# Drug Class Review

# Disease-modifying Drugs for Multiple Sclerosis

**Final Update 1 Report**

**August 2010**

**The Agency for Healthcare Research and Quality has not yet seen or approved this report**

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**The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.**

# STRUCTURED ABSTRACT


## Purpose

We compared the effectiveness and safety of disease-modifying drugs for the treatment of multiple sclerosis: Glatiramer acetate (Copaxone®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®).

## Data Sources

We searched Ovid MEDLINE® and the Cochrane Library and the Database of Abstracts of Reviews of Effects through December 2009. For additional data we also hand searched reference lists, government web sites and dossiers submitted by pharmaceutical companies.

## Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

## Results

In patients with relapsing remitting multiple sclerosis, little difference in relapse outcomes were found between interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®), while interferon beta-1a IM (Avonex®) was less effective than interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) based on 4 fair-quality head-to-head trials. Direct evidence from 5 fair-quality head-to-head trials was conflicting on disease progression outcomes between the interferons. Pooled analysis of direct and indirect trial data found no difference between the interferons on changes in disability and no difference between interferon beta-1a SC (Rebif®) and interferon beta-1a IM (Avonex®) on disease progression but did find interferon beta-1b (Betaseron®) to be superior to interferon beta-1a IM (Avonex®) on disease progression (relative risk, 0.48; 95% CI, 0.27 to 0.86). There was no difference in relapse or disease progression between glatiramer and interferon beta-1a SC (Rebif®) or interferon beta-1b (Betaseron®) based on 2 head-to-head trials. Evidence is insufficient to make any judgments regarding effectiveness in primary progressive or secondary progressive multiple sclerosis.

Evidence suggested that 3 interferon beta-1 products and glatiramer reduced the probability of converting from clinically isolated syndrome to clinically definite multiple sclerosis over 2 to 5 year periods.

Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2% to 8.5%, starting around 9 months of treatment. With interferon beta-1a SC (Rebif®) antibodies occurred later with rates of immunogenicity between 12% and 46%, and with interferon beta-1b SC (Betaseron®) neutralizing antibodies appeared as early as 3 months in 30% to 40% of patients. Evidence for interferon beta-1b SC (Betaseron®) and interferon beta-1a SC (Rebif®) indicated that consistent positive neutralizing antibody status with high titer increased relapse rates, by one-half to two-thirds, during longer

periods of follow-up. This difference was not seen with follow-up of 2 years or less, and there was inadequate evidence to conclude that there is an impact on disease progression.

No difference was found in withdrawal rates among beta interferons in head-to-head trials. Transaminase elevations were common with all beta interferon products, with little difference in rates of occurrence. There was a lower rate of depression in patients taking interferon beta-1a (Rebif®) compared with the other interferons based on limited trial data. Interferon beta-1a IM (Avonex®) was associated with the highest rates of flu-like syndrome compared with the other beta interferons. Interferon beta-1b SC (Avonex®) was associated with the lowest rates of injection site reactions whereas interferon beta-1b SC (Betaseron®) and interferon beta-1b SC (Rebif®) had similar rates. Significant long-term concerns included progressive multifocal leukoencephalopathy in patients receiving natalizumab >12 months, lipoatrophy with prolonged use of glatiramer, and permanent amenorrhea in older women receiving higher total dose of mitoxantrone.

There was some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors one product over another. Evidence is insufficient to make conclusions about the safety of these drugs in pregnancy. A post hoc subgroup analysis of a head-to-head trial of interferon beta-1a products (Avonex® and Rebif®) found that African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with white patients over the course of the study.

## Conclusion

There was fair evidence that interferon beta-1a IM (Avonex®) is less effective than interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) for preventing relapse in patients with relapsing remitting multiple sclerosis. On other outcomes and in other populations, direct evidence is either lacking or shows few differences in effectiveness or safety among the disease-modifying drugs used to treat multiple sclerosis.

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*Published in a separate document.*

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# INTRODUCTION

Multiple sclerosis is a chronic, autoimmune disease of the central nervous system affecting 2.1 million people worldwide and approximately 250 000 to 400 000 people in the United States.[2] Most patients are diagnosed between the ages of 20 and 50 years with women being affected to a greater degree than men by a ratio of 1.6 females to 1 male.[2] The highest prevalence of multiple sclerosis is found in Caucasian women, persons of Northern European descent, and in those who live in northern latitudes. Multiple sclerosis can cause physical, mental, and emotional disability in individuals, independent of age. From a societal perspective, in 2004 multiple sclerosis costs were estimated at $47,215.00 per patient per year, including $16,050.00 (34%) spent on disease-modifying drugs used in the treatment of multiple sclerosis.[3]

Diagnostic criteria for multiple sclerosis include a clinical presentation of 2 or more attacks *and* objective clinical evidence of 2 or more lesions in the myelinated regions of the central nervous system found by magnetic resonance imaging.[4] The Revised McDonald Criteria defines an attack as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature.[4] A diagnosis of multiple sclerosis may also be made in a clinically isolated syndrome with presentation of a single attack and evidence of 1 or more lesions. To maintain specificity, criteria have become stricter such that magnetic resonance imaging dissemination in space and time are critical, and cerebral spinal fluid analysis may be needed to identify oligoclonal bands or increased immunoglobulin G that are often present in multiple sclerosis.

Progression of multiple sclerosis is measured by the disability caused by the disease. The Expanded Disability Status Scale is a common measure of multiple sclerosis disability and is the primary clinical outcome in many multiple sclerosis clinical trials.[5, 6] The scale ranges from 0, defined by a normal neurological examination, to 10, defined as death due to multiple sclerosis.[5] An Expanded Disability Status Scale <6 indicates the patient can walk without aid for limited distances.[5] An Expanded Disability Status Scale ≥6 and <8 indicates the patient is severely restricted in movement with aids or assistance.[5] An Expanded Disability Status Scale >8 indicates the person is restricted to a bed, and use of arms and legs are severely restricted.[5] The Multiple Sclerosis Functional Composite is also used to measure disability but has rarely been used as an outcome measure in clinical trials. Four main types of multiple sclerosis have been characterized: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of multiple sclerosis patients have relapsing-remitting multiple sclerosis at the onset of the disease, and about 10% have primary progressive multiple sclerosis.[7] Relapsing-remitting multiple sclerosis is characterized by well-defined acute relapses (attacks) of neurological symptoms followed by full or partial recovery. Relapsing-remitting multiple sclerosis rarely progresses between relapses, although the patient may never fully recover after a relapse. On the contrary, primary progressive multiple sclerosis progresses from the onset without acute attacks. Most patients with relapsing-remitting multiple sclerosis will eventually develop secondary progressive multiple sclerosis, which is a progressive form of the disease that may or may not have superimposed relapses. Progressive relapsing multiple sclerosis occurs in about 5% of the multiple sclerosis population and progresses from the onset with superimposed relapses of neurological symptoms followed by full or partial recovery.[7]

Multiple sclerosis causes demyelination of neuronal axons that form lesions within the white matter of the central nervous system (cerebral white matter, brain stem, cerebellar tracts, optic nerves, or spinal cord) when viewed on a magnetic resonance imaging. Demyelination may

cause an abnormal proliferation of sodium channels within the membrane that slows, or even blocks, axonal conduction.[8] A sodium-calcium exchanger is also upregulated within the membrane, which increases sodium efflux and calcium influx and results in neuronal degeneration.[8] The impairment of conduction down neurons ultimately causes the neurological symptoms associated with multiple sclerosis. Indeed, the classification of symptoms as monofocal or multifocal are often associated with the location and number of lesions in the central nervous system. For example, vision loss reflects a lesion in the optic nerve.

Although more data is becoming available, the pathogenesis of multiple sclerosis remains elusive. Myelin-reactive T cells and B cells are present in multiple sclerosis.[7] Environmental factors, such as infectious agents, seem to facilitate the movement of these cells from the periphery, across the blood brain barrier, and into the central nervous system in persons genetically susceptible to multiple sclerosis. The migration of T cells and antibodies across the blood brain barrier occurs because adhesion molecules, in addition to proteases that break down the endothelial cells that make up the barrier, are activated.[7] Once within the central nervous system, the T cells secrete interferon γ and interleukin 17.[7] The antigen-presenting cells and T helper cells form a complex by binding to a self-antigen, such as myelin basic protein via the major histocompatibility complex and T cell receptor, respectively.[7] Antigen presentation to these cells causes an enhanced immune response. Depending on other interacting molecules, the T helper cell-antigen-presenting cell complex may cause type 1 T helper cells (Th1) to secrete pro-inflammatory cytokines, such as interferon γ, or type 2 T helper cells (Th2), to secrete anti-inflammatory cytokines, such as interleukin 4. Macrophages, cytotoxic T cells, auto-antibodies secreted from B cells, and pro-inflammatory cytokines secreted from T helper cells are also activated during this process.[8]Acute inflammatory, demyelinating plaques occur when myelin undergoes phagocytosis by macrophages when coated with antibodies for myelin basic protein and myelin oligodendrocyte glycoprotein.[8] In addition, cytotoxic T cells and pro-inflammatory cytokines may directly damage the myelin.[8]

The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management with appropriate agents, and disease modification with disease-modifying drugs. For example, when acute exacerbations occur (such as vision loss or loss of coordination), they are commonly treated with a short duration of high-dose oral or intravenous corticosteroid. If spasticity occurs, it can be addressed with muscle relaxants, however therapy with disease-modifying drugs is designed to prevent relapses and progression of disability rather then treat specific symptoms or exacerbations of the disease. These agents modify the immune response that occurs in multiple sclerosis through various immunomodulatory or immunosuppressive effects. Table 1 summarizes the pharmacology, dosing, and indications of the current disease-modifying drug treatments options for multiple sclerosis.

## Table 1. Pharmacology, indications, and dosing of included drugs[9-15]

| Agent | Dosage and administration | Indication | Mechanism of Action |
|---|---|---|---|
| Glatiramer Acetate Copaxone® | 20 mg Subcutaneously QD | Reduce frequency of relapses in patients with RRMS including patients who experienced a first clinical episode and have MRI features consistent with MS | May interfere with antigen presentation by mimicking and competing with MBP, a self-antigen, for binding to the MHC on the APC. The glatiramer-MHC competes with the MBP-MHC for binding to the TCR on T helper cells, which down-regulates Th1 activity and promotes a Th2 cell response, leading to increased anti-inflammatory cytokine production |
| Interferon beta-1a Avonex®, Avonex PS | 30 mcg Intramuscularly 1x/wk | Treatment of patients with relapsing forms of MS to slow accumulation of physical disability and decrease frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS | Modulates the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of metalloproteases on the vascular endothelium that constitutes the blood brain barrier. These agents may also inhibit the generation of pro-inflammatory cytokines from Th1 cells (TNFα, IFNγ, IL-12). |
| Interferon beta-1a Rebif® | 22 or 44 mcg Subcutaneously 3x/wk | Treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability | |
| Interferon beta-1b Betaseron® | 0.25 mg Subcutaneously Every other day | Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS | |
| Interferon beta-1b Extavia® | 0.25 mg Subcutaneously Every other day | Treatment of relapsing forms of MS to reduce frequency of clinical exacerbations. Effective in patients who experienced a first clinical episode and have MRI features consistent with MS | |

| Agent | Dosage and administration | Indication | Mechanism of Action |
|---|---|---|---|
| Mitoxantrone Novantrone®[a] | 12 mg/m$^2$ Intravenously Every 3 mos (Max cumulative dose is 140 mg/m$^2$) | Reduce neurologic disability and/or the frequency of clinical relapses in SPMS, PRMS or worsening RRMS | Inhibits cell division and impairs the proliferation of T cells, B cells and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs. |
| Natalizumab Tysabri®[b] | 300 mg Intravenously Every 4 wks | Treatment of relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce frequency of clinical exacerbations | Binds to $\alpha_4$ integrins expressed on leukocytes, which prevents binding to adhesion cells VCAM-1 and MAdCAM-1 on the vascular endothelium and prevents migration of leukocytes from the periphery into the CNS. |

Abbreviations: APC, antigen-presenting cell; CIS, clinically isolated syndrome; CNS, central nervous system; DNA, deoxyribonucleic acid; IL, interleukin; MAdCAM-1, mucosal vascular addressin cell adhesion molecule-1; MBP, myelin basic protein; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; MS, multiple sclerosis; RNA, ribonucleic acid; PRMS, progressive relapsing multiple sclerosis; PS, prefilled syringes; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TCR, T cell receptor; Th, T-helper; TNF, Tumor Necrosis Factor; VCAM-1, vascular cell adhesion molecule-1; wk, week.
[a] Generic products available in Canada.
[b] Recommended for patients who have had an inadequate response to or are unable to tolerate an alternate multiple sclerosis therapy.

Four of the immunomodulatory agents are type 1 beta interferons: interferon beta-1b SC (Betaseron® and Extavia®) and interferon beta-1a IM and SC (Avonex® and Rebif®). Extavia (interferon beta-1b SC) is the same medicinal product and contains the same active ingredients as Betaseron. It was approved by the US Food and Drug Administration in August 2009 using the clinical trials in the Betaseron Prescribing Information. The fifth agent is glatiramer acetate (Copaxone®).

Natalizumab (Tysabri®) was initially approved by the US Food and Drug Administration in November 2004, withdrawn by the manufacturer in February 2005 due to safety concerns, and reintroduced in June 2006. In February 2010, the US Food and Drug Administration issued a safety announcement alerting the public that the risk of developing progressive multifocal leukoencephalopathy, associated with the use of natalizumab (Tysabri®), increases with the number of Tysabri® infusions received. This new safety information, based on reports of 31 confirmed cases of progressive multifocal leukoencephalopathy received by the US Food and Drug Administration as of January 21, 2010, will now be included in the Tysabri® drug label and patient *Medication Guide.* Since the US Food and Drug Administration safety announcement, the number of progressive multifocal leukoencephalopathy cases has increased, with 55 cases reported as of June 7, 2010 (http://www.reuters.com/article/idUSN1725307720100617). In addition, the US Food and Drug Administration information about the occurrence of immune reconstitution inflammatory syndrome in patients who have developed progressive multifocal leukoencephalopathy. The following is an excerpt from the US Food and Drug Administration statement about the drug's reintroduction in 2006:

*Tysabri® is available only through the Risk Management Plan, called the TOUCH Prescribing Program. In order to receive Tysabri®, patients must talk to their doctor and understand the risks and benefits of Tysabri® and agree to all of the instructions in the TOUCH Prescribing Program.*

Mitoxantrone (Novantrone®) is an antineoplastic agent originally approved for adult acute myeloid leukemia and later approved for secondary progressive, progressive relapsing, and worsening relapsing-remitting multiple sclerosis as an immunosuppressant drug. This drug carries a black box warning about the risk of cardiotoxicity and acute myelogenous leukemia and has a lifetime cumulative dose limit of 140 $mg/m^2$.

## Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the efficacy and effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians and then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

## Scope and Key Questions

The purpose of this review is to compare the effectiveness and safety of different disease-modifying drugs for the treatment of multiple sclerosis. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?

2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of interferon beta neutralizing antibodies?

3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?

4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

5. Do disease-modifying treatments for multiple sclerosis differ in harms?

6. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

# METHODS

## Inclusion Criteria

### *Population(s)*

- Adult outpatients (age ≥18 years) with multiple sclerosis[16, 17]
    - Relapsing-remitting multiple sclerosis
    - Secondary progressive multiple sclerosis
    - Primary progressive multiple sclerosis
    - Progressive relapsing multiple sclerosis
- Adult outpatients with a clinically isolated syndrome (also known as "first demyelinating event", first clinical attack suggestive of multiple sclerosis, or monosymptomatic presentation).[17]

### *Interventions (all formulations)*

The following 7 drugs are available in the United States and Canada. Black box warnings associated with each drug are listed in Appendix B.

- Glatiramer acetate (Copaxone®)
- Interferon beta-1a (Avonex®, Rebif®)
- Interferon beta-1b (Betaseron®, Extavia® [not available in Canada])
- Mitoxantrone (Novantrone®)
- Natalizumab (Tysabri®)

### *Effectiveness outcomes*

Multiple sclerosis

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)

Clinically isolated syndrome

- Disability
- Clinical exacerbation/relapse of symptoms
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to multiple sclerosis diagnosis

*Note: Magnetic resonance imaging findings are not included, as they are intermediate or surrogate outcomes.*

### *Harms*

- Overall rate of adverse effects
- Withdrawals due to adverse effects
- Serious adverse events
- Specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy, secondary cancers, etc.)

