scores were 5.2 and 5.1. 42.5% and 47.2% respectively of patients had an EDSS score of 6 or higher. Between 28% and 32% of patients had no relapses in the two years preceding the trial. One hundred and eighty-seven (187) patients (27%) discontinued treatment prematurely; 57 patients were lost to follow-up.
At two years, the interim analysis found a disease progression (increase of at least one point in EDSS score, 0.5 point if baseline EDSS score was 6 or 6.5) in 49.7% of patients treated with placebo versus 38.9% in the INF-β group. 24.6% of patients treated with placebo and 16.7% of patients treated with INF-β had an EDSS score of 7 or higher.

The results of four further studies[33,34,35,36] did not demonstrate any superiority of interferon beta over placebo.
Post-hoc subgroup analyses[37,38] suggest that the patients who might benefit from treatment are patients who continue to have relapses.

[31] O'Connor P, Filippi M, Arnason B, Comi G et al. 250 µg or 500 µg interferon beta-1b versus glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol 2009;8:889-97.

[32] European Study Group on interferon β-1b in secondary progressive MS. Placebo-controlled multicenter randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998;352:1491-7.

[33] The North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS. Results from a 3-year controlled study. Neurology 2004;63:1788-95.

[34] Secondary progressive efficacy clinical trial of recombinant interferon beta 1-a in MS (Spectrims) study group. Randomized controlled trial of interferon beta 1a in secondary progressive MS. Clinical results. Neurology 2001;56:1496-504.

[35] Cohen JA et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59;679-87.

[36] Andersen O et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2004;75:706-10.

[37] Kappos L et al. Interferon beta-1b in secondary progressive MS. A combined analysis of the two trials. Neurology 2004;63:1779-87.

[38] Kappos L. Final analysis of the European multicenter trial on INF-1b in secondary-progressive MS. Neurology 2001;57:1969-75.

II. OBSERVATIONAL STUDIES

II.1 Observational studies of patients treated with interferon beta[39,40,41]

The Rio prospective single-centre Spanish cohort study[42] followed RRMS patients treated with interferon beta (INF-β-1a or INF-β-1b) between 1995 and 2004. Three hundred and eighty-two (382) of the 495 patients recruited were followed for a period of at least 24 months. At two years, 50-59% of patients had not relapsed. Disease progression was observed in 10.5-18.6% of patients. At four years, only 236/495 patients (48%) had been followed; 24.4% (BETAFERON), 23.4% (AVONEX) and 34.8% (REBIF) of these patients had an increase of at least one point in EDSS score.

The Patti Italian prospective non-randomised cohort study[43] compared interferon beta-1b 250 μg SC/2 days and interferon beta-1a 30 μg IM at six years in 126 RRMS patients recruited between February and December 1997 in two specialist neurology centres. At inclusion, the annualised relapse rate in these patients was 1.3. Between 62% and 66% of patients had a baseline EDSS score below 3. At six years, 7.5% (n=53) and 7.4% (n=54) of patients had not relapsed. EDSS score increased by ≥ 1 in 38% and 36% of patients. There was no difference between the two treatment groups in mean EDSS score at six years (3.2 and 3.3 respectively).

A prospective Italian cohort study[44] recruited 255 patients with MS (87% RRMS) who had started treatment with INF-β-1a between July 1997 and August 2003. At three years 153 patients could be assessed. Baseline EDSS score for the 106 patients (41.5%) who had continued treatment was 2.1; 58% of these patients had no disease progression.

The Trojano Italian prospective non-randomised cohort study[45] compared disease progression over seven years in RRMS patients treated with interferon beta (n=1103) with progression in untreated patients (n=401). The reasons for not being treated were: refusal of any disease-modifying therapy (19%), desire for pregnancy (15%), concomitant disease (23%), discontinuation of disease-modifying therapy because of adverse events (20%) and minor or no disease progression (23%). The estimated percentage of patients reaching an EDSS score of 6 in the INF-β group was lower than in the untreated group (HR 0.6, 95% CI 0.38 to -0.95). For incidence of secondary progressive MS, the hazard ratio was HR 0.38, 95% CI 0.24 to 0.58. However, a number of initial patient characteristics differed between the two groups, particularly age at onset of disease. Median baseline EDSS scores were 2.0 (INF-β) versus 1.0 (untreated).