### *Study designs*

- For effectiveness, controlled clinical trials and good-quality systematic reviews. Observational studies with 2 concurrent arms of at least 100 patients each and duration ≥1 year are included (e.g. cohort, case-control).
- For harms, in addition to controlled clinical trials, observational studies are included.

## Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1966 - December 2009), the Cochrane Database of Systematic Reviews® (4th quarter 2009), the Cochrane Central Register of Controlled Trials® (4th quarter, 2009), and the Database of Abstracts of Reviews of Effects (4th Quarter 2009) using terms for included drugs, indications, and study designs (see Appendix C for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technology in Health, and the National Institute for Health and Clinical Excellence web sites for medical and statistical reviews and technology assessments. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® XI, Thomson Reuters).

## Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Results published *only* in abstract form were not included because inadequate details were available for quality assessment, however if we were provided with enough information to conduct quality assessment we did include the study. Additional results from fully published studies (e.g. relating to secondary outcome measures) found only in abstract form were included because the study quality could be assessed through the complete publication.

## Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. Data were abstracted by one reviewer and checked by a second. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available.

## Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[18, 19] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had fatal flaws were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid in that the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist.

A particular randomized trial might receive 2 different ratings: 1 for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

The criteria for observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality (see appendix C) based on pre-defined criteria, based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

## Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[20] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk

of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of disease-modifying drugs for multiple sclerosis. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

We chose outcomes related to relapse and disease progression. Magnetic resonance imaging findings were considered intermediate outcomes and were not assessed.

**Table 2. Definitions of the grades of overall strength of evidence [21]**

| Grade | Definition |
|---|---|
| High | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. |
| Low | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. |
| Insufficient | Evidence either is unavailable or does not permit estimation of an effect. |

## Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated 1 disease-modifying drug for multiple sclerosis against another provided *direct* evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare a disease-modifying drug for multiple sclerosis to placebo can also provide evidence about effectiveness.[22, 23] This is known as an *indirect* comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Data from indirect comparisons are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and heterogeneity across studies in study design, patient

population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Random-effects models were used to estimate pooled effects.[24] The Q statistic and the $I^2$ statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[25, 26] Meta-analysis was performed using Stats Direct (Cam code, United Kingdom) and the meta package in R.[27]

If necessary, indirect meta-analyses were done to compare interventions for which there were no head-to-head comparisons and where there was a common comparator intervention across studies. We used the method described by Bucher et al, to perform indirect analyses.[23] Indirect comparisons usually agree with direct comparisons, though large discrepancies have been reported in some cases.[28, 29] In addition, indirect comparisons also result in less precise estimates of treatment effects compared with the same number of similarly sized head-to-head trials because methods for indirect analyses incorporate additional uncertainty from combining different sets of trials.[22, 23] Because of this, we pursued an exploratory analysis combining the indirect and direct pooled estimates using a Bayesian approach. Data from indirect comparisons was synthesized with data from direct, head-to-head studies when possible. Using a Bayesian data analytical framework, effect size estimated from the indirect analysis was used as the prior probability distribution in a meta-analysis of the data from the direct head-to-head studies. Bayesian analysis was conducted using Open BUGS and the BRugs package in R.[27, 30]

### Peer Review and Public Comment

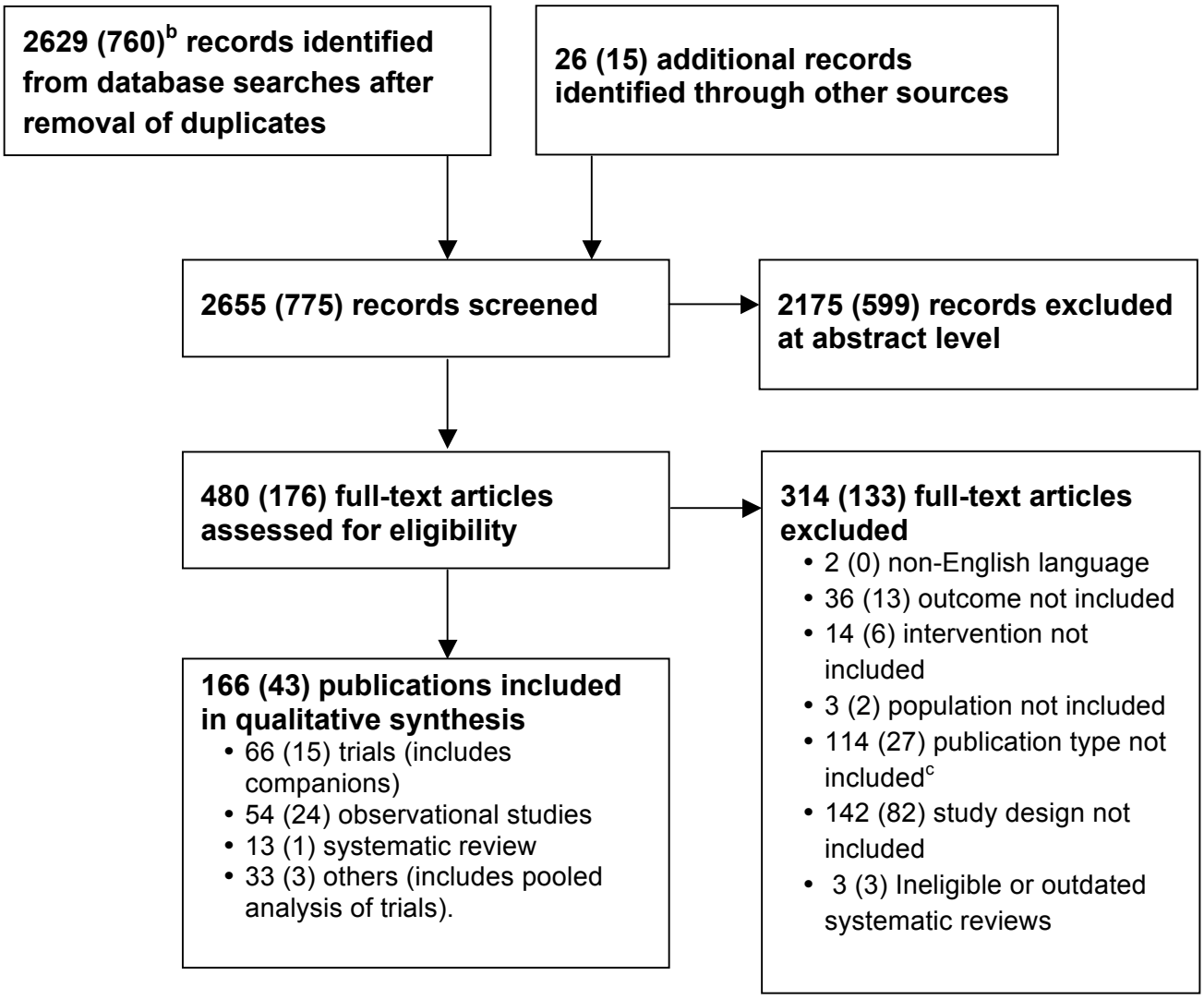
We requested and received peer review of the report from 2 content and methodology experts. Their comments were reviewed and, where possible, incorporated into the final document. A draft of this report was also posted to the Drug Effectiveness Review Project website for public comment. We received comments from 6 pharmaceutical companies. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

## RESULTS

### Overview

Literature searches identified 2655 citations. For Update 1, we received dossiers from 5 pharmaceutical manufacturers: Bayer, Biogen Idec, EMD Serono Inc., Novartis, and Teva Neuroscience Inc. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 480 citations. After re-applying the criteria for inclusion, we ultimately included 166 publications, comprising 43 for Update 1. See Appendix D for a list of excluded studies and reasons for exclusion at this stage. Figure 1 shows the flow of study selection. Throughout the report we generally refer to the included drugs by their full name, including trade name. This was done in an effort to avoid confusing the drugs, particularly the beta interferons, which have differing doses and routes of administration.

**Figure 1. Results of literature search[a]**




[a] A modified PRISMA diagram was used.[1]
[b] Numbers in parentheses are results of the literature search new to Update 1.
[c] Includes letter, editorial and non systematic review.

## Key Question 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?

## Summary of the Evidence

### *Relapsing-remitting multiple sclerosis*

#### Beta interferons

- In placebo-controlled trials, the rates of progression in beta interferon groups at 2 years ranged from 11.4% to 26.6% compared with 20.3% to 36.4% in placebo groups, while in the head-to-head trials the rates ranged from 13% to 57%. Annualized relapse rates for beta interferon groups ranged from 0.61 to 1.83 in placebo-controlled trials compared with 0.9 to 2.56 in placebo groups and 0.5 to 0.71 in head-to-head trials.
- The evidence supported a benefit of interferon beta-1b SC (Betaseron®) over interferon beta-1a IM (Avonex®) in relapse outcomes (% relapse-free relative risk, 1.51; 95% CI, 1.11 to 2.07; number needed to treat, 6). There was conflicting evidence on disease progression outcomes with only 1 trial reporting on percent progressed and finding a significant benefit of interferon beta-1b SC (Betaseron®) over interferon beta-1a IM (Avonex®) (relative risk, 0.44; 95% CI, 0.25 to 0.79; number needed to treat, 6), however, despite a trend toward benefit, there was no statistically significant difference in mean change in Expanded Disability Status Scale score (−0.330; 95% CI, −0.686 to +0.025).
- Three head-to-head trials suggested a benefit of interferon beta-1a SC (Rebif®) over interferon beta-1a IM (Avonex®) in terms of relapse outcomes. No differences in disease progression outcomes were found, although the larger trial followed patients for only 16 months such that differences may not yet have been seen. Indirect analyses of placebo-controlled trial data did not result in a significant difference. A Bayesian analyses did agree with the results for the outcome of being relapse-free.
- Current evidence is unable to identify differences between interferon beta-1b SC (Betaseron®) and interferon beta-1a SC (Rebif®) in terms of effectiveness. Indirect analyses of placebo-controlled trial data and a Bayesian analyses agreed with these results.

#### Glatiramer acetate

- No difference in relapse related outcomes were seen in head-to-head trials comparing glatiramer acetate (Copaxone®) and interferon beta-1b SC (Betaseron®) or interferon beta-1a (Rebif®). In trials comparing glatiramer acetate to placebo, there was no difference in percentage of relapse-free patients (relative risk, 1.23; $P$=0.086). The mean difference in relapse rate between glatiramer acetate and placebo was statistically significant (−0.64; 95% CI, −1.19 to −0.09; $P$=0.02) when results from 3 trials were pooled.
- The effect of glatiramer acetate on disease progression was unclear. There was no statistically significant difference in disease progression between glatiramer acetate and interferon beta-1b SC (Betaseron®) or interferon beta-1a (Rebif®) in head-to-head trials.
- Mean change in Expanded Disability Status Scale was reported as a secondary outcome in 1 placebo-controlled trial. Two-year data showed that while glatiramer acetate was associated with a statistically significant ($P$=0.023) change in Expanded Disability Status

Scale (−0.05) when compared with placebo (0.21), the clinical significance of such a difference is questionable.

### Natalizumab

- Natalizumab (Tysabri®) was consistently more effective than placebo for both relapse-related outcomes and disease progression in 2 trials. One of those trials included interferon beta-1a IM (Avonex®) used concomitantly with the natalizumab and placebo arms, however this did not appear to impact the findings of that trial in terms of effectiveness outcomes.

### Mitoxantrone

- Limited evidence from 1 small trial showed that mitoxantrone (Novantrone®) was more effective than placebo for both disease progression and relapse rate.

## *Secondary progressive multiple sclerosis*

### Beta interferons

- Based on 5 placebo-controlled trials, there is evidence that interferon beta-1b SC (Betaseron®) was effective in slowing progression in patients with secondary progressive multiple sclerosis, particularly those with more active disease. Evidence for the beta-1a interferons (IM or SC; Avonex® or Rebif®) was less convincing for slowing progression based on the Expanded Disability Status Scale, although the newer measure, the Multiple Sclerosis Functional Composite, allowed a benefit to be seen with interferon beta-1a IM (Avonex®). Whether this difference is clinically important and the other beta interferons would have a similar impact is not clear. Studies indicated that all of the beta interferons do have an impact by reducing relapse rates. Again, those with more active disease appeared to benefit more.
- No studies of natalizumab (Tysabri®) or mitoxantrone (Novantrone®) in patients with secondary progressive multiple sclerosis were found.

## *Mixed populations: Relapsing-remitting and secondary progressive multiple sclerosis*

### Beta interferons

- Quality of life improved with interferon beta-1b SC (Betaseron®)-treated patients when compared with untreated controls, however the effect diminished based on higher baseline disability scores.

### Natalizumab

- Based on limited data from 4 trials, there was no statistically significant difference between natalizumab (Tysabri®) and placebo in change in Expanded Disability Status Scale, although 1 of the trials did find that natalizumab significantly impacted relapse rate. These findings must be interpreted with extreme caution as these trials were of relatively

short durations and this finding was markedly different from that of the 2 larger natalizumab trials in relapsing-remitting multiple sclerosis patients alone.

### Mitoxantrone

- Pooled data from 4 trials provided evidence that mitoxantrone (Novantrone®) was superior to placebo for relapse-related outcomes and disease progression.

## *Primary progressive multiple sclerosis*

- One systematic review of 2 small trials comparing interferon to placebo (1 interferon beta-1a IM [Avonex®] and 1 interferon beta-1a SC [Betaseron®]) found no difference in relapse related and disease progression outcomes when the data was pooled. The pooling did not allow for comparative effectiveness and results were limited by the small number (N=143).
- One indirect study (N=943) found no difference in delay in time to sustained disability based on changes in Expanded Disability Status Scale scores (hazard ratio, 0.87; 95% CI, 0.71 to 1.07).
- No studies of natalizumab (Tysabri®) or mitoxantrone (Novantrone®) in patients with primary progressive multiple sclerosis were found.

## *Mixed populations: Primary and secondary progressive multiple sclerosis*

### Glatiramer acetate

- In a 2-site study conducted in a "chronic progressive" patient population, glatiramer acetate (Copaxone®) was found to be superior to placebo for disease progression and Expanded Disability Status Scale change at 24 months at 1 of 2 centers. There were no other significant differences between the glatiramer acetate and placebo groups in effectiveness outcomes. No studies of beta interferons, natalizumab, or mitoxantrone in a mixed primary and secondary progressive multiple sclerosis population were found.

## *Progressive relapsing multiple sclerosis*

- No studies were identified that assessed the use of 1 of the included drugs in patients with progressive relapsing multiple sclerosis.

## *Mixed populations: Clinically isolated syndrome + relapsing-remitting multiple sclerosis*

- One small fair-quality study compared interferon beta-1b SC (Betaseron®) to glatiramer acetate and found no difference on relapse related outcomes.

## Detailed Assessment

### *Previously conducted systematic reviews of disease-modifying drugs for multiple sclerosis*

We found 6 systematic reviews that assessed multiple drugs for the treatment of multiple sclerosis.[31-37] One of these reviews was updated in 2009 but without new evidence of the outcomes of interest this review was not analyzed further.[38] One review focused on treatment of symptoms rather than disease modification and will not be discussed here.[33] Another focused on the association of depression with beta interferon and glatiramer acetate treatment and is discussed under Key Question 3 below.[34] The 4 remaining reviews included beta interferons, glatiramer acetate, and mitoxantrone. The best quality review was the one conducted for the National Institute for Clinical Excellence by Clegg and Bryant and a related article that updated that review.[31, 32] This review assessed the general effectiveness of the interventions compared with placebo. No attempts were made to compare the drugs to one another; however the review will be used in the appropriate sections below. Additional systematic reviews of individual drugs are considered as appropriate below.

### *Relapsing-remitting multiple sclerosis*

#### Beta interferons

While we found 1 systematic review that directly compared the interferons,[37] 2 additional studies directly comparing beta interferons have since been published, limiting the usefulness of that review for our purposes.

##### *Direct evidence*

Five trials directly compared one beta interferon to another, ranging from 16 to 24 months in duration in patients with relapsing-remitting multiple sclerosis.[39-43] While these were all fair-quality trials, there was variation in their features and risk of bias. However, none met all criteria for good quality, and none presented sets of flaws that appeared to indicate high risk for bias. The INCOMIN trial of interferon beta-1a IM (Avonex®) and interferon beta-1b SC (Betaseron®) was open-label, while the other 4 were single-blinded studies. The EVIDENCE trial compared the [2] beta-1a interferons to each other and original data was published in 2002.[44] A crossover phase followed in which all patients were either switched to or continued on interferon beta-1a SC (Rebif®). Given the lack of comparative data on this crossover phase, it will only be included in the discussion of harms that follows.[45] The 2 Etemadifar trials compared all 3 beta interferons to another, and in the most recent trial, also to azathioprine. This later study did not report relapse related outcomes.[43] Both Etemadifar studies were small, ≤30 patients per group and as low as 13 in the second trial. In the first trial, the baseline mean or median Expanded Disability Status Scale in the groups ranged from 1.9 to 2.98 and the mean number of relapses in the 2 years prior to the study ranged from 1.38 to 3.2. In the second trial the mean baseline Expanded Disability Status Scale score was 1.55 and although the authors provide data on the mean Expanded Disability Status Scale score for each drug, it was not designed to compare the 3 drugs to each other. While dosing for interferon beta-1b SC (Betaseron®) 250 µg every other day and interferon beta-1a IM (Avonex®) 30 µg once weekly were consistent across the studies, the dosing for interferon beta-1a SC (Rebif®) ranged from 22 µg *once weekly* to 44 µg 3 times a

week. Additionally, the Danish Multiple Sclerosis Study Group patients were more severely ill compared with the other studies, and the studies differed in terms of whether the endpoint reported was primary or secondary. Results from these trials are presented in Tables 3 and 4 below. We limited the pooling of data to the 44 µg dose of interferon beta-1a SC (Rebif®) only. Overall, these studies supported the use of the beta interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes.

### Table 3. Relapse-related outcomes in trials comparing beta interferons

| Study<br>N, duration | Intervention, dose | Annualized relapse rate | Relapse-free (%) | Rate of steroid use |
|---|---|---|---|---|
| Durelli 2002<br>INCOMIN trial<br>N=188, 2 years | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | 0.7 vs. 0.5<br>*P*=0.03 | 36% vs. 51%<br>*P*=0.03 | 0.5 vs. 0.38<br>*P*=0.09 |
| Panitch 2002<br>EVIDENCE trial<br>N=677, 16 months | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg | 0.65 vs. 0.54<br>*P*=0.033 | 48% vs. 56%<br>*P*=0.023 | 0.28 vs. 0.19<br>*P*=0.033 |
| Koch-Henriksen 2006<br>Danish Multiple Sclerosis Study Group<br>N=301, 2 years | Interferon β-1a SC (Rebif®) 22 mcg *weekly* vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | 0.70 vs. 0.71<br>*P*=0.91 | NR | 0.21 vs. 0.20<br>*P*=0.77 |
| Etemadifar 2006<br>N=90, 2 years | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | (mean) 1.2 vs. 0.6 vs. 0.7 | 20% vs. 57% vs. 43% *P*<0.05<br>Betaseron® vs. Rebif® *P*=0.3017 | NR |
| Pooled Relative Risk | Interferon β-1b SC (Betaseron®) 250 mcg vs.<br>Interferon β-1a IM (Avonex®) 30 mcg | -- | **RR 1.51 (1.11 to 2.07)**[a] | -- |

Abbreviations: IM, intramuscular; SC, subcutaneous.
[a] RR = Relative risk (95% confidence interval), random effects model.

## Table 4. Disease progression-related outcomes in trials comparing beta interferons

| Study<br>N, duration | Intervention, dose | Disease progression[a] | Mean change in EDSS | Mean EDSS at endpoint |
|---|---|---|---|---|
| Durelli 2002<br>INCOMIN trial<br>N=188, 2 years | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | 30% vs. 13%<br>*P*=0.0036 | 0.54 vs. 0.13<br>*P*<0.0001 | 2.5 vs. 2.1<br>*P*=0.0002 |
| Koch-Henriksen 2006<br>Danish Multiple Sclerosis Study Group<br>N=301, 2 years | Interferon β-1a SC (Rebif®) 22 mcg weekly vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | 36% vs. 33%<br>*P*=0.3736 | NR | NR |
| Etemadifar 2006<br>N=90, 2 years | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | NR | −0.1 vs. −0.3 vs. −0.7<br>Interferon β-1b SC (Betaseron®) vs. Interferon β-1a SC (Rebif®) *P*=0.001 | 1.8 vs. 1.8 vs. 1.2<br>Interferon β-1b SC (Betaseron®) vs. Interferon β-1a SC (Rebif®) *P*=0.0023 |
| Etemadifar 2007<br>N=47, 1 year | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg vs.<br>Interferon β-1b SC (Betaseron®) 250 mcg | NR | −0.2 vs −0.4 vs −0.1 *P*<0.05 | 1.4 (0.7 SD) vs 1.2 (0.7 SD) vs 1.4 (1.0 SD) |
| Panitch 2002<br>EVIDENCE trial<br>N=677, 16 months | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg | 54% vs. 57% | NR | NR |
| Pooled weighted mean difference: | Interferon β-1b SC (Betaseron®) 250 mcg vs.<br>Interferon β-1a IM (Avonex®) 30 mcg | -- | −0.330 (95% CI, −0.686 to 0.025)<br>$I^2$=59.9% | -- |
| Pooled weighted mean difference EDSS: | Interferon β-1a IM (Avonex®) 30 mcg vs.<br>Interferon β-1a SC (Rebif®) 44 mcg | -- | 0.200 (95% CI, −0.076 to 0.476)<br>$I^2$=0% | |

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; NR, not reported; SD, SC, subcutaneous.
[a] Weighted mean difference, random effects model.

### *Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a SC (Rebif®)*

One small study by Etemadifar (2007) showed a statistically significant improvement in Expanded Disability Status Scale scores with interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®), whereas an earlier trial by Etemadifar found interferon beta-1b SC (Betaseron®) numerically superior to interferon beta-1a SC (Rebif®) for outcomes related to disease progression (endpoint and mean change in Expanded Disability Status Scale; see Table 4 above).[41, 43] Due to the significant heterogeneity between the 2 studies, the results could not be combined ($I^2$=83.1%). In both trials, the difference between the scores was small, most likely were not clinically important, and given the discrepant results, conclusions could not be made. Only the earlier Etemadifar study evaluated relapse related outcomes and found no difference between interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®). Koch-Henrikson enrolled a somewhat more severely ill population and used a lower dose of interferon beta-1a SC (Rebif®) dosed once weekly. They did not find significant differences in annualized relapse rates, rate of steroid use, or the proportion with disease progression at 2 years. Other outcomes reported in the Koch-Henriksen trial also were unable to identify a difference between the 2 beta interferons, including exacerbations requiring

hospitalization and time to confirmed progression. The lower dose and dosing frequency in this trial limits our ability to draw conclusions from this trial.

***Interferon beta-1a IM (Avonex®) compared with interferon beta-1a SC (Rebif®)***

Three trials compared the 2 forms of interferon beta-1a SC (Rebif®) and IM (Avonex®).[39, 41, 43] Two trials found higher rates of patients who were relapse-free at the end of the study in the interferon beta-1a SC (Rebif®) groups compared with interferon beta-1a IM (Avonex®).[39, 41] Statistical heterogeneity was large enough to discourage statistical pooling in this case ($P$=0.0278). Additionally, the EVIDENCE trial[39] also found interferon beta-1a SC (Rebif®) superior to interferon beta-1a IM (Avonex®) in annualized relapse rates (a secondary outcome measure in this trial), the use of steroids to treat relapse, and in the time to first relapse (median 13.4 months compared with 6.7 months; hazard ratio, 0.70; 95% CI, 0.56 to 0.88). The Etemadifar trials did not report these outcomes, but 1 trial did report a greater change in relapses per person-per year in the interferon beta-1a SC (Rebif®) group compared with the interferon beta-1a IM (Avonex®) group (1.8 compared with 0.8; $P$<0.001).[41]

Disability-related outcomes were reported differently in the trials, but statistically significant differences between the drugs were not found.[39, 41, 43] Disease progression was very similar in the EVIDENCE study regardless of the classification scheme, although this study was only 16 months in duration, shorter than the standard 2 years for monitoring progression of multiple sclerosis. The Expanded Disability Status Scale at endpoint was identical between the groups in the 2 studies. While Etemadifar noted that the change from baseline Expanded Disability Status Scale was statistically significant in the interferon beta-1a SC (Rebif®) group in both trials (mean change 0.3 and 0.4) and not in the interferon beta-1a IM (Avonex®) group (mean change 0.1 and 0.2), the combined mean difference did not find this to be statistically significant. Additionally, the difference between the scores was small and most likely not clinically important.[39, 43]

***Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a IM (Avonex®)***

Three trials evaluated the comparison of interferon beta-1b SC (Betaseron®) and interferon beta-1a IM (Avonex®) with only 2 reporting relapse-related outcomes. They found higher rates of patients who were relapse-free at 2 years with interferon beta-1b SC (Betaseron®) (pooled relative risk, 1.51; 95% CI, 1.11 to 2.07).[41, 42] However, data for disease progression were conflicting. The mean change in the Expanded Disability Status Scale was greater with interferon beta-1a IM (Avonex®) in the Durelli trial (INCOMIN) and the second Etemadifar trial, but larger with interferon beta-1b SC (Betaseron®) in the first trial by Etemadifar. The combined weighted mean difference was −0.330 (95% CI, −0.686 to +0.025; $I^2$=59.5%), indicating no significant difference. The INCOMIN trial was the only 1 of the 3 that measured disease progression and found it to be significantly lower in the interferon beta-1b SC (Betaseron®) group compared with the interferon beta-1a IM (Avonex®) group. Of the 5 head-to-head trials, these 3 represented the lowest-quality evidence such that these findings should be interpreted with caution.

***Observational studies***

Of 5 published observational studies, 3 met inclusion criteria.[46-49] The best of these studies was a retrospective cohort study based on data from patients in Austria, Switzerland, and Germany, with 4754 patients exposed to 1 of the 3 interferons.[49] Eighty-four percent of these patients were exposed to the interferon as their first disease-modifying drug. The group receiving interferon

beta-1b (Betaseron®) was older, had multiple sclerosis longer, and had higher baseline Expanded Disability Status Scale scores compared with the other groups, and the group receiving interferon beta-1a SC 44 mcg (Rebif®) was smaller and patients were more likely to be receiving it as "follow-up" therapy, rather than initial therapy. In the "initial therapy" group the analyses of disability data revealed no differences in the mean change in Expanded Disability Status Scale among the groups, but for the proportion progression-free at 2 years, interferon beta-1a IM (Avonex®) was found superior to interferon beta-1b (Betaseron®) (83.4% compared with 76.2%; *P*=0.001), and superior to interferon beta-1a SC 44 mcg (Rebif®) group (83.4% compared with 69.4%; *P*<0,001), but not significantly different to interferon beta-1a SC (Rebif®) 22 µg (83.4% compared with 82.9%). The analyses controlled for baseline Expanded Disability Status Scale, age, and duration of multiple sclerosis, but an analysis of patients who received treatment within 1 year of diagnosis revealed no differences among the drugs. No differences were found between the drugs based on relapse rates over 1 and 2 years, including the group treated within 1 year of diagnosis.

### *Indirect evidence*

Multiple systematic reviews have reviewed placebo-controlled trials of beta interferons.[31, 32, 35, 50] Two good-quality and comprehensive reviews included all the studies relevant to this review.[31, 50] The review by Rice et al conducted for the Cochrane Collaboration pooled all interferons together, including interferon α, while the review by Clegg and Bryant considered data on the 2 interferon beta-1a products together. These reviews were based on the 5 trials of beta interferons; a pilot study and a multicenter trial of interferon beta-1b SC (Betaseron®),[51, 52] 1 multicenter trial of 2 doses of interferon beta-1a IM (Avonex®),[53, 54] and 2 trials of interferon beta-1a SC (Rebif®) (1 including 2 doses 3 times weekly compared with placebo, the other comparing the same 2 doses once weekly to placebo but only 48 weeks in duration).[55, 56] The authors of these reviews identified multiple problems with some of these studies, including the poor blinding in the study of interferon beta-1b SC (Betaseron®) and the early discontinuation and lack of intention-to-treat analysis in the trial of interferon beta-1a IM (Avonex®). Table 5 summarizes the findings reported in these reviews. Although the trials included different doses of interferon beta-1a SC (Rebif®), the authors only pooled the standard dosing data of 44µg 3 times weekly.

## Table 5. Interferon beta-1b and 1a compared with placebo: Efficacy measures

| Outcome measure | Interferon beta-1b SC (Betaseron®) | Interferon beta-1a IM (Avonex®) | Interferon beta-1a SC (Rebif®) 44 µg |
|---|---|---|---|
| *Disability progression* | | | |
| Progressed at 2 yrs<br>RR (95% CI) vs. placebo, NNT<br>Absolute risk, % | 0.73 (0.46 to 1.15)<br>20.2% vs. 27.6% | 0.56 (0.33 to 0.97), NNT 12<br>11.4% vs. 20.3% | 0.73 (0.54 to 0.99), NNT 11[b]<br>26.6% vs. 36.4% |
| Difference in mean change in EDSS vs. placebo (95% CI) | −0.28 (−0.64 to +0.08) | -- | −0.24 (−0.48 to +0.00)[b] |
| *Relapses* | | | |
| Patients with ≥ 1 relapse at 2 yrs[a]<br>RR (95% CI) vs. placebo, NNT<br>Absolute risk, % | 0.83 (0.71 to 0.98), NNT 8<br>63.7% vs. 76.4% | 0.75 (0.56 to 1.00), NNT 9<br>33.5% vs. 44.8% | 0.81 (0.72 to 0.91), NNT 7[b]<br>67.9% vs. 84.0% |
| Annualized/mean relapse rate, *P* value | 0.96 1.6 MIU vs. 1.12, *P*=0.0057<br>0.78 8 MIU vs.1.12, *P*=0.0006 | 0.61 vs. 0.90, *P*=0.002 | 1.82 22 mcg 3/wk vs. 2.56 *P*<0.05[b]<br>1.73 44 mcg 3/wk vs. 2.56, *P*<0.05[b]<br>1.08 22 mcg vs. 1.08, NS[c]<br>0.87 44 mcg vs. 1.08, *P*=0.0069[c] |

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; MIU, NNT, number needed to treat; NS, not significant; SC, subcutaneous; wk, week; yr, year.
[a] Inverse of % relapse-free.
[b] PRISMS trial data, 2 years.
[c] OWIMS trial data, 48 weeks.

Overall, the data indicated that both interferon beta-1a products resulted in reductions in the proportions of patients having progressed at 2 years, while interferon beta-1b SC (Betaseron®) was not statistically significantly different to placebo (pooled analysis from the review Rice et al).[50] The mean change in Expanded Disability Status Scale was not different to placebo. The proportions of patients relapse-free and the annualized or mean relapse rates were significantly lower in the interferon groups (pooled analysis from the review Rice et al).[50] The shorter study of interferon beta-1a SC (Rebif®) using weekly instead of thrice weekly dosing was unable to show a difference between the beta interferon and placebo at 48 weeks.[54]

Adjusted indirect comparison meta-analysis indicated no significant differences between the drugs for progression, the change in the Expanded Disability Status Scale (data available only for comparison of interferon beta-1a SC [Rebif®] 44 µg SC twice weekly and interferon beta-1b [Betaseron®]) or the proportion without relapse at 2 years (see Table 6). Inadequate data were available to conduct this analysis with annualized relapse rates.

**Table 6. Adjusted indirect analyses of placebo-controlled trials in relapsing-remitting multiple sclerosis**

| | Betaseron® vs. Rebif® 44 µg | Betaseron® vs. Avonex® | Rebif® 44 µg vs. Avonex® |
|---|---|---|---|
| Progression rates[a] | RR 1.00 (0.58 to 1.73) | 1.30 (0.64 to 2.64) | 1.30 (0.70 to 2.42) |
| EDSS change[b] | –0.04 (–0.41 to 0.33) | NA | NA |
| Relapse free[a] | 1.02 (0.85 to 1.23) | 1.11 (0.80 to 1.53) | 1.08 (0.79 to 1.48) |

Abbreviations: EDSS, Expanded Disability Status Scale; NA, not applicable.
[a] Relative Risk (95% CI).
[b] Weighted mean difference (95% CI).