The Veugelers study[46] followed 1752 MS patients from the Canadian Halifax DMSRU database between 1980 and 2004. Median follow-up was 5.8 years. One thousand four hundred and seventy-two (1472) patients (84%) had RRMS. Median duration of treatment in the 742 patients who had

[39] Limmroth V et al. Quality Assessment in Multiple Sclerosis Therapy (QUASIMS). A comparison of interferon beta therapies for relapsing-remitting multiple sclerosis. J Neurol 2007;254:67-77.

[40] O'Rourke K et al. Outcome of beta-interferon treatment in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol 2007;254:1547-1554.

[41] Vermersch P, de Seze J, Stojkovic T, Hautecoeur P, on behalf of the G-SEP. Interferon-β1a (AVONEX®) treatment in multiple sclerosis: similarity of effect on progression of disability in patients with mild and moderate disability. J Neurol 2002;249:184-7.

[42] Rio J et al. Interferon β in relapsing-remitting multiple sclerosis. An eight year experience in a specialist multiple sclerosis center. J Neurol 2005;252:795-800.

[43] Patti F et al. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. Acta Neurol Scand 2006;113:241-7.

[44] Coppola G et al. Long term clinical experience with weekly interferon beta-1a in relapsing multiple sclerosis. Europ J of Neurol 2006;13:1014-21.

[45] Trojano M et al. New Natural History of interferon β Treated Relapsing Multiple Sclerosis. Ann. Neurol. 2007;61:300-6.

[46] Veugelers PJ et al. Disease progression among multiple sclerosis patients before and during a disease-modifying drug program: a longitudinal population-based assessment. Multiple Sclerosis 2009;15(11):1286-94.

received an immunomodulator (INF-β or glatiramer acetate) was 2.5 years (n=742). Analysis of the data showed that the increase in EDSS score slowed down when the immunomodulators indicated in MS were introduced in 1998.

II.2 Observational studies of patients treated with glatiramer acetate

Two hundred and twenty-eight (228) patients with RRMS according to the Poser criteria and with an EDSS score < 6 were treated with Copaxone 20 mg SC/day between June 1995 and November 1998 as part of the compassionate use protocol in fifteen Belgium centres.[47] The disease had been diagnosed approximately five years earlier.
EDSS scores after a mean treatment period of 5.8 years could only be collected for 134 patients (59%). Mean baseline EDSS score in these patients was 2.4. Worsening of the score (increase of at least one point; of at least 0.5 point in patients with an EDSS score > 5.5) was observed in 37.3%. 10% of patients discontinued treatment.

Two hundred and fifty-five (255) (55%) of the 637 patients treated with COPAXONE under the temporary authorisation for use by a named patient (ATU) scheme approved in 1997 (CI 24% or inability to tolerate INF-β 76%) were followed for seven years.[48] Mean baseline EDSS score in these patients was 3.2. Fifty-one percent (51%) of patients had had more than three relapses a year in the two years preceding the study.
One hundred and thirteen (113) patients were treated for at least four years; 11% (9/81) had disease progression (increase of at least one point in EDSS score).
The most common adverse events were local reactions at the injection site (81%) and transient systemic immediate post-injection reactions (49%).

II.3 Follow-up of patients treated with glatiramer acetate after treatment with interferon[49,50,51]

The efficacy of glatiramer acetate as a replacement for interferon in patients who fail or who cannot tolerate interferon has not been studied in randomised controlled trials. A reduction in annualised relapse rate in patients previously treated with interferon was observed in follow-up studies over treatment periods of one to three years.

II.4 Post-Marketing Authorisation studies of patients treated with immunomodulators in France

At the request of the French Ministry of Health, the first patients treated with immunomodulators in France were followed-up in studies.