### *Synthesis of direct and indirect evidence*

In the placebo-controlled trials, the rates of progression at 2 years ranged from 11.4% to 26.6% while in the head-to-head trials the rates ranged from 13% to 57%. While the placebo-controlled trial of interferon beta-1b SC (Betaseron®) would indicate a lower potential for benefit in disease progression compared with the interferon beta-1a drugs, the head-to-head trials and our adjusted indirect analysis of placebo-controlled trial data contradict this conclusion. These differences could be attributed to differences in definition of progression, or baseline population characteristics, but the proportion of patients relapse-free at 2 years also showed some differences between head-to-head and placebo-controlled trials. For interferon beta-1b SC (Betaseron®) the rate in the placebo-controlled trial was 56%, while the head-to-head trial rates were somewhat lower (43% and 51%). Rates for interferon beta-1a SC (Rebif®) were better in head-to-head trials (57% and 56%) than in the placebo-controlled trial (31.1%). The largest difference between placebo-controlled and head-to-head trial results lies in the rates of relapse-free patients with interferon beta-1a IM (Avonex®). The placebo-controlled trial rate was good (66.5%), while the head-to-head trial rates were lower (20% and 36%), resulting in interferon beta-1a IM (Avonex®) being inferior to the other beta interferons.

Because there was only a small amount of evidence available from which to make these comparisons, we undertook an exploratory Bayesian analysis using the adjusted indirect analysis of the placebo-controlled trials as the "prior" assumptions and the direct evidence from head-to-head trials as the primary evidence. The dose of interferon beta-1a SC (Rebif®) 22 µg 3 times weekly was used in this analysis and resulted in no statistically significant differences for the comparison of interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®). For the comparison of interferon beta-1a IM (Avonex®) with either interferon beta-1b SC (Betaseron®) or interferon beta-1a SC (Rebif®) the results of our exploratory analysis was consistent with the findings of our direct and indirect analyses with both interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®) being superior to interferon beta-1a IM (Avonex®) in percent relapse-free, and with interferon beta-1b SC (Betaseron®) being superior to interferon beta-1a IM (Avonex®) in progression rates (see Table 7). Inadequate data were available to conduct this analysis with annualized relapse rates.

**Table 7. Exploratory Bayesian analysis of direct and indirect evidence in relapsing-remitting multiple sclerosis**

| | Betaseron® vs. Rebif® 22 µg | Betaseron® vs. Avonex® | Rebif® 22 µg vs. Avonex® |
|---|---|---|---|
| Progression rates[a] | 1.18 (0.80 to 1.71) | **0.48 (0.27 to 0.86)** | 1.05 (0.93 to 1.22) |
| EDSS change[b] | −0.30 (−0.60 to +0.015) | NA | NA |
| Relapse free[a] | 0.85 (0.56 to 1.25) | **1.48 (1.11 to 2.02)** | **1.22 (1.06 to 1.41)** |

Abbreviations: EDSS, Expanded Disability Status Scale; NA, not applicable.
[a] Relative Risk (95% CI).
[b] Weighted mean difference (95% CI).

## Glatiramer acetate

### *Direct evidence*

Three trials directly comparing glatiramer acetate (Copaxone®) to another disease-modifying drug were identified, 2 comparing to interferon beta-1b (Betaseron®) and 1 comparing to interferon beta-1a (Rebif®).[57-59] The BEYOND trial comparing glatiramer acetate (Copaxone®) to interferon beta-1b (Betaseron®) was a good-quality study[59] while the other 2 trials were fair quality. The BECOME trial was small with a mixed population of patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome and will be discussed under mixed populations. In both the double-blinded BEYOND trial, which lasted up to 3.5 years, and the single-blinded REGARD trial, no significant differences were found at 96 weeks between the drugs in relapse-related or disease progression outcomes. The primary outcome in the REGARD trial was time to first relapse, however there were fewer relapses than expected which meant that the study was under-powered to show a significant difference. The results however are consistent with the BEYOND trial. Results of these trials are presented in Table 8 below.

**Table 8. Relapse and progression outcomes: Glatiramer acetate compared with interferons**

| Study N, Duration | Intervention, dose | Annualized relapse rate[a] | Relapse-free (%)[b] | Proportion of steroid use | Disease progression |
|---|---|---|---|---|---|
| **O'Connor 2009 BEYOND trial N=2244, 3.5 years** | Glatiramer actetate (Copaxone®) 20 mg | 0.34 | 59% | 32% | 21% |
| | vs. Interferon β-1b SC (Betaseron®) 250 mcg | 0.36, *P*=0.79 | 58%, *P*=0.72 | 34%, *P*=0.43 | 27%, *P*=0.68 |
| | vs. Interferon β-1b SC (Betaseron®) 500 mcg | 0.33, *P*=0.42 | 60%, *P*=0.17 | 32%, *P*=1.0 | 22%, *P*=0.71 |
| **Mikol 2008 REGARD trial N=764, 96 weeks** | Glatiramer acetate (Copaxone®) 20 mg | 0.29 | 62% | 31% | 8.7% |
| | vs. Interferon β-1a SC (Rebif®) 44 mcg 3 times weekly | 0.30, *P*=0.83 | 62%, *P*=0.96 | 35%, *P*=0.39 | 11.7%, *P*=0.12 |

Abbreviations: SC, subcutaneous.
[a] *P* value vs. glatiramer acetate.
[b] Year 2; *P* value compared with glatiramer acetate.

The effectiveness results of the head-to-head trials were contrary to 2 observational studies that analyzed clinical databases to compare glatiramer acetate (Copaxone®) to the interferons: One compared with all 3 beta interferons (interferon beta-1a SC [Rebif®] 22 µg dose)[60] and the other to interferon beta-1a SC (Rebif®), dose not reported.[61] Castelli-Haley et al included both an intention-to-treat cohort of 845 patients as well as a continuous use cohort of 410 for which no other disease-modifying therapy was used during the 2-year period after the index date. There were limitations to both studies including differences in the baseline demographics with the interferon groups having a more severely ill population, use of only 22 µg dosing of interferon beta-1a SC (Rebif®) in the Haas et al study, and the fact that glatiramer acetate (Copaxone®) was only available in exceptional circumstances for at least some portion of the study period. Both analyses attempted to control for these potential confounders.[60, 61] They both found a significantly greater reduction in relapse rate at 2 years with glatiramer acetate. The Haas et al study also evaluated the percentage of patient progression free but found no difference in this outcome.[60] The results are presented in Table 9. While these data appeared to support the superiority of glatiramer acetate in relapse over interferon, the fact that no difference was found in the direct comparison studies and the limitations of the observational studies raises the concern that potentially important differences may have contributed to these results. Further good-quality direct comparison studies are needed to confirm the findings.

**Table 9. Comparison of disease-modifying drugs at 2 years in observational data[60]**

| Trial | Outcome measure | Interferon β-1b | Interferon β-1a SC | Interferon β-1a IM | Glatiramer acetate | *P* value |
|---|---|---|---|---|---|---|
| Haas, 2005<br>N=283<br>24 months | Annualized relapse rate | 0.69 | 0.66 | 0.8 | 0.36 | *P*<0.001 |
| | % Relapse-free | 45.5 | 45.8 | 35.4 | 58.2 | *P*=0.22 |
| | Discontinued treatment 6-24 mos | 22.9 | 31.2 | 32.9 | 8.9 | *P*<0.001 |
| | % Progression-free | 71.7 | 73.3 | 74.5 | 87.5 | *P*=0.13 |
| Castelli-Haley, 2008<br>N=845 ITT<br>N=410 continuous use group | Annualized relapse rate<br>ITT group | NR | 0.054 | NR | 0.03 | *P*=0.035 |
| | Continuous use group | | 0.045 | | 0.009 | *P*=0.005 |

Abbreviations: IM, intramuscular; ITT, intention-to-treat; mo, month; NR, not reported; SC, subcutaneous.

### *Indirect evidence: Placebo-controlled trials and single-group studies*

One fair-quality meta-analysis[62] and 1 good-quality systematic review[63] analyzed trials of glatiramer acetate compared with placebo. Martinelli Boneschi[62] only included trials (N=3) in relapsing-remitting multiple sclerosis patients while Munari[63] included the same 3 trials and an additional trial of glatiramer acetate compared with placebo in chronic progressive multiple sclerosis patients. Further discussion of the use of glatiramer acetate in chronic progressive

multiple sclerosis patients appears in the "Mixed populations: Primary and secondary progressive multiple sclerosis" section below.

The 2 reviews used different meta-analytic methods and drew different conclusions regarding the effectiveness of glatiramer acetate. Martinelli Boneschi concluded that glatiramer acetate was effective at "reducing relapse rate and disability accumulation"[62] while Munari concluded that there was no evidence of a "beneficial effect on the main outcome measures in multiple sclerosis, such as disease progression, and (glatiramer acetate) does not significantly affect the risk of clinical relapses."[63] Due to the conflicting nature of these conclusions, we conducted a separate analysis of the 3 relevant trials[64-66] and found a small but significant difference in mean relapse rate between glatiramer acetate and placebo (−0.64; 95% CI, −1.19 to −0.09), no difference in the percentage of relapse-free patients (relative risk, 1.23; *P*=0.086), and inadequate data to pool annualized relapse rates although rates were lower for glatiramer acetate in the trials that reported this outcome.

Two of the 3 trials included in these reviews also provided evidence on other effectiveness outcomes. The single trial providing data on the proportion of patients requiring use of rescue medications showed no difference between the glatiramer acetate and placebo groups (33.6% compared with 39.2%; *P*=0.557). There was a significantly higher percentage of hospitalizations due to uncontrolled exacerbations in the placebo group in the same trial (13.4% glatiramer acetate compared with 25.0% placebo; *P*=0.046).[65] Mean change in Expanded Disability Status Scale was reported as a secondary outcome in 1 trial. Two-year data showed that while glatiramer acetate was associated with a statistically significant (*P*=0.023) change in Expanded Disability Status Scale (−0.05) when compared with placebo (0.21), the clinical significance of such a difference was likely minimal.[66] Overall, there appeared to be a statistically significant effectiveness of glatiramer acetate in relapse and disease progression outcomes in relapsing-remitting multiple sclerosis but the effect appeared to be small and the clinical significance is likely minimal.

## Natalizumab

### *Direct evidence*

No studies compared natalizumab (Tysabri®) to another disease-modifying drug for multiple sclerosis.

### *Indirect evidence*

Two well-conducted trials compared natalizumab (Tysabri®) to placebo in patients with relapsing-remitting multiple sclerosis (Table 10).[67, 68] Patient population, natalizumab dose, and study duration were similar in the 2 trials, however in 1 of these trials,[68] interferon beta-1a IM (Avonex®) was used concomitantly in both groups. Both cumulative probability of disease progression and annualized relapse rate at 2 years were significantly lower with natalizumab when compared with placebo, while the proportion of relapse-free patients was significantly higher (Table 11). These data indicated that natalizumab was more effective than placebo in patients with relapsing-remitting multiple sclerosis. Post-hoc analysis of 2-year data in the AFFIRM trial found a significantly higher number of patients in the natalizumab group with no relapse at 2 years (absolute difference, 27.3%; 95% CI, 20.6 to 34.0) and had no disease progression by Expanded Disability Status Scale at 2 years (absolute difference, 12.0%; 95% CI, 5.9 to 17.9).[69] Additionally, the number with the composite outcome "free of clinical disease

activity" (a combination of no relapse and no progression) was significantly higher in the natalizumab group (absolute difference, 25.4%; 95% CI, 18.7 to 32.1%).[69]

**Table 10. Trials of natalizumab in relapsing-remitting multiple sclerosis**

| Trial | Patient characteristics | Interventions | Study duration |
|---|---|---|---|
| Polman 2006[67] AFFIRM | N=942<br>Mean EDSS: 2.3<br>Mean relapse rate: 1.52/yr | 300 mg every 4 wks vs. placebo | Up to 116 wks |
| Rudick 2006[68] SENTINEL | N=1171<br>Mean EDSS: 2.4<br>Mean relapse rate: 1.47/yr | 300 mg every 4 wks + 30 ug interferon β-1a IM (Avonex®) 1/wk vs. placebo every 4 wks+ 30 ug interferon β-1a IM (Avonex®) 1/wk | Up to 116 wks |

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; wk, week; yr, year.

**Table 11. Effectiveness outcomes in natalizumab trials in patients with relapsing-remitting multiple sclerosis**

| Outcome at 2 years | Trial | Natalizumab vs. placebo, *P* value |
|---|---|---|
| Cumulative probability of disease progression | Polman 2006[67] | 17% vs. 29%, *P*<0.001 |
| | Rudick 2006[68] | 23% vs. 29%, *P*=0.02 |
| Annualized relapse rate | Polman 2006[67] | 0.23 vs. 0.73, *P*<0.001 |
| | Rudick 2006[68] | 0.34 vs. 0.75, *P*=0.001 |
| Proportion of relapse-free patients | Polman 2006[67] | 67% vs. 41%, *P*<0.001 |
| | Rudick 2006[68] | 61% vs. 37%, *P*<0.001 |

Two studies evaluated the secondary outcome results of the AFFIRM and SENTINEL trials, 1 assessing the efficacy of natalizumab on health-related quality of life, and 1 assessing the efficacy on prevention of visual loss.[70, 71] Natalizumab offered a significant improvement in the physical component scale of the short-form-36 health-related quality of life questionnaire at week 104 (AFFIRM: odds ratio, 1.54; 95% CI, 1.06 to 2.23; SENTINEL: odds ratio, 1.47; 95% CI, 1.08 to 2.03).[71] Vision testing, including low-contrast testing using a Sloan chart which is known to best identify visual dysfunction in multiple sclerosis cohorts, was performed in both trials as a predefined tertiary outcome. Post hoc analysis found that clinically significant visual loss (2 line worsening of acuity sustained over 12 weeks) was seen in the natalizumab group in the AFFIRM trial at the 2.5% contrast level (absolute difference, 47%; hazard ratio, 0.53%; 95% CI, 0.36 to 0.76; *P*<0.001), and at the 1.25% contrast level (absolute difference, 35%; hazard ratio, 0.65; 95% CI, 0.47 to 0.90; *P*=0.008).[70] In the SENTINEL trial where patients received interferon beta-1a IM (Avonex®) +/- natalizumab, there was a significant reduction in visual acuity only at the 1.25% contrast level (hazard ratio, 0.72; 95% CI, 0.54 to 0.98; *P*=0.038).[70]

### Mitoxantrone

#### *Direct evidence*

No studies offered direct evidence comparing mitoxantrone (Novantrone®) to another disease-modifying drug for patients with relapsing-remitting multiple sclerosis.

#### *Indirect evidence*

One small trial compared mitoxantrone to placebo in 51 patients with relapsing-remitting multiple sclerosis.[72] The primary outcome of this 2-year study was confirmed disease progression, as measured by a 1-point increase in the Expanded Disability Status Scale. At the conclusion of the study, 2 of 27 (7%) mitoxantrone patients and 9 of 24 (37%) placebo patients had confirmed disease progression (absolute risk difference, 30%; 95% CI, 8 to 52; number needed to treat, 3). Mitoxantrone patients also fared better than placebo patients both in the number of exacerbations experienced during the course of the study (0.89 compared with 2.62; $P$=0.0002) and in the number of exacerbation-free patients at the study's conclusion (63% compared with 21%; $P$=0.006; number needed to treat, 2.4). An interim, subgroup analysis of 25 patients at 1-year of follow-up found a similar pattern in the rates of confirmed disease progression.[73]

## *Secondary progressive multiple sclerosis*

### Beta interferons

#### *Indirect evidence*

Five trials reported in multiple publications of beta interferons compared with placebo provided evidence on the effectiveness of interferon beta-1a IM (Avonex®) in secondary progressive multiple sclerosis.[74-83] These included 1 study of interferon beta-1a IM (Avonex®),[80] 2 studies of interferon beta-1a SC (Rebif®),[81, 83] 2 studies of interferon beta-1b SC (Betaseron®),[75, 78, 79, 81, 82] and 1 combined analysis of these 2 trials.[77] Trial characteristics are summarized in Table 12. The primary outcome measures assessed progression and disability, reflecting the nature of secondary progressive multiple sclerosis. Relapse was evaluated as a secondary outcome only. While 3 studies used time to progression as an outcome measure, there were differences in how the outcome was defined or confirmed, and 1 trial used a measure of functionality (the Multiple Sclerosis Functional Composite) in an effort to avoid the potential lack of sensitivity and variability associated with the Expanded Disability Status Scale.[84] Across the studies, the patient populations appeared similar, although the specific interferon and dosing varied.