II.4.1 BETAFERON

A follow-up study of the first 1 159 patients treated with BETAFERON was carried out between July 1995 and January 2000.
Mean age of patients was 37 years. Mean disease duration was seven years. Mean initial EDSS score was 2.9. Mean number of relapses during the two years preceding start of treatment was two. Seventeen (17) patients (1.5%) had previously received treatment with another beta interferon. At

[47] Sindic CJ, Seeldrayers P, Vande Gaer L, De Smet E, Nagels G, De Deyn PP, et al. Long-term follow up of glatiramer acetate compassionate use in Belgium. Acta neurologica Belgica 2005;105(2):81-5.

[48] Debouverie M, Moreau T, Lebrun C, Heinzlef O, Brudon F, Msihid J. A longitudinal observational study of a cohort of patients with relapsing-remitting multiple sclerosis treated with glatiramer acetate. Eur J Neurol 2007;14(11):1266-74.

[49] Caon C, Din M, Ching W, Tselis A, Lisak R, Khan O. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. Eur J Neurol 2006;13(5):471-4.

[50] Carra A, Onaha P, Luetic G, Burgos M, Crespo E, Deri N, Halfon M, Jaacks G, Lopez A, Sinay V and Vrech C. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. Eur J Neurol 2008;15:386-93

[51] Zwibel HL. Glatiramer acetate in treatment-naive and prior interferon-beta-1b-treated multiple sclerosis patients. Acta Neurologica Scandinavica 2006;113(6):378-86.

inclusion, eight patients were also receiving corticosteroids and fifteen patients were receiving immunosuppressant therapy.

At one year, 855 patients (74%) had been followed. Two hundred and fifty-four (254) patients (30% of patients followed) had definitively discontinued treatment:

- poor general tolerability (30.4%)
- poor local tolerability (29.0%)
- loss of efficacy[52] (23.4%)
- change of treatment (switch) (16.2%)
- constraints of treatment (15.6%)
- other reasons (23.5%).

Sixty-four (64) patients discontinued treatment temporarily; mean duration of discontinuation was 1.5 months.
EDSS score had increased by at least one point in 94 patients (data available for 855 EDSS scores) and 452 patients (53%) had at least one relapse.

At two years, 509 patients (44%) had been followed. Four hundred and eighty-seven (487) patients (92% of patients followed) had definitively discontinued treatment.
EDSS score had increased by at least one point in 88 patients (data available for 509 EDSS scores) at two years. Sixty-six percent (66%) of patients followed had at least one relapse.

Ninety-two percent (92%) of patients (n=448) had at least one adverse event. The most common events were fatigue (58%), headache (37%), flu-like syndrome (70%). 10.5% of patients had depression during the 24 month follow-up period. Injection site pain was reported by 45.5% of patients.
Abnormal laboratory values, mainly in the blood count, were reported for 43% of patients over the two-year period.

II.4.2 REBIF

A follow-up study of the first 1381 patients treated with REBIF was carried out between January 1999 and January 2001. Follow-up results at two years were submitted in July 2004 and results at four years in January 2006.

Mean age of patients was 37 years. Mean disease duration was seven years. Mean initial EDSS score was 2.6. Ninety-three percent (93%) of patients had an EDSS score below 5.5. Mean number of relapses during the two years preceding start of treatment was three.
Four hundred and fifty-eight (458) patients (33%) had previously received treatment with another beta interferon. At inclusion, 26 patients were also being treated with corticosteroids and 10 patients were being treated with immunosuppressants.

At one year, 838 patients (61%) had been followed; 134 patients (16%) had definitively discontinued treatment. EDSS score had increased by at least one point in 103 patients (data available for 777 EDSS scores) and 402 patients (49.4%) had at least one relapse.

At two years, 757 patients had been followed (55%); 45% of patients had been lost to follow-up. Two hundred and thirty-one (40%) of the 757 patients had definitively discontinued treatment:

- poor general tolerability (31.5%)
- loss of efficacy (22.8%)
- poor local tolerability (20.4%)
- other reasons (25.3%).

A hundred and twenty (120) patients discontinued treatment temporarily; mean duration of discontinuation was four months.

[52] Loss of efficacy was defined as progression to secondary progressive MS (disease progression over six months without relapse) or at least three courses of corticosteroids or ACTH required during one year of treatment with REBIF.

EDSS score had increased by at least one point in 235 patients (data available for 543 EDSS scores) at two years. Sixty-three percent (63%) of patients followed had at least one relapse.

Ninety-five percent (95%) of patients (n=437) had at least one adverse event. The most common adverse events were fatigue (65%) and headache (57%), flu-like syndrome (62%): muscle pain 50%, fever 28%, shivering 33%, sweating 21%). Nearly 10% of patients had depression during the 24 month follow-up period. Injection site pain was reported by 63% of patients.
Abnormal laboratory values, mainly differential blood count abnormalities, were reported in 53% of patients over the two-year period.

At four years, 283 patients (20%) had been followed up. A hundred and nineteen (119) patients (39% of patients followed) had definitively discontinued treatment:

- loss of efficacy (45.4%)
- poor general tolerability (29.4%)
- poor local tolerability (26.9%)
- other reasons (36.2%).

Sixty-three (63) patients discontinued treatment temporarily; mean duration of discontinuation was five months.

An increase of at least one point in EDSS score was observed in 45 patients (data available for 106 EDSS scores) at four years. Seventy-one percent (71%) of patients followed had at least one relapse.

Ninety-five percent (95%) of patients (n=101) had at least one adverse event. Nearly 15% of patients had depression during the 48 month follow-up period. Pain at the injection site was reported by 80% of patients. Abnormal laboratory values, mainly differential blood count abnormalities, were reported in 61% of patients over the four-year period.

II.4.3 AVONEX

A follow-up study of the first 1 000 patients treated with AVONEX was carried out between February 1997 and March 2001. Results after two years of follow-up were submitted in November 2004. A follow-up diary was issued as a prescription aid from December 1997 to December 2004.

Mean age of patients was 38 years. Mean disease duration was eight years and mean baseline EDSS score was 2.9. Ninety-nine percent (99%) of patients had an EDSS score below 5.5. Mean number of relapses during the three years preceding start of treatment was 3.8.
Three hundred and twenty-one (321) patients (32%) had previously received treatment with another beta interferon (90% as monotherapy), 75% of them for between one and two years. Reasons for changing treatment were medical in 75% of patients, i.e. poor local tolerability (44%), poor general tolerability (29%), lack of efficacy (21%). Twenty-eight (28) patients had previously been treated with immunosuppressants. At inclusion, 51 patients were receiving corticosteroids.

At one year, 732 patients had been followed. One hundred and five (105) patients (14%) had discontinued treatment prematurely. EDSS score had increased by at least one point in 123 patients (data available for 693 EDSS scores). Fifty-seven percent (57%) of patients followed had at least one relapse.

At two years, 524 patients had been followed up; 48% of patients had been lost to follow-up. Two hundred and nine (209) patients (40% of patients followed) had discontinued treatment prematurely:

- loss of efficacy (46%)
- poor general tolerability (26.5%)
- other reasons (22%).

Loss of efficacy was defined as progression to secondary progressive MS (disease progression over six months without relapse) or at least three courses of corticosteroids or ACTH needed during one year of treatment with AVONEX.
A hundred and nine (109) patients discontinued treatment temporarily; mean duration of discontinuation was four months.

EDSS score had increased by at least one point in 100 patients (data available for 489 EDSS scores) at two years. Sixty-seven percent (67%) of patients followed had at least one relapse.