## Table 12. Characteristics of studies of beta interferons for secondary progressive multiple sclerosis

| Study name, Year<br>N | Patient characteristics | Interventions<br>duration of follow-up | Primary outcomes |
|---|---|---|---|
| **Interferon beta-1a IM (Avonex®)** | | | |
| IMPACT 2002<br>N=436 | Mean age 48 yrs<br>Baseline EDSS 5.2<br>MS Duration 16.5 yrs | Interferon β-1a (Avonex®) 60µg or placebo IM weekly x 2 years | Change in MSFC from baseline to 24 months |
| **Interferon beta-1a SC (Rebif®)** | | | |
| SPECTRIMS 2001<br>N=618 | Mean age 43 yrs<br>Baseline EDSS 5.4<br>MS Duration 13 yrs | Interferon β-1a SC (Rebif®) 22 or 44µg or placebo SC 3 x weekly x 3 years | Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline ≥ 5.5 x 2 measurements |
| Andersen 2004<br>N=364 | Mean age 46<br>Baseline EDSS 4.8<br>MS Duration 14 yrs | Interferon β-1a (Rebif®) 22µg or placebo SC weekly x 3 years | Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline ≥ 5.5 x 2 measurements |
| **Interferon beta-1b (Betaseron®)** | | | |
| North American Study Group 2004<br>N=939 | Mean age 48<br>Baseline EDSS 5.1<br>MS Duration 15 yrs | Interferon β-1b (Betaseron®) 250 µg or 160 µg/m$^2$ or placebo SC every other day x 3 years | Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline 6-6.5 x 2 measurements |
| European Study Group 2001<br>N=718 | Mean age 441<br>Baseline EDSS 5.2<br>MS Duration 13 yrs | Interferon β-1b (Betaseron®) 250 µg or placebo SC every other day x 3 years | Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline 6-6.5 x 2 measurements |

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; SC, subcutaneous.

Only 2 studies found a significant benefit of beta interferons in slowing progression.[80, 82] In IMPACT [80] (interferon beta-1a IM [Avonex®] 60µg compared with placebo) a significant difference in the change on the Multiple Sclerosis Functional Composite score was found (a difference in Z-score of 0.133), however the clinical importance of such a difference was not clear. Similar to the other studies, no significant difference was found using the Expanded Disability Status Scale time to progression measure (hazard ratio, 0.98; 95% CI, 0.68 to 1.4).

Two studies of interferon beta-1a SC (Rebif®) were unable to differentiate beta interferon and placebo on time to progression with either 22 or 44 µg doses.[81, 83] However, the larger study did find a benefit on annualized relapse rates and hospitalizations with both doses. While the rates of relapse were different between the 2 trials, the relative benefit of interferon beta-1a SC (Rebif®) were similar, with a pooled relative risk for yearly relapse of 0.76 (95% CI, 0.59 to 0.97). The SPECTRIMS study found that women responded better to interferon ß1a SC (Rebif®) than men. These results are discussed in Key Question 3 below.

The 2 studies of interferon beta-1b SC (Betaseron®) used the same outcome measure and had conflicting results. Both studies were stopped early, based on planned interim analyses, but for opposite reasons. In the European study[82] the time to progression for the beta interferon 250 µg SC group was similar to that seen in the North American study (893 compared with 981 days,

respectively), but the placebo groups differed (549 compared with 750 days, respectively). Kappos et al[77] investigated potential differences between the studies using primary data from both trials. While this analysis showed that there was a 6.5% greater variability in the Expanded Disability Status Scale scores from the North American study, the difference was not large enough to account for the difference in study findings. Pooled results indicated an overall benefit (see Table 13), and in further analysis those with active disease (higher relapse rates and greater progression at entry) appeared to benefit the most. In the SPECTRIMS study of interferon beta-1a SC (Rebif®), a similar finding was observed.

Making indirect comparisons across these trials in a qualitative way, there was evidence that interferon beta-1b SC (Betaseron®) is effective in slowing progression in patients with secondary progressive multiple sclerosis, particularly those with more active disease. Evidence for the beta-1a interferons (IM or SC; Avonex® or Rebif®) was less convincing for slowing progression based on the Expanded Disability Status Scale, although the newer measure, the Multiple Sclerosis Functional Composite, allowed a benefit to be seen with interferon beta-1a IM (Avonex®). Whether this difference was clinically important and whether the other beta interferons would have a similar impact is not clear. Studies indicated that all of the beta interferons did have an impact by reducing relapse rates. Those with more active disease appeared to benefit more.

## Table 13. Results of studies of beta interferons for secondary progressive multiple sclerosis

| Study Name, Year<br>N | Primary Outcomes<br>Interferon vs. placebo (95% CI) | Secondary Outcomes<br>Interferon vs. placebo (95% CI) |
|---|---|---|
| **Interferon beta-1a IM (Avonex®)** | | |
| IMPACT 2002<br>N=436<br>Interferon β1-a 60µg IM vs. placebo | Change in MSFC<br>−0.362 vs. −0.495 (40% difference; *P*=0.033) | Annualized relapse rate<br>0.2 vs. 0.3 (*P*=0.008)<br>Relapse free<br>74% vs. 63% (*P*=0.023)<br>HRQOL<br>Interferon significantly better on 8 of 11 subscales |
| **Interferon beta-1a SC (Rebif®)** | | |
| SPECTRIMS 2001<br>N=618<br>Interferon β1-a SC 22 vs. 44µg vs. placebo | Time to progression<br>44µg vs. PL HR 0.83 (0.65 to 1.07)<br>22 µg vs. PL HR 0.88 (*P*=0.31) | Annualized relapse rate<br>44µg 0.5 vs. 22 µg 0.5 vs. 0.71<br>44µg vs. placebo: RR 0.69 (0.56 to 0.85)<br>22 µg vs. placebo: RR 0.69 (0.56 to 0.84)<br>Hospitalizations<br>44µg vs. placebo: RR 0.63 (0.46 to 0.88)<br>22 µg vs. placebo: 0.64 (0.46 to 0.88) |
| Andersen 2004<br>N=364<br>Interferon β1-a SC 22µg vs. placebo | Time to Progression<br>HR 1.13 (0.82 to 1.57)<br>Proportion with progression:<br>41% vs. 38% (NS) | Annualized relapse rate<br>0.25 vs. 0.27<br>RR 0.9 (0.64 to 1.27)<br>Relapse free<br>61% vs. 62%<br>OR 1.03 (0.67 to 1.58)<br>Time to first relapse and hospitalizations: NS |
| **Interferon beta-1b SC (Betaseron®)** | | |
| North American Study Group 2004<br>N=939<br>Interferon β1-b 250 µg vs. 160 µg/m$^2$ vs. placebo SC | Time to progression<br>Days to event: 981 vs. 668 vs. 750<br>250 µg vs. PL *P*=0.61<br>160 µg vs. PL /m$^2$ = 0.26<br>Proportions progressing<br>32% vs. 39% vs. 34% (NS) | Annualized relapse rate<br>0.16 vs. 0.2 vs. 0.28<br>250 µg vs. placebo: *P*=0.009<br>160 µg vs. placebo: *P*=0.109<br>Combined interferon vs. placebo: *P*=0.014 |
| European Study Group 2001<br>N=718<br>Interferon β1-b SC 250 µg vs. placebo | Time to progression<br>Days to event: 893 vs. 549, *P*=0.0008<br>Proportion with progression:<br>50% vs. 39% | Annualized relapse rate<br>0.44 vs. 0.64; *P*=0.002<br>Hospitalizations<br>46% vs. 53%, *P*=0.04<br>HRQOL<br>Interferon significantly better on physical scale at 6+12 months and last visit. Total and psychosocial scores not different to placebo. |
| Kappos 2004<br>Pooled Analysis of European and North American Studies | Time to progression<br>HR 0.79 (0.66 to 0.93)<br>Patients with relapses and Δ EDSS >1 at baseline: HR, 0.53 (95% CI, 0.37 to 0.78) | Data not pooled |

Abbreviations: EDSS, Expanded Disability Status Scale; HRQOL, health-related quality of life; IM, intramuscular; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; NS, not significant; SC, subcutaneous.

While mixed results were found for disease progression, relapse rates were more consistently affected by the beta interferons. Four trials indicated that beta interferon therapy reduces relapse and associated hospitalizations in patients with secondary progressive multiple sclerosis compared with placebo. Body surface area dosing (160 µg/m$^2$) of interferon beta-1b SC (Betaseron®) was generally less effective than the 250 µg dose. Health-related quality of life was

measured in 2 studies using different tools, both finding a benefit of the respective beta interferon used.[79, 80]

### Glatiramer acetate and natalizumab

No studies of glatiramer acetate (Copaxone®) or natalizumab (Tysabri®) in patients with secondary progressive multiple sclerosis were found.

## *Primary progressive multiple sclerosis*

### Beta interferons

#### *Indirect evidence*

The primary evidence of the effectiveness of drug treatment in primary progressive multiple sclerosis came from a single small (N=50) trial of interferon beta-1a IM (Avonex®) at doses of 30 µg, 60 µg, or placebo once weekly for 2 years.[85] While no statistically significant differences were found between the groups at baseline, the baseline Expanded Disability Status Scale in the placebo group was 1 point lower (4.5 compared with 5.5) compared with either beta interferon group. The time to sustained progression (increase of ≥1 point on Expanded Disability Status Scale at baseline ≤ 5.0, ≥ 0.5 point if Expanded Disability Status Scale at baseline, ≥ 5.5 seen at 2 consecutive 3-month visits) was not different between the placebo and beta interferon groups at either dose. There was no sample size calculation completed by the study authors; the small sample size and potentially clinically important differences at baseline left the possibility of benefit in a larger trial open to speculation. Statistically significant differences on secondary outcome measures (the 10-minute walk test and the 9-hole peg test) were also not found. However, the authors suggested that a benefit in right hand side 9-hole peg test was seen with the beta interferon 30 µg group ($P$=0.08) and related this to the sensitivity of the test to upper extremity changes, while the Expanded Disability Status Scale is more affected by lower extremity changes. While a pilot trial of interferon beta-1b SC (Betaseron®) has been done, it has only been partially reported to date.[86] Details in this publication were inadequate for inclusion here. One systematic review by Rojas et al of the Cochrane collaboration reviewed data from both of these trials including unpublished data from the pilot trial by Montalban.[36] This trial data found a no significant differences between interferon beta-1b SC (Betaseron®) and placebo in sustained progression of disease and mean Expanded Disability Status Scale change over a 2 year period.[36] The review pooled data from both interferons, which did not allow interpretation for comparative effectiveness, however, they found no difference in relapse related and disease progression outcomes when the data was pooled. These results were limited by the small number (N=143).

#### ***Glatiramer acetate***

One indirect fair quality study, N=943, compared glatiramer acetate to placebo in patients with primary progressive multiple sclerosis.[87] The duration of the study was intended to be 36 months but was stopped early due to lack of efficacy. At that time 60% of patients randomized to Glatiramer and 59% of those randomized to placebo had received the study drug for 24 months, and 18% and 15% respectively had received the study drug for 36 months. The study found no significant difference in delay to sustained disability (hazard ratio, 0.87; 95% CI, 0.71 to 1.07).

***Natalizumab and mitoxantrone***

No studies of natalizumab or mitoxantrone in patients with primary progressive multiple sclerosis were found. One study of glatiramer acetate included a mixed population (see below).

### *Mixed populations: Clinically isolated syndrome and relapsing-remitting multiple sclerosis*

One small single-blinded head-to-head trial (N=75) comparing interferon beta-1b (Betaseron®) to glatiramer acetate evaluated clinical exacerbations over 2 years as a secondary outcome.[57] Randomization was stratified by clinical site and presence of enhancement on screening magnetic resonance imaging, which introduced bias to the results. There was no specific criterion for defining relapse, including change in Expanded Disability Status Scale and/or a decrease in the Scripps Neurological Rating Scale of at least 7 points, and a neurological examination was performed by a blinded examining neurologist. Most of the patients had relapsing-remitting multiple sclerosis (79%) with a baseline median annualized relapse rate and Expanded Disability Status Scale score of 1.85 (0-7.5) and 2.0 (0-5.5) respectively. No difference was found in the annualized relapse rate (interferon beta-1b [Betaseron®] 0.37, glatiramer acetate 0.33, *P*=0.68) or percent relapse-free at 18 months (interferon beta-1b [Betaseron®] 62%, glatiramer acetate 70%). Because these were secondary outcomes, the study may not have had an adequate sample size (statistical power) to identify a statistically significant difference if one exists. It did, however, agree with findings from 2 other trials where the population was restricted to relapsing-remitting multiple sclerosis, both of which found no difference in clinical measures including relapse rate between the interferon studied and glatiramer acetate (see section on relapsing-remitting multiple sclerosis, above).[58, 59]

### *Mixed populations: Relapsing-remitting and secondary progressive multiple sclerosis*

#### Beta interferons

A cohort study of relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis patients compared quality of life in patients treated with interferon beta-1b (Betaseron®) to untreated controls.[88] Patients were recruited during regular office visits and asked to complete a quality-of-life questionnaire based on the previous month. Additional data regarding hospitalizations and days of work/leisure time lost for the 3 months preceding study entry were also collected. When patients were stratified according to disease severity, those patients with the lowest Expanded Disability Status Scale (<3.0) fared the best in terms of quality of life, hospitalizations, and work/leisure time lost (Table 14). While these data suggested that baseline disease severity had an important impact on quality-of-life measures, additional data from well-designed randomized controlled trials and/or observational studies assessing these measures are needed in order to draw more definitive conclusions.

**Table 14. Quality-of-life measures by disease severity[88]**

| | EDSS <3.0 | | EDSS 3.0-6.0 | | EDSS >6.0 | |
|---|---|---|---|---|---|---|
| Outcome | Interferon β-1b SC (Betaseron®) n=30 | Untreated controls n=53 | Interferon β-1b SC (Betaseron®) n=32 | Untreated controls n=58 | Interferon β-1b SC (Betaseron®) n=18 | Untreated controls n=40 |
| **Summary QOL physical score (±SD)** | 67.2 (±22.4) | 47.8 (±19.5) | 47.3 (±19.2) | 43.5 (±7.8) | 34.8 (±17.5) | 31.5 (±19.0) |
| **Summary QOL mental score (±SD)** | 63.7 (±25.0) | 57.9 (±27.9) | 57.9 (±20.2) | 54.1 (±22.5) | 52.5 (±20.8) | 47.8 (±21.7) |
| **Hospitalizations[a]** | 2 (7%) | NR | 1 (3%) | NR | 3 (17%) | NR |
| **Days of work lost[a]** | 2.0 | 15.6 | 25.0 | 29.9 | NR | NR |
| **Other time lost[a] (i.e. leisure time)** | 33.8 | 41.9 | 53.1 | 46.0 | 65.7 | 67.4 |

Abbreviations: EDSS, Expanded Disability Status Scale; NR, not reported; QOL, quality of life; SC, subcutaneous; SD, standard deviation.
[a] During the 3 months preceding study entry.

## Natalizumab

### *Indirect evidence*

Three trials compared natalizumab (Tysabri®) to placebo in relapsing-remitting and secondary progressive multiple sclerosis patients.[89-91] While there were some similarities in patient characteristics across the trials, the size and quality of the trials varied and relevant baseline data was not uniformly reported across all trials. Natalizumab doses were weight-based in 2 of the trials whereas in the O'Connor et al trial, the patients were randomized to placebo, a 1 mg/kg dose, or a 3 mg/kg dose and received only 1 infusion at study entry.[90] The only infusing dosage that was common amongst the trials was 3 mg/kg but the total accumulated dose varied considerably from 1 mg/kg to 18 mg/kg. All of the trials reported effectiveness outcomes.[89-91] The longest trial, Miller et al,[89] had a duration of 12 months, while the other trials were considerably shorter (14 weeks for O'Connor and 24 weeks for Tubridy[91]).