Ninety-six percent (96%) of patients (n=491) had at least one adverse event. Adverse events mainly occurred during the first six months of treatment. The most common events were flu-like syndrome (muscle pain 73%, fever 57%, shivering 59%, sweating 39%), fatigue (76%) and headache (62%). Fourteen percent (14%) of patients had depression during the 24 month follow-up period. Injection site pain was reported by 26% of patients.
Abnormal laboratory values, mainly differential blood count abnormalities, were reported in 38% of patients over the two-year period.

II.4.4 Copaxone

A five-year follow-up study of 1 000 patients treated with Copaxone in France was started in November 2005. Eight hundred and fifteen (815) patients had been enrolled as at 30 March 2008. An intermediate analysis is planned 2.5 years after the end of recruitment, i.e. in 2010.

ADVERSE EFFECTS

I. Interferons

The adverse events most commonly associated with interferon beta are related to a flu-like syndrome. The most commonly reported flu-like symptoms are muscle pain, fever, shivering, excessive sweating, fatigue, headache and nausea. These symptoms tend to be more marked at the start of treatment, becoming less common as treatment continues. Reactions at the injection site (from erythema to necrosis) are common, particularly after subcutaneous administration of interferon. Liver function tests and haematological values may be abnormal. Rare cases of thyroid disorders and other autoimmune diseases have very occasionally been reported.

The Marketing Authorisation for AVONEX was renewed in December 2006. On 16 May 2009, the estimated number of patients exposed was 375 450, representing about 1 250 000 patient-years. The Marketing Authorisation of REBIF was renewed in 2003. The Marketing Authorisation of BETAFERON was renewed in 2005. On 3 November 2009, estimated exposure to REBIF was 720 123 patient-years.

In 2006, on the opinion of the European pharmacovigilance group, the CHMP (Committee for medicinal products for human use) finalised a review of the therapeutic category of all beta interferons licensed for the treatment of multiple sclerosis (AVONEX, BETAFERON and REBIF) concerning the sections relating to contraindications, special warnings and precautions for use, and pregnancy. This review was based on data obtained from clinical trials, postmarketing data and published data. As a result of the review, these sections in the Summary of Product Characteristics (SmPC) for AVONEX, BETAFERON and REBIF were changed:

Deletion of the absolute contraindication in patients with epilepsy whose seizures are not satisfactorily controlled by antiepileptic therapy, and change to the section 'Special warnings' indicating that interferon beta should be administered with caution to patients with a history of seizures and/or to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics.
Modification of the contraindication in pregnant women, restricted to initiation of treatment in pregnancy.
Modification of the contraindication in patients with a history of severe depression with or without suicidal ideation, replaced by patients presenting severe depression and/or suicidal ideation.

With regard to pharmacovigilance monitoring of these products, no recent alerts or major pharmacovigilance problems have been reported.

In 2007, tolerance data collected in children and adolescents made it possible to revise the section "Posology" in the SmPC for interferons:
No formal clinical or pharmacokinetic studies have been carried out in children or adolescents. However, a few published data suggest that the tolerance profile of interferons in adolescents aged 12-16 years is similar to that observed in adults. As there are very few data on their use in children aged under 12 years, interferons should not be used in this population.

II. Glatiramer acetate

The most common adverse events of glatiramer acetate are reactions at the injection site. Immediate post-injection reactions are common, and are usually transient. More severe adverse events such as lipoatrophy and lymphadenopathy may occur.

The first Marketing Authorisation for Copaxone was issued in 1996 (Israel and the United States).
Data from three pivotal studies carried out in RRMS were collected from 269 patients receiving Copaxone and 271 patients receiving placebo. The most common adverse event was a reaction at the injection site (82.5% versus 48% receiving placebo). Immediate post-injection reactions were reported in 41% of patients (versus 20% receiving placebo).

Copaxone is currently licensed in 49 countries. Tolerance data acquired during clinical trials and the periodic tolerance update report for Copaxone covering the period from 01 December 2001 to 30 November 2007 confirm the known tolerance profile of the product. No change to the summary of product characteristics was required. The latest version of the company core data sheet (CCDS) (September 2005) has not needed to be changed since then, and no recommendations for special clinical or laboratory value monitoring have been made.
As at 31 August 2009, more than 162 000 patients have been exposed, representing more than 929 400 patient-years.

TARGET POPULATION

The prevalence[53,54,55] of patients with MS, estimated in several regions in France, is currently more than 100 per 100 000 inhabitants, i.e. between 60 000 and 65 000 patients. It is estimated that 58% of these patients have relapsing-remitting MS, i.e. between 35 000 and 40 000 patients.

According to centralised data at the EDMUS Coordination Centre in Lyon on MS patients who have been seen or hospitalized in one of the 13 French centres participating in the project (more than 18 000 records), 46% of patients with a remitting-relapsing form have been treated with interferon or another disease-modifying therapy.

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USAGE DATA

According to the IMS Permanent Survey of Medical Prescription (EPPM) panel, prescriptions of interferons account for more than 36 000 prescriptions a year (cumulative annual figure, August 2009):

AVONEX	16 418 (45%)
BETAFERON	7 944 (22%)
REBIF	4 402 (12%)
COPAXONE	7 708 (21%)

GERS institute for statistics hospital data:

Common dispensing unit	Units sold in 2008
COPAXONE 20MG INJ SRG1ML	12 180
BETAFERON 250MCG INJ VIAL +SRG	90
BETAFERON 250 INJ VIAL +SRG+NEC	2 385
REBIF 22MCG INJ SRG0.5ML 1	660
REBIF 8.8/22MCG INJ SRG	0
REBIF 44MCG INJ SRG0.5ML	804
AVONEX 30MCG/0.5ML INJ SRG	552

GERS data for community prescriptions:

CIP heading	Units sold in 2008
COPAXONE 20MG INJ SRG1ML 28	64 852
BETAFERON 250MCG INJ VIAL +SRG 15	228
BETAFERON 250 INJ VIAL +SRG15+NEC	44 912
REBIF 22MCG INJ SRG0.5ML 12	16 045
REBIF 8.8/22MCG INJ SRG 12	206
REBIF 22MCG INJ SRG0.5ML 12	41 343
AVONEX 30MCG/0.5ML INJ SRG 4	109 411

CONCLUSION

The following observations may be made in the light of the data from randomised placebo-controlled trials carried out over 2-3 years:

- in patients with relapsing-remitting multiple sclerosis, interferon beta reduces the frequency of relapses by about a third over two years.
- in view of the data from open follow-up under active treatment of patients included in the randomised placebo-controlled trials, interferon may reduce long-term disease progression by reducing the inflammatory process and the frequency of relapses responsible for permanent neurological lesions and residual disability; this effect appears to be modest.
- in patients with a first neurological event consistent with MS, early initiation of treatment with interferon beta delays the second relapse. This effect may persist for more than two years.
- in patients with relapsing-remitting multiple sclerosis, glatiramer acetate reduces frequency of relapses.

Data on long-term disease progression obtained from the observational studies concerned small percentages of patients originally treated, because of the large number of patients lost to follow-up and the percentage of treatment dropouts because of insufficient efficacy or adverse events[56,57] These data do not make it possible to evaluate the effect of these treatments on the irreversible progression of long-term disability or the impact of reduction of relapses on this disability.

Treatment with interferon remains the first-line disease-modifying therapy in RRMS. Glatiramer acetate is also indicated in RRMS but has no proven beneficial effect on disease progression; this immunomodulator is mainly prescribed to patients who cannot tolerate interferon.
Interferon β-1b and interferon β-1a IM are indicated in patients after a first demyelinating event consistent with MS. Criteria predictive of rapidly progressive disease in these patients have yet to be established.
Interferon β-1b is indicated in progressive-relapsing MS (SPMS) on the basis of efficacy data at two years.
None of these treatments has a Marketing Authorisation in primary progressive MS.