Effectiveness data appears in Table 15. For data comparing the same infusion dose of 3 mg/kg, we pooled the data to find the combined mean difference in Expanded Disability Status Scale score and found no significant difference between the natalizumab and placebo groups at the final time point (−0.049; 95% CI, −0.301 to +0.204),[89-91] although trials of longer duration are needed to confirm this finding. The total number of relapses reported in each study arm varied considerably between the trials. Miller et al reported a 4% relapse rate, O'Connor a 2% relapse rate, and Tubridy reported a 39% relapse rate. Relapse rates for placebo were 21%, 5%, and 44% respectively, resulting in a significant difference between natalizumab and placebo in only 1 of the trials.[89] Possible reasons for this discrepancy include total natalizumab dose (18 mg/kg compared with 1 or 3 mg/kg compared with 9 mg/kg respectively), trial duration (12 months compared with 14 weeks compared with 24 weeks of follow-up), and criteria used to assess relapse. Miller et al used a more restrictive criterion to determine relapse (physician-assessed, sustained for at least 48 hours) than did Tubridy (Poser criteria, either objectively or subjectively defined, sustained for 24 hours).[16] Due to the heterogeneity of the 3 trials

($I^2$=79.3%), we did not combine the relapse outcome data. Due to these discrepant findings, it is difficult to draw a definitive conclusion regarding the effect of natalizumab on relapse rate.

**Table 15. Effectiveness of natalizumab compared with placebo in relapsing-remitting and secondary progressive multiple sclerosis**

| Trial | Patient characteristics | Natalizumab regimen | Disease progression outcomes | Relapse outcomes |
|---|---|---|---|---|
| Miller et al 2003[89]<br>N=213 | Mean EDSS: 4.3<br>Mean relapses 2 yrs prior to study: 3.0 | 3 mg/kg<br>or<br>6 mg/kg<br>every 28 days for 6 total doses | Mean change in EDSS:<br>3 mg/kg: −0.14<br>6 mg/kg: −0.03<br>placebo: 0.03 | Total relapses<br>3 mg/kg: 3 (4%); *P*=0.004 vs. placebo<br>6 mg/kg: 8 (11%); *P*=0.11 vs. placebo<br>Placebo: 18 (21%)<br>Use of rescue medication for relapse<br>3 mg/kg: 5/13 pts; *P*<0.001 vs. placebo<br>6 mg/kg: 7/14 pts; *P*=0.002 vs. placebo<br>placebo: 22/27 pts |
| Tubridy 1999[91]<br>N=72 | Mean EDSS: 4.8<br>≥ 2 relapses in 18 mos prior to study entry | 3 mg/kg every 28 days for 2 total doses[a] | Mean change in EDSS:<br>3 mg/kg: −0.02<br>placebo: 0.02 | Total relapses:<br>3 mg/kg: 15/38 (39%)<br>Placebo: 4/9 (44%) |
| O'Connor et al, 2004<br>N=180 | Mean EDSS ≤5.5 but >3.0 at study entry<br>Acute MS relapse for >24 hours but <96 hours prior to receiving study medication | 1mg/kg vs 3 mg/kg vs placebo once on day 1 | Mean change in EDSS:<br>1mg/kg: −1.5<br>3mg/kg: −1.3<br>Placebo: −1.5<br>Ns | Total relapses: NS<br>1mg/kg: 3/57 (5.%)<br>3mg/kg: 1/60 (2%)<br>Placebo: 2/63 (3%) *P*=0.077<br>Use of rescue medication for relapse: NS<br>1mg/kg: 24/57 (42%)<br>3mg/kg: 17/60 (28%)<br>Placebo: 19/63 (30%)<br>*P*=0.619 |

Abbreviations: EDSS, Expanded Disability Status Scale; NS, not significant
[a] Natalizumab given at weeks 0 and 4; outcomes based on follow-up of up to 24 weeks.

## Mitoxantrone

### *Indirect evidence*

A well-conducted systematic review compared mitoxantrone (Novantrone®) to placebo using data from 4 trials (Table 16).[92] A second review included the same 4 trials as well as preliminary and unpublished data from an ongoing study.[93] Among the 4 trials included in both reviews, there was some heterogeneity among the types of patients, mitoxantrone doses employed, and study duration. Three of the studies enrolled mixed patient populations[94-96] while the remaining study enrolled only relapsing-remitting multiple sclerosis patients[72] and had a lower mean baseline Expanded Disability Status Scale score (further discussion of the results of this trial appear in the relapsing-remitting multiple sclerosis section of this report). Mitoxantrone doses also varied widely across the included studies, while study duration ranged from 6 to 32 months.

Mitoxantrone was found to be more effective than placebo in reducing relapse rate and disease progression.[92] No statistically significant difference in Expanded Disability Status Scale at 1 year was detected in a small subset of patients (data available from 1 study) but 2-year results from a larger group of patients did statistically favor mitoxantrone (Table 17).

## Table 16. Placebo-controlled trials of mitoxantrone

| Trial | Patient characteristics | Mitoxantrone dose | Comparator | Study duration |
|---|---|---|---|---|
| Edan, 1997[94] N=44 | RRMS or SPMS<br>Mean baseline EDSS: 4.6 (±1.7)<br>Mean relapses 1 year prior to study entry: 2.8 (±1.8) | 20mg/mo + methylprednisolone | methylprednisolone | 6 months |
| Millefiorini, 1997[72] N=51 | RRMS<br>Mean baseline EDSS: 3.6(±1.1)<br>Mean relapses 2 years[a] prior to study entry: 2.8 (±1.2) | 8 mg/m² of body surface/month | Placebo | 12 months |
| Van de Wyngaert, 2001[95] N=49 | RRMS or SPMS<br>Mean baseline EDSS: 5.2<br>Mean relapses 1 year prior to study entry: 2.3 (±1.1) | 12 mg/m² of body surface/mo for 3 months, then every 3 months | Placebo | 32 months |
| Hartung, 2002[96] N=188 | SPMS or worsening RRMS<br>Mean baseline EDSS: 4.6 (±1.01)<br>Mean relapses 1 year prior to study entry: 1.3 (±1.2) | 5 mg/m² of body surface every 3 months[a]<br>12 mg/m² of body surface every 3 months | Placebo | 24 months |

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
[a] Mean relapse rate at 1 year not reported in this study.
[b] Results from this study arm were excluded from the systematic review analysis. The study authors determined that the dose was too difficult to compare to the dosing schedules employed in the other studies.

## Table 17. Effectiveness outcomes in trials of mitoxantrone compared with placebo[92]

| Outcome | Time point | Number | Results |
|---|---|---|---|
| Relapse rate | 6mo/1 year[a] | N=93 | 68.7% vs. 28.8%<br>OR 5.4 (95% CI, 2.2 to 13.1; *P*=0.0002) |
| | 2 years | N=179 | 56.6% vs. 31.4%<br>OR 3.11 (95% CI, 1.68 to 5.72; *P*=0.0003) |
| Disease progression[b] | 1 year | N=51 | 7.4% vs. 25%<br>OR 0.24 (95% CI, 0.04 to 1.33; *P*=0.1) |
| | 2 years | N=179 | 6.6% vs. 23.6%<br>OR 0.23 (95% CI, 0.09 to 0.59; *P*=0.0002) |
| EDSS – treatment effect | 1 year | N=25 | −0.35 (95% CI, −0.86 to +0.16; *P*=0.18) |
| | 2 years | N=175 | −0.36 (95% CI, −0.7 to −0.02; *P*=0.04) |

Abbreviations: EDSS, Expanded Disability Status Scale.
[a] Based on fixed effects model.
[b] Based on confirmed disease progression and change in EDSS at end of study.

### *Mixed populations: Primary and secondary progressive multiple sclerosis*

#### Glatiramer acetate

An early, good-quality study of glatiramer acetate (Copaxone®) was conducted in a population of 106 patients described as chronic progressive (a chronic progressive course for at least 18 months, no more than 2 exacerbations in the past 2 years, Expanded Disability Status Scale ≥2 and ≤6.5, and exhibiting progression in a pre-trial period).[97] Many clinicians consider this group of patients to represent a mix of patients with what would now be called primary or secondary progressive multiple sclerosis. The drug used in this study was available from 2 laboratories in Israel and was not the commercially available glatiramer acetate (known as COP-1 at the time). The dosing of the drug was 15 mg subcutaneously twice daily, a dose that is higher than currently used (20 mg subcutaneously daily). The mean baseline Expanded Disability Status Scale was slightly higher in the glatiramer acetate group (5.7 compared with 5.5) and both mean baseline scores are higher than seen in other glatiramer acetate studies. Comparing time to sustained progression curves (the primary outcome) while the glatiramer acetate curve showed slower progression, no significant difference was found between the groups over a 2-year period. This study did not conduct a sample size calculation, and with 106 patients may have been underpowered to show a difference of this magnitude. Further, subgroup analyses indicated that patients enrolled at the 2 centers responded differently while on study, and that overall patient disease activity differed on trial compared with the pre-trial assessment period.

Analysis of secondary outcomes indicated that statistically significant differences in proportions with progression (defined as an increase on Expanded Disability Status Scale of ≥ 1 if baseline ≥ 5, and 1.5 if baseline < 5) were not seen at 12 and 24 month time points, although glatiramer acetate was numerically superior (11% compared with 18.5%, $P$=0.088 and 20.4% compared with 29.5%, $P$=0.086 respectively). The authors also explored a definition of progression of an increase of only 0.5 points on the Expanded Disability Status Scale from baseline. Using this definition, the probability of progression was significantly lower with glatiramer acetate compared with placebo only at the 24-month time point (44.6% compared with 58.3%, $P$=0.03).

## Key Question 2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of interferon beta neutralizing antibodies?

## Summary of the Evidence

- Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2% to 8.5% reported, starting around 9 months of treatment.
- With interferon beta-1a SC (Rebif®) antibodies occurred somewhat later (9 months) with rates of immunogenicity as low as 12% and as high as 46%, and with interferon beta-1b SC (Betaseron®) neutralizing antibodies appeared as early as 3 months into treatment in 30% to 40% of patients.
- 40% to 50% of antibody positive patients will become antibody negative over time, while small numbers of patients will become antibody positive into the second year of treatment.

## Detailed Assessment

Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness.

Two systematic reviews summarized the current state of understanding about the impact of these antibodies on relapse and disease progression, and how the products differ.[98, 99] There were several factors that can impact the prevalence of such antibodies, including assay method (varying sensitivity/specificity), dose (conflicting evidence), host cell source (*Escherichia coli* more antigenic than mammalian source), definition of positive status, and route of administration (subcutaneous more antigenic than intramuscular). Because there is no standardized universal assay, comparisons across studies of the beta interferons is fraught with uncertainty. It appears that the rate of antibody development occurs earlier and in greater frequency with interferon beta-1b SC (Betaseron®), appearing as early as 3 months into treatment in approximately 30% to 40% of patients. Evidence reported in the Namaka review[99] indicated that antibodies occur somewhat later (9 months) with interferon beta-1a SC (Rebif®), with rates as low as 12% and as high as 46% (see Table 18). Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity with rates of 2% to 8.5% reported, starting around 9 months of treatment. Importantly, 40% to 50% of antibody-positive patients will become antibody-negative over time, while small numbers of patients will become antibody-positive into the second year of treatment.

**Table 18. Comparison of neutralizing antibodies in beta interferon products[99]**

| | Avonex | Betaseron | Rebif |
|---|---|---|---|
| Percent developing neutralizing antibodies | 2% to 6% | 30% to 40% | 12% to 25% |
| Time to appear | First 9-15 months | First 3-6 months, can occur up to month 18 | First 9-15 months |

Data from 9 comparative observational studies reporting the presence of neutralizing antibodies in patients taking beta interferons are shown in Table 19 below.[100-108] The proportion of patients developing antibodies was lower for interferon beta-1a IM (Avonex®), 0% to 14%, compared with 11% to 44% with interferon beta-1a SC (Rebif®) and 15% to 44% with interferon beta-1b SC (Betaseron®), consistent with findings from the Namaka systematic review. The usefulness of these studies in making comparisons across drugs was limited because most did not study patients on therapy for more than 2 years.

**Table 19. Proportion of patients testing neutralizing antibody-positive after beta interferon therapy reported in comparative observational studies**

| Author, year | Duration of treatment | Avonex® | Betaseron® | Rebif® | Association of clinical outcomes with neutralizing antibody status |
|---|---|---|---|---|---|
| Boz, 2007 | ≥3 years | 0/12 (0%) | 18/119 (15%) | 16/131 (12.2%) | More relapses in neutralizing antibody-positive patients in years 3 and 4. |
| Farrell, 2008 | >3 years | 4/242 (6%) | 11/115 (28%) | 24/292 (30%) | Relapse rates higher in neutralizing antibody-positive groups, risk greater in those with higher titres |
| Dubois, 2006 | Median 26 months, range 2-85 months | 0/18 (0%) | 12/32 (38%) | 10/23 (44%) | No significant association between antibody status and outcomes. |
| Kivisakk, 2000 | 1-46 months | 1/20 (5%) | 21/48 (44%) | | No effect of neutralizing antibodies on clinical outcome |
| Koch-Henriksen 2009 | 21,963 months of observation | | N=417 33.0% | N=892 31.4% | Effect of neutralizing antibody status on relapses did not differ between treatments (*P*=0.89) |
| Sbardella, 2009 | At least 1 year | 1/12 (6%) | 5/36 (29%) | 22 mcg: 6/48 (35%) 44 mcg: 5/45 (29%) | Significant interaction between clinical response and neutralizing antibody development, but only 17% of patients with a poor response were neutralizing antibody-positive |
| Aarskog 2009 | At least 1 year | 4.6% | 45.1% | 33.9% | Not reported |
| Fernandez, 2001 | 1 year | 3/22 (14%) | 7/31 (23%) | | No association with antibody status and relapse rate in either group. |
| Malucchi 2008 | 1 year | 2/34 (5.1%) | 6/20 (20.7%) | 22 mcg: 4/33 (10.8%) 44 mcg: 5/26 (15.6%) | Time to first relapse shorter in neutralizing antibody-positive groups; more neutralizing antibody-negative patients were relapse-free. |

Several additional non-comparative observational studies reported the rate of neutralizing antibodies associated with beta interferon therapy. They are not discussed in detail here because they provided no additional evidence beyond the Namaka and Goodin systematic reviews.[80, 107, 109-116]

## Key Question 3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?

### Summary of the Evidence

- Evidence for interferon beta-1b SC (Betaseron®) and interferon beta-1a SC (Rebif®) indicated that consistent positive neutralizing antibody status with high titer adversely affected the impact of these drugs on relapse rates, by one-half to two-thirds, during longer periods of follow-up.
- This difference was not seen for any of the products in shorter follow-up (2 years or less), and there was inadequate evidence to conclude that there is an impact on disease progression.

### Detailed Assessment

The duration of many studies was not adequate to assess the impact of antibody status on progression clearly. Namaka et al found that in the first 2 years of treatment a difference in outcome based on antibody status could not be identified, but that relapse rates were lower in years 3 and 4 among patients who were antibody-positive (Table 20). The review by Goodin et al[98] also found that relapse rates were affected by positive neutralizing antibody status of high titer only in studies of 2 years or longer in duration. The evidence for the impact on disease progression was less compelling, with only 2 of 8 studies showing a significant increase in progression among those with neutralizing antibodies.

### Table 20. Duration of treatment and clinical impact of antibody status[99]

| Duration | Interferon β-1b SC (Betaseron®) | Interferon β-1a SC (Rebif®) | Interferon β-1a IM (Avonex®) |
|---|---|---|---|
| 2nd year | "correlation not observed" | 1.8 vs. 1.77 22 mcg (NS)<br>1.75 vs. 1.74 44 mcg (NS) | "No clinical impact of relapse rate or disease progression" |
| 13 to 36 months | 1.08 vs. 0.56 | -- | -- |
| 4th year follow-up | -- | 0.81 vs. 0.5 | -- |

Abbreviations: NS, not statistically significant.

Two trials published subsequent to the Goodin and Namaka systematic reviews reported rates of interferon beta neutralizing antibodies occurring in enrolled patients. Most of these may not have been of sufficient duration to show clinical effects of antibody development, however. In the EVIDENCE trial, which compared interferon high-dose, high-frequency interferon beta-1a (Rebif®) 44 mcg to low-dose interferon beta-1a IM (Avonex®) 30 mcg over 2 years, neutralizing antibodies were detected at least once in 26% of patients receiving high-dose Rebif® and in 3% of those receiving low dose Avonex® ($P<0.001$). Neutralizing antibodies developed earlier with high-dose treatment (58% by week 24, compared with 14% in the low-dose group). Relapse rates were similar in antibody-positive and antibody-negative patients.[45]

The proportion of patients developing neutralizing antibodies was reported in the REGARD study of interferon beta-1a (Rebif®). The rate was 60/138 (16%) at 24 weeks, 93/355

(26%) at 48 weeks, 91/319 (29%) at 72 weeks, and 102/374 (27%) at 96 weeks or last observation carried forward. Neutralizing antibodies had no effect on clinical efficacy: there was no difference in time to first relapse for those positive at any time and those negative (hazard ratio, 1.24; 95% CI, 0.86 to 1.77), although the study may not have been long enough to show clinical effects.