It has not been shown that these treatments modify long-term disease progression. Cohort studies describing the natural history of the disease[58,59] before these disease-modifying therapies became generally available, have made it possible to estimate the median time to reaching the main levels of irreversible disability. Disease progression seems to be related to age at disease onset and not to be affected significantly by the initial course of the disease (remitting or progressive); relapses (recurrent multifocal acute inflammation) would appear to have little impact on disease progression (diffuse chronic neurodegeneration).
However, there are two stages in the development of MS: during the first stage, below an irreversible threshold of disability, focal inflammation causes residual deficit and affects the onset of a second, progressive, stage of disease which is independent of focal markers of inflammation[60]; the effect of early treatment on long-term development of disability has not yet been assessed in patients who have been treated from the time of the first demyelinating event.

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Injection site reactions occur frequently during treatment with immunomodulators, particularly after subcutaneous injection. The most common adverse event of interferon is a flu-like syndrome. Glatiramer acetate frequently causes immediate post-injection reactions. Differential blood count with platelets and hepatic enzymes should be monitored at regular intervals in patients treated with interferons.

It is difficult to assess the long-term benefit of treatment with interferon or glatiramer acetate in this disabling disease. The decision to discontinue these treatments should be taken in accordance with clinical criteria suggesting loss of efficacy or limited efficacy (frequency of relapses, development of progressive MS without relapse), onset of adverse events or any desire for pregnancy.

ANNEXES

ANNEX I

Type of study/subject		Search period	Number of references
	Terms used		
Multiple sclerosis/ Guidelines - Consensus conferences		Jan. 2004 - May 2009	108
Step 1	multiple sclerosis/ti,ab OR sclerose plaque/ti,ab OR SEP/ti,ab OR multiple sclerosis/term		
AND			
Step 2	guideline/ti OR recommendation/ti OR recommandation/ti OR guide/ti OR standard/ti OR dt=guideline OR dt=practice guideline OR dt=consensus development conference, NIH OR dt=consensus development conference OR consensus conference/ti,ab OR consensus statement/ti,ab OR consensus/ti		
Interferon beta / Guidelines - Consensus conferences		Jan. 2004 - May 2009	17
Step 3	interferon beta/ti,ab OR IFN beta/ti,ab OR BETAFERON/ti,ab OR avonex/ti,ab OR rebif/ti,ab OR interferon-beta/descripteur OR beta1 interferon/descripteur		
AND			
Step 2			
Interferon beta in MS / Meta-analyses - Systematic reviews		Jan. 2004 - May 2009	23
Step 1 AND Step 3			
AND			
Step 4	metaanalys/ti OR meta analys/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR dt=meta-analysis OR systematic review/ti,ab OR systematic review/de		
Interferon beta in MS /Randomised controlled trials		Jan. 2004 - May 2009	158
Step 1 AND Step 3			
AND			
Step 5	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR dt=randomized controlled trial OR dt=controlled clinical trial OR random allocation/de OR randomization/de OR random/ti OR cross-over studies/de OR crossover procedure/de OR crossover study/de		
Interferon beta in MS / Other clinical trials		Jan. 2004 - May 2009	237
Step 1 AND Step 3			
AND			
Step 6	clinical trial/de OR clinical trials as topic/de OR dt=clinical trial OR case-control stud/de OR retrospective stud/de OR comparative study/de OR dt=comparative study OR versus/ti OR compar/ti		
Interferon beta in MS / Cohort studies		Jan. 2004 - May 2009	69
Step 1 AND Step 3			
AND			
Step 7	cohort stud/de OR cohort stud/ti OR cohort analysis/de OR longitudinal stud/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud/de		