Eight observational studies reported clinical outcomes based on antibody status.[101-108] Although there was an association between neutralizing antibody status and clinical outcome shown in several studies, none found the detrimental effect of positive antibody status to be greater with one of the beta interferons than another. The conclusions that could be drawn from these studies were limited for several reasons: most were not of sufficient duration to show an effect of neutralizing antibodies on clinical status, the numbers of patients taking each drug may not have been sufficient to show a difference between treatments, and lack of control for confounding factors limited the validity of their results.

Evidence correlating comparative clinical outcomes to the antibody status of the individual beta interferons was incomplete and inadequate to make conclusions. Longer-term trials will be needed to clarify the role of this difference in antigenicity and its correlation of clinical outcomes over longer periods of time.

### *Development of antibodies to natalizumab*

An analysis of the AFFIRM and SENTINEL trials reported the incidence and clinical effects of antibodies to natalizumab that developed over 2 years of therapy.[117] In AFFIRM, 57 of 625 patients (9%) tested positive for antibodies at any time during the study; 3% were transiently positive and 6% were persistently positive throughout the study. Most (88%) patients developed antibodies by week 12 of treatment. Results were similar in SENTINEL, in which natalizumab was added to interferon beta-1a therapy, with 12% of patients testing positive for antibodies to natalizumab during the 2-year study, 5% transiently positive, and 96% showing antibodies by week 12 of treatment. In AFFIRM, 34% of patients who were persistently antibody-positive had sustained disability progression, compared with 17% of patients who were antibody-negative. The proportion of patients with sustained disability progression who were transiently antibody-positive was identical to that of patients who were antibody-negative. In contrast, in the SENTINEL study, patients who were persistently antibody-positive did not show a reduced effect of natalizumab on disability progression compared with those who were antibody-negative ($P$=0.503). The cumulative proportion of patients with sustained disability progression over 2 years was 24% in antibody-negative patients, 19% in transiently-positive patients, and 20% in persistently positive patients.

## Key Question 4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

## Summary of the Evidence

- Evidence suggested that all 3 interferon beta-1 products and glatiramer acetate reduced the probability of converting from clinically isolated syndrome to clinically definite multiple sclerosis over 2 to 5 year periods.

- At 3 years, interferon beta-1a IM (Avonex®) was superior to placebo (relative risk, 0.56; 95% CI, 0.38 to 0.81; number needed to treat, 7).
- At 3 years, glatiramer was superior to placebo (hazard ratio, 0.55; 95% CI, 0.40 to 0.77; *P*=0.0005; number needed to treat, 5).
- At 2 years, both Betaseron® and Rebif® 22 mcg were also superior to placebo: relative risks, 0.50 (95% CI, 0.36 to 0.70; number needed to treat, 6) and 0.65 (95% CI, 0.45 to 0.94; number needed to treat, 9) respectively.
- No evidence was found for natalizumab or mitoxantrone in patients with clinically isolated syndrome.
- No head-to-head trials have been conducted.

## Detailed Assessment

### *Previous systematic review*

A Cochrane systematic review evaluated the efficacy and safety of treatment with beta interferons on the proportion of patients delayed to convert from clinically isolated syndrome to clinically definite multiple sclerosis.[118] Three trials were included in the review: CHAMPS,[119] ETOMS,[120] and BENEFIT.[121] Searches were conducted through June 2007. This review did not include a comparison of interferon beta-1a to interferon beta-1b; it combined the interferons and considered them as a group for analysis. Overall, meta-analysis showed that fewer patients converted to CDMS with beta interferon treatment compared with placebo after 1 year (pooled odds ratio, 0.53; 95% CI, 0.40 to 0.71) and after 2 years (pooled odds ratio, 0.52; 95% CI, 0.38 to 0.70).

### Direct evidence

No head-to-head trials have been conducted.

### Indirect evidence

Five placebo-controlled trials (in 12 publications) assessed disease-modifying drugs in patients with a clinically isolated syndrome (Tables 21 and 22).[119-130] One trial was rated good quality[121] and the rest were fair. All 5 trials showed a statistically significant reduction in the proportion of patients and the time to converting to clinically definite multiple sclerosis compared with placebo with relative risks or hazard ratios in the 0.50 to 0.65 range and numbers needed to treat ranging from 5 (glatiramer acetate and Avonex®) to 10 (Rebif®). Because there were apparent clinical differences in the populations enrolled, an indirect meta-analysis of these data was not undertaken.

The 3 trials of interferon beta-1a products were low dose with weekly injections, while the study of interferon beta-1b (Betaseron®), the BENEFIT study, used every other day dosing. The dose of interferon beta-1a SC (Rebif®) in the ETOMS study was 22 mcg. The dose of glatiramer acetate in the PreCIS study was 20 mg daily, the standard dose for treatment of multiple sclerosis. The patient populations enrolled in the studies were somewhat different, with the study of interferon beta-1a SC (Rebif®)[120] enrolling patients with multifocal presentation, a higher percentage with gadolinium enhancing brain lesions, and lesions with larger median volume compared with the other studies (see Table 21).[121, 126] All patients enrolled in CHAMPS

received standardized corticosteroid treatment for the initial episode and were enrolled within 2 weeks of initial symptom presentation, while patients in the other studies were enrolled within 2 or 3 months of initial presentation and treatment of the episode was not standardized. Only patients with monofocal lesions were enrolled in the trial of glatiramer acetate.[127] In contrast, the BENEFIT study of interferon beta-1b (Betaseron®) and 1 of the studies of interferon beta-1a (Avonex®)[130] enrolled patients with at least 2 silent magnetic resonance imaging lesions, and may represent patients at higher risk for progressing to multiple sclerosis.[131] While the primary endpoint of conversion to clinically definite multiple sclerosis was defined slightly differently in the studies, they were based primarily on a relapse of the initial or new symptoms. The BENEFIT trial also used the McDonald criteria, which incorporate magnetic resonance imaging findings.

All of the studies reported a 3-year follow-up, with the exception of ETOMS, which followed patients for 2 years.[120] The CHAMPS trial was stopped early after a planned interim analysis indicated a significant difference in benefit between the groups.[126] Patients enrolled in the CHAMPS who had not converted to multiple sclerosis at the end of the 3-year trial were offered enrollment in CHAMPIONS, a 5-year open-label, investigator-initiated extension study.[123] Fifty-three percent (203 of 383) of patients who had participated in CHAMPS enrolled in CHAMPIONS. Patients who had been assigned to interferon beta-1a during the trial were considered the immediate treatment group and those assigned to placebo and given interferon beta-1a during the extension study were considered the delayed treatment group. The analysis compared the conversion rate between these 2 groups and found that the 5-year cumulative incidence rate in the immediate treatment group was 36% compared with 49% in the delayed treatment group (adjusted hazard ratio 0.57; 95% CI, 0.38 to 0.86). Multivariate analysis indicated that the factors associated with conversion to multiple sclerosis were randomization to the delayed treatment group and younger age at enrollment in the CHAMPS.

The BENEFIT trial included a 5-year follow-up phase. Patients were eligible to enter the follow-up phase after 2 years in the placebo-controlled phase, and were offered treatment with interferon beta-1b (Betaseron®) 250 mcg SC every other day for up to 5 years.[129] Patients initially randomized to interferon beta-1b (Betaseron®) were considered the early treatment group and those initially randomized to placebo were considered the delayed treatment group. Eighty-nine percent (418 of 468) of patients who participated in the placebo-controlled phase entered the follow-up phase. After 5 years, the risk for clinically definite multiple sclerosis was lower in the early treatment group (46%) than the delayed treatment group (57%) (hazard ratio, 0.63; 95% CI, 0.48 to 0.83; number needed to treat, 9).

## Table 21. Efficacy of drugs for multiple sclerosis in patients with a clinically isolated syndrome

| Study Quality | Drug dose/schedule Duration | N | Baseline presentation Mean age | Conversion to multiple sclerosis |
|---|---|---|---|---|
| ***Interferon beta-1a*** | | | | |
| CHAMPS Jacobs 2000 (Avonex®) Fair | 30 mcg IM weekly 3 years | 383 | % treated with steroids: 100% % with gadolinium enhancing lesions 28% Median volume of lesions on T2 weighted MRI 2051 $mm^2$ 33 years | Cumulative probability Interferon β-1a 35% Placebo 50% Relative risk 0.56 (95% CI, 0.38 to 0.81) NNT 7 |
| Pakdaman 2007 (Avonex®) Fair | 30 mcg IM weekly 3 years | 217 randomized 202 completed | Mean number of T2-weighted MRI lesions 4.9 Avonex, 5.5 placebo 28 years | Completers analysis (202 of 217 randomized, unable to calculate ITT results): Avonex: 38/104 (36.6%) Placebo: 57/98 (58.2%) Relative risk (calculated): 0.63 (95% CI, 0.46 to 0.85) NNT 5 Annual relapse rate: 13% vs 22% |
| ETOMS Comi 2001 (Rebif®) Fair | 22 mcg SC weekly 2 years | 309 | % treated with steroids: 70% % with gadolinium enhancing lesions on T1: 58% Median volume of lesions on T2 weighted MRI: 4964 to 5542 $mm^2$ 29 years | Interferon β-1a 52/154 (34%) Placebo 69/154 (45%) Relative risk 0.65 (95% CI, 0.45 to 0.94) NNT 10 |
| ***Interferon beta-1b*** | | | | |
| BENEFIT Kappos 2006 (Betaseron®) Good | 250µg SC every other day 2 years | 468 | % treated with steroids: 71% Monofocal- 53% Multifocal- 47% % with gadolinium enhancing lesions on T1: 42% Median volume of T2 lesions: 1951.5 to 1858.5 $mm^2$ (range 592 to 5029) | Poser criteria (CDMS): Interferon beta-1b 75/292 (26%) Placebo 77/176 (44%) Hazard ratio 0.50 (95% CI, 0.36 to 0.70) NNT 6 HRQOL: No significant change from baseline in either group |
| ***Glatiramer acetate*** | | | | |
| PreCISe Comi 2009 Fair | 20 mg daily 3 years | 481 | % treated with steroids: 64% Monofocal: 100% Median volume of T2 lesions: 3.9 mL (range 0.2 to 54.1) 31 years (range 18 to 46) | Glatiramer: 60/243 (25%) Placebo:102/238 (43%) HR 0.55 (95% CI, 0.40 to 0.77; *P*=0.0005) NNT 5 |

Abbreviations: CDMS, HRQOL, health-related quality of life; IM, intramuscular; ITT, intention-to-treat; MRI, magnetic resonance imaging; NNT, number needed to treat; SC, subcutaneous.
[a] Total exceeds 100% - more than 1 site counted.

In a post hoc analysis of the CHAMPS data, only patients considered at high risk of conversion to multiple sclerosis (≥9 T2-weighted hyperintense lesions and ≥1 gadolinium enhanced lesion) were included. This was a small group of patients (N=91; 24% of the total enrolled). The relative risk of conversion to multiple sclerosis was found to be 0.34 (95% CI, 0.17 to 0.70; *P*=0.002). This compared with a relative risk of 0.56 (95% CI, 0.38 to 0.81; *P*=0.002) in the total population. In the BENEFIT study of interferon beta-1b (Betaseron®), multiple subgroup analyses were undertaken, examining the effects in monofocal compared with multifocal presentation, and patients with or without gadolinium enhanced lesions or ≥ 9 T2-weighted hyperintense lesions. The results indicated a significant benefit in all groups, with hazard ratios for conversion to multiple sclerosis ranging from 0.40 in patients with <9 T2 lesions to 0.63 in patients with multifocal presentation (compared with a hazard ratio of 0.50; 95% CI, 0.36 to 0.70 in the overall study group). In the trial of glatiramer acetate, post hoc subgroup analyses showed a better response in women (hazard ratio, 0.52; 95% CI, 0.34 to 0.81), in patients younger than age 30 years (hazard ratio, 0.47; 95% CI, 0.27 to 0.80), and in patients with 1 or more gadolinium enhancing lesions at baseline (0.29; 95% CI, 0.16 to 0.54).[127] In patients with 9 or more T2 lesions at baseline, the hazard ratio was 0.42 (95% CI, 0.27 to 0.64) compared with placebo. Because these were subgroup analyses, with relatively small numbers of patients in each group, these results should be interpreted with caution.

### *Adverse events*

Rates of discontinuation of assigned treatment for reasons other than conversion to multiple sclerosis are shown in Table 22. All comparisons are to placebo; there is no direct evidence. In the BENEFIT trial of interferon beta-1b (Betaseron®) more patients either discontinued interferon early or were lost to follow-up compared with placebo (21% compared with 16%). Withdrawals due to adverse events were significantly higher with interferon beta-1b (Betaseron®) than placebo, and higher with glatiramer acetate compared with placebo, but significantly *lower* with interferon beta-1a IM (Avonex®) compared with placebo.[119] The trial of interferon beta-1a SC 22 mcg (Rebif®) reported only 3 withdrawals due to adverse events, but did not specify to which group(s) the patients had been assigned.

The studies did not describe methods of ascertaining adverse events and the reporting of adverse events was sparse. The incidence of adverse events was significantly higher in the beta interferon and glatiramer acetate groups compared with the placebo groups for most commonly occurring adverse events such as influenza-like syndrome and injection-site reactions. Rates of serious adverse events were not different from placebo in any trial, and rates of depression were not significantly higher than placebo in the 2 trials reporting this outcome (interferon beta-1b (Betaseron®) and interferon beta-1a (Avonex®).

## Table 22. Adverse events of beta interferons in patients with a clinically isolated syndrome

| Study | Interferon Dose/schedule | Withdrawal due to adverse events | Adverse event rates Treatment vs. placebo, *P* value |
|---|---|---|---|
| ***Interferon beta-1a*** | | | |
| CHAMPS 2000 (Avonex®) | 30 mcg IM weekly x 3 years | Interferon β-1a 4/193 (0.5%)<br>Placebo 7/190 (4%)<br>*P*=0.0355[a] | Flu-like syndrome (1st 6 mos)<br>54% vs. 26% *P*<0.001<br>Depression<br>20% vs.13%, *P*=0.0645<br>Serious adverse events<br>6% vs.10%, NS |
| Pakdaman 2007 (Avonex®) | 30 mcg IM weekly x 3 years | NR | Serious adverse events: 9.2% vs 6.7%<br>Flu-like syndrome: 76% vs 64%; *P*=0.002) |
| ETOMS Comi 2001 (Rebif®) | 22 mcg SC weekly x 2 years | A total of 3 withdrew due to adverse events – stratification by group not reported. (0.78% overall; 1.95% if assumed all from Rebif® group) | Injection site reactions<br>60% vs. 12%, *P*<0.0001[a]<br>Fever<br>28% vs. 12%, *P*=0.0006[a]<br>Myalgia<br>17% vs. 9%, *P*=0.0419[a]<br>Chills<br>11% vs. 5%, *P*=0.0604[a]<br>Serious adverse events<br>4% vs. 3%, NS[a] |
| ***Interferon beta-1b*** | | | |
| BENEFIT Kappos 2006 (Betaseron®) | 250µg SC every other day 2 years | Interferon β-1b 32/292 (11%)<br>Placebo 1/176 (0.6%)<br>*P*<0.0001[a] | Injection-site reactions<br>48.3% vs 8.5%, *P*<0.0001[a]<br>Flu-like syndrome<br>44.2% vs 18.2%, *P*<0.0001[a]<br>Fever<br>13.0% vs 4.5%, *P*=0.003[a]<br>Depression<br>10.3% vs 11.4%, *P*=NS<br>Serious adverse events<br>6.8% vs 6.8%, NS<br>ALT elevation (≥5x baseline)<br>17.8% vs 4.5%, *P*<0.0001[a]<br>AST elevation (≥5x baseline)<br>6.2% vs 0.6%, *P*=0.0027[a] |
| ***Glatiramer acetate*** | | | |
| PreCISe Comi 2009 | 20 mg daily 3 years | Glatiramer: 14/ 243 (6%)<br>Placebo: 4/238 (2%) | Serious adverse events<br>8% vs 5%<br>Flu-like syndrome<br>4.1% vs 0.8%<br>Injection-site reaction<br>3% vs 0%<br>Death (suicide): 1 in glatiramer group |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; NR, not reported; NS, not significant; SC, subcutaneous.
[a] Calculated using chi-square test, Stats Direct.