Interferon beta in MS / Other literature reviews		Jan. 2004 - May 2009	84
Step 1 AND Step 3			
AND			
Step 8	review/de OR review literature as topic/de OR bibliographic survey/de OR dt=review		
Interferon beta / Adverse events		Jan. 2004 - May 2009	166
Step 3			
AND			
Step 9	interferon-beta/adverse effects/de OR beta1 interferon/adverse drug reaction/de OR interferon beta/ti OR IFN beta/ti OR BETAFERON/ti OR avonex/ti OR rebif/ti OR interferon-beta/de OR beta1 interferon/de AND toxic/ti OR safe/ti OR tolerance/ti OR adverse effect/ti OR side effect/ti OR adverse event/ti OR secur/ti OR innocuit/ti OR iatrogen/ti OR tolerance/ti OR iatrogenic disease/de OR tolerance management/de OR risk/ti OR risk/de OR risk management/de OR risk assessment/de OR risk adjustment/de OR tolerance management/de OR adverse event/ti OR effet secondaire/ti,ab OR effet indesirable/ti,ab		
glatiramer acetate / Guidelines - Consensus conferences		Jan. 2004 - May 2009	4
Step 10	glatiramer acetate/ti,ab OR acetate glatiramere/ti,ab OR copaxone/ti,ab		
AND			
Step 2			
glatiramer acetate in MS / Meta-analyses - Systematic reviews		Jan. 2004 - May 2009	10
Step 1 AND Step 10 AND Step 4			
glatiramer acetate in MS / Randomised controlled trials		Jan. 2004 - May 2009	36
Step 1 AND Step 10 AND Step 5			
glatiramer acetate in MS Other clinical trials		Jan. 2004 - May 2009	161
Step 1 AND Step 10 AND Step 6			
glatiramer acetate in MS / Cohort studies		Jan. 2004 - May 2009	23
Step 1 AND Step 10 AND Step 7			
glatiramer acetate in MS / Other literature reviews		Jan. 2004 - May 2009	86
Step 1 AND Step 10 AND Step 8			
glatiramer acetate / Adverse events		Jan. 2004 - May 2009	55
Step 10			
AND			
Step 11	toxic/ti OR safe/ti OR tolerance/ti OR adverse effect/ti OR side effect/ti OR adverse event/ti OR secur/ti OR innocuit/ti OR iatrogen/ti OR tolerance/ti OR iatrogenic disease/de OR tolerance management/de OR risk/ti OR risk/de OR risk management/de OR risk assessment/de OR risk adjustment/de OR tolerance management/de OR adverse event/ti OR effet secondaire/ti,ab OR effet indesirable/ti,ab		

ANNEX II

DIAGNOSTIC CRITERIA FOR MS

After Polman CH et al. Diagnostic Criteria for multiple Sclerosis: 2005 Revisions to the "McDonald Criteria"
Ann Neurol 2005;58:840-6.

Clinical presentation	Additional data needed for MS diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None[a]
Two or more attacks; objective clinical evidence of one lesion.	Dissemination in space, demonstrated by: - MRI[b] *or* - Two or more MRI-detected lesions consistent with MS plus positive CSF[c] *or* - Await further clinical attack implicating a lesion in a different site
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: - MRI[d] *or* - Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation, clinically isolated syndrome)	Dissemination in space, demonstrated by: - MRI[b] *or* - Two or more MRI-detected lesions consistent with MS plus positive CSF[c] *and* Dissemination in time, demonstrated by: - MRI[d] *or* - Second clinical attack
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) *and* Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF[c]

a. However, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered.
b. MRI demonstration of space dissemination: Barkhof et al. (1997) and Tintoré (2000).
c. Oligoclonal bands detected by isoelectric focusing or an increased IgG index
d. MRI criteria for dissemination in time: McDonald criteria (2005).

ANNEX III

EDSS: EXPANDED DISABILITY STATUS SCALE

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. one 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 or four FS grade 2, others 0 or 1), 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.
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 some 500 metres.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full 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 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 300 metres.
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities. (Usually, one FS grade 5, others 0 or 1; or combinations of lesser grades 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.
6.0	Intermittent or constant unilateral assistance (cane, crutch, or brace), required to walk about 100 metres with or without resting.
6.5	Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting.
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.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms.
8.5	Essentially restricted to bed for much of the day; has some effective use of arms; retains some self-care functions.
9.0	Helpless bed patient; can communicate and eat.
9.5	Totally helpless bed patient; unable to communicate or effectively eat/swallow.
10	Death due to MS.

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