In a 5-year, open-label extension arm of the CHAMPS study, only serious adverse events (N=13 in 6% of patients overall) were reported and none were considered related to interferon beta-1a.[123] Other typical and concerning adverse events associated with interferon beta-1a were not discussed or reported. In the 5-year follow-up phase of the BENEFIT trial, the incidence and nature of adverse events was similar to that reported at the end of the 2-year placebo-controlled

period. More patients in the delayed treatment group discontinued due to adverse events (12% compared with 2%).[129]

## Key Question 5. Do disease-modifying treatments for multiple sclerosis differ in harms?

### Summary of the Evidence

#### *Adverse events and long-term safety*

Beta interferons

- Comparative adverse event reporting was limited with multiple studies using different doses of the same product, most frequently with interferon beta-1a SC (Rebif®). We have used data pertaining to interferon beta-1a SC (Rebif®) 44µg SC 3 times weekly dosing when pooling all trial data.
- Although generally well tolerated, adverse events were reported frequently with all 3 beta interferon products and although the ranges were wide, differences between the products were apparent (Table 23):

**Table 23. Comparative tolerability of beta interferon**

| Adverse event | Relative frequencies based on pooled trial rates |
|---|---|
| Injection site reaction | Interferon β-1a SC (Rebif®) 60.6% (22.8 to 88.9) ~ Interferon β-1b SC (Betaseron®) 58.9% (48.6 to 69.3) > Interferon β-1a IM (Avonex®) 8.5% (4.5 to 15.2) |
| Flu-like syndrome | Interferon β-1a IM (Avonex®) 62.2% (39.0 to 80.8) >Interferon β-1b SC (Betaseron®) 41.7% (25.0 to 58.5) > Interferon β-1a SC (Rebif®) 28.7 (16.5 to 45.1) |
| Fatigue | Interferon β-1b SC (Avonex®) 26.3% (4.1 to 74.6) > Interferon β-1a SC (Rebif®) 10.2% (2.8 to 30.9) |
| Fever | Interferon β-1b SC (Betaseron®) 38.1% (12.4 to 63.7) > Interferon β-1a IM (Avonex®) 20.4% (5.6 to 52.5) > Interferon β-1a SC (Rebif®) 4.9% (0.7 to 26.9) |
| Depression | Interferon β-1a IM (Avonex®) 19.7% (10.8 to 33.1) ~ Interferon β-1b SC (Betaseron®) 18.4% (8.1 to 28.6) >Interferon β-1a SC (Rebif®) 14.4% (5.6 to 32.0) |
| Overall withdrawal | Interferon β-1b SC (Betaseron®) 19.4% >Interferon β-1a SC (Rebif®) 14.2% (8.3 to 23.2) >Interferon β-1a IM (Avonex®) 13.1% (8.7 to 19.4) |
| Discontinuation due to adverse event | Interferon β-1b SC (Betaseron®) 7.5% (3.7 to 11.5) >Interferon β-1a SC (Rebif®) 6.1% (4.6 to 8.0) > Interferon β-1a IM (Avonex®) 3.6% (1.7 to 7.4) |

Abbreviations: IM, intramuscular; SC, subcutaneous.

- Evidence from non-randomized studies suggested that there is no difference among the beta interferons in risk of developing thyroid dysfunction, although rates were slightly, but not significantly, higher with interferon beta-1b SC (Betaseron®).

- Elevated liver enzymes were also very common among beta interferon-treated patients, particularly during the first year of treatment. Withdrawal rates due to elevated liver enzymes were very small across the trials.
- Mixed data from non-randomized studies found rates of depression ranging from 5% to 12% for interferon beta-1a SC (Rebif®) and of 18% for interferon beta-1a IM (Avonex®).
- In patients with secondary progressive multiple sclerosis, Pooled analysis suggested significantly higher rates of injection site reactions (2.51; 95% CI, 1.56 to 4.04; number needed to harm, 3), abnormal liver function tests (3.38; 95% CI, 2.16 to 5.27; number needed to harm, 8), and withdrawal due to adverse events (2.61; 95% CI, 1.23 to 5.53; number needed to harm, 30) with interferon beta-1a SC (Rebif®) and flu-like syndrome (1.37; 95% CI, 1.02 to 1.85; number needed to harm, 7) and withdrawal due to adverse events (2.24; 95% CI, 1.26 to 4.00; number needed to harm, 32) with interferon beta-1b SC (Betaseron®) compared with placebo.

### Glatiramer acetate

- Tolerability adverse events were reported in 2 head-to-head trials comparing glatiramer acetate to beta interferon products. They revealed similar tolerability with glatiramer acetate having higher rates of injection site reactions and post-injection systemic response while the interferons reported higher rates of flu-like syndrome, elevated liver enzymes, fever, myalgia, and headache. Lipoatrophy was reported only in patients receiving glatiramer acetate.
- Adverse event rates were higher for glatiramer acetate when compared with placebo, most notably post-injection systemic reactions and injection-site reactions (usually of limited duration for both; $P<0.0001$), as were withdrawals due to adverse events (3.7% compared with 1.1%; $P=0.08$).
- Evidence on the safety of glatiramer acetate from 5 non-comparative, non-randomized studies was consistent with that from randomized trials. No additional serious adverse events were reported in any of these studies, with the exception of the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use.
- Withdrawal rates for glatiramer acetate were consistently significantly higher in observational studies when compared with placebo but lower when compared with interferons in observational studies.

### Natalizumab

- Natalizumab (Tysabri®) use has been linked to 55 cases of progressive multifocal leukoencephalopathy worldwide.
- Adverse event rates were similar in 2 placebo-controlled trials in patients with relapsing-remitting multiple sclerosis and there were no significant differences between the comparisons, although more natalizumab patients withdrew due to adverse events. Two cases of progressive multifocal leukoencephalopathy led to cessation of 1 of these trials (SENTINEL). There is now a black box warning issued by the US Food and Drug Administration due to reported cases of progressive multifocal leukoencephalopathy associated with natalizumab use with risk being directly proportional to total cumulative dose. There are no cases in patients who received infusions for 12 months or less.
- In the mixed population of relapsing-remitting and secondary progressive multiple sclerosis, adverse events and withdrawal rates varied widely among the 3 studies reporting

safety outcomes, however there were no overall differences between the natalizumab and placebo groups.

### Mitoxantrone

- In placebo-controlled trials of patients with relapsing-remitting multiple sclerosis and a mixed population of relapsing-remitting and secondary progressive multiple sclerosis, mitoxantrone (Novantrone®) use was associated with amenorrhea, nausea and vomiting, and urinary tract infections. In the mixed population studies, pooled data found more withdrawals due to adverse events in the mitoxantrone group compared with placebo as well as a non-significant decrease in left ventricular ejection fraction below 50%.
- Adverse events in non-randomized studies of mitoxantrone were consistent with those in trials, most commonly nausea/vomiting, alopecia, and amenorrhea in women.
- Observational studies and 2 open-label studies found relatively low rates of cardiac adverse events (congestive heart failure: 0.15%; asymptomatic left ventricular ejection fraction <50%: 2.18%). Subgroup analysis suggested that higher cumulative doses of mitoxantrone were potentially associated with greater risk of asymptomatic left ventricular ejection fraction <50%, although this failed to reach statistical significance (*P*=0.06). One small study (N=18) found transient reduction of left ventricular ejection fraction in 11% when monitored more frequently, but larger trials are needed to determine the validity of this finding as well as the long-term clinical significance.
- The risk of therapy-related acute leukemia (t-AL) appeared to be dose related. A meta-analysis that included 1620 patients found the overall rate of t-AL to be very low overall (0.12%).
- Risk of permanent amenorrhea may be associated with older age (odds ratio, 1.18; 95% CI, 1.10 to 1.27; *P*=0.01) and higher cumulative dose (odds ratio, 1.02; 95% CI, 1.01 to 1.04; *P*=0.01) based on 1 observational study (N=189).

## Detailed Assessment

### *Beta interferon*

Three head-to-head trials (N=1166) comparing the interferons in patients with relapsing-remitting multiple sclerosis reported adverse events.[40, 42, 44] Additional data was obtained from placebo-controlled trials (5 placebo-controlled trials in patients with relapsing-remitting multiple sclerosis,[51-56] 5 placebo-controlled trials in patients with secondary progressive multiple sclerosis,[75-83, 132] 2 placebo-controlled trials [85, 87] and 1 systematic review[36] in patients with primary progressive multiple sclerosis, and 1 meta-analysis of 6 placebo-controlled trials in chronic progressive multiple sclerosis) and observational studies.

Adverse events were considered typical in all of the trials, with flu-like syndrome and injection site reactions being common. However, across the studies and types of beta interferons, the ranges were wide even within studies of the same beta interferon. For example, in the 5 trials of patients with secondary progressive multiple sclerosis, the range of flu-like syndrome was 37% with 22 µg of interferon beta-1a SC (Rebif®) to 70% with interferon beta-1a IM (Avonex®).[74-83] Clearly dosing, definition, and ascertainment varied among the studies. In this

analysis, we have pooled only to the same dose and dosing schedule of interferon beta-1a SC (Rebif®).

In the head-to-head trials comparing the beta interferon products, adverse events were not well reported, with 2 of the 5 trials not reporting adverse events.[41] The dose of interferon beta-1a SC (Rebif®) was 22 µg weekly in the Koch-Henrisksen study and they only reported combined incidence for a few selected adverse events. Withdrawal or early discontinuation due to an adverse event or any other reason was not found to be different between this low dose of interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) 250 µg. Typical adverse events reported included flu-like symptoms, injection-site reactions, fever, and withdrawal. The comparative frequency of these events is outlined in the section that follows.

The Cochrane systematic review of placebo-controlled trials in patients with relapsing-remitting multiple sclerosis evaluated the frequency of adverse events, reporting only on the 44 µg dosing of interferon beta-1a (Rebif®) however they did include data from a once weekly dosing schedule from the OWIMS trial. The data is summarized below. Only 3 times weekly interferon beta-1a SC (Rebif®) was not associated with significantly increased rates of flu-like syndrome, fever, and myalgias (Table 24). The incidence of leukopenia, however, was significantly higher with 3 times weekly interferon beta-1a SC (Rebif®), while interferon beta-1b SC (Betaseron®) and interferon beta-1a IM (Avonex®) were not. Comparing the 2 dosing regimens of interferon beta-1a SC (Rebif®), dosing once weekly resulted in statistically significantly greater rates of flu-like syndrome, fever, and headache while dosing 3 times weekly did not. Of note, standard dosing for (Rebif®) is 3 times weekly.

### Table 24. Interferon beta-1b and 1a compared with placebo in patients with relapsing-remitting multiple sclerosis: adverse events

| Adverse event | Interferon beta-1b SC (Betaseron®) | Interferon beta-1a IM (Avonex®) | Interferon beta-1a SC (Rebif®) |
|---|---|---|---|
| | RR (95% CI) vs. placebo | RR (95% CI) vs. placebo | RR (95% CI) vs. placebo |
| Flu-like syndrome | 2.89 (1.91 to 4.37) | 1.52 (1.20 to 1.93) | 1.13 (0.80 to 1.60) PRISMS<br>1.70 (1.23 to 2.37) OWIMS |
| Injection site reaction | 12.19 (5.88 to 25.26) | 2.00 (0.22 to 17.89) | 2.83 (2.11 to 3.79) PRISMS<br>5.78 (3.35 to 9.99) OWIMS |
| Fever | 1.70 (1.28 to 2.27) | 1.86 (1.11 to 3.12) | 1.86 (0.95 to 3.65) PRISMS<br>3.50 (1.58 to 7.74) OWIMS |
| Myalgias | 1.69 (1.16 to 2.46) | 2.28 (1.45 to 3.59) | 1.69 (0.92 to 3.11) PRISMS<br>1.86 (0.94 to 3.67) OWIMS |
| Fatigue | -- | 1.66 (0.98 to 2.81) | 1.19 (0.76 to 1.87) PRISMS<br>1.02 (0.30 to 3.41) OWIMS |
| Headache | -- | 1.17 (0.98 to 1.40) | 1.08 (0.86 to 1.36) PRISMS<br>1.44 (1.03 to 2.02) OWIMS |
| Lymphopenia | 1.60 (1.15 to 2.23) | -- | 3.48 (1.54 to 7.89) PRISMS |
| Leukopenia | 8.93 (0.49 to 164.08) | 0 | 5.08 (1.50 to 17.26) PRISMS |
| Increased AST | 2.73 (0.89 to 8.33) | 0 | 3.05 (0.62 to 14.91) PRISMS |
| Increased ALT | 2.76 (1.34 to 5.66) | 0 | 6.10 (1.38 to 26.87) PRISMS |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; SC, subcutaneous.

In the 5 placebo-controlled trials in patients with secondary progressive multiple sclerosis, withdrawal due to adverse events was generally less than 10%, with most studies showing double the rate of discontinuation in the beta interferon arm compared with the placebo arm, but differences across the beta interferons were not apparent.[74-83] Two of these trials used a 22 µg dose of interferon beta-1a SC (Rebif®) and for this reason we only pooled this dose for adverse event analysis. Pooled analysis of these trials suggested significantly higher rates of injection site reaction, abnormal liver function tests, and withdrawal due to adverse events with interferon beta-1a SC (Rebif®) 22 µg and flu-like syndrome and withdrawal due to adverse events with interferon beta-1b SC (Betaseron®) compared with placebo (Table 25).

## Table 25. Adverse events in trials of beta interferons in patients with secondary progressive multiple sclerosis (beta interferon compared with placebo)

| Study | Flu-like syndrome | Injection site reactions | Depression | Elevated LFTs | Myalgia | Withdrawal due to adverse events |
|---|---|---|---|---|---|---|
| **Interferon beta-1a IM (Avonex®) vs. placebo** | | | | | | |
| IMPACT 2002<br>N=436<br>Interferon β1-a 60 µg IM vs. placebo | 70% vs. 33%<br>*P*<0.001 | 16% vs. 20%<br>*P*=0.261 | 26% vs. 22%<br>*P*=0.435 | NR | 30% vs. 31%<br>*P*=0.917 | 8% vs. 4%<br>*P*=0.05 |
| **Interferon beta-1a SC (Rebif®) vs. placebo** | | | | | | |
| SPECTRIMS 2001<br>N=618<br>Interferon β1-a SC 22 vs. 44 µg vs. placebo | 50% vs. 51% vs. 52% (ns) | 87% vs. 81% vs. 41%<br>*P*<0.05 for each interferon vs. placebo | 35% vs. 32% vs. 29%<br>NS | 36% vs. 33% vs. 10%<br>*P*<0.05 for each interferon vs. placebo | NR | 3% vs. 3.8% vs. 1.5% (NS) |
| Andersen 2004<br>N=364<br>Interferon β1-a SC 22 µg vs. placebo | 37% vs. 22%<br>*P*=0.002 | 27% vs. 8%<br>*P*<0.001 | 20% vs. 14%<br>*P*=0.128 | 3% vs. 0%<br>*P*=0.061 | 15% vs. 8%<br>*P*=0.048 | 8.6% vs. 3.4%<br>*P*=0.036 |
| **Pooled analysis of 22 µg dose RR (95% CI)** | 1.27<br>(0.73 to 2.19) | **2.51<br>(1.56 to 4.04)** | 1.25<br>(0.98 to 1.59) | **3.38<br>(2.16 to 5.27)** | -- | **2.61<br>(1.23 to 5.53)** |
| **Interferon beta-1b (Betaseron®) vs. placebo** | | | | | | |
| North American Study Group 2004<br>N=939<br>Interferon β1-b 250 µg vs. 160 µg/m$^2$ vs. placebo SC | 43% vs. 45% vs. 33%<br>*P*=0.0107 for 250 µg,<br>*P*=0.003 for 160 µg/m$^2$ | 55% vs. 52% vs. 13%<br>*P*<0.001 for both FN doses | NR | NR | 29% vs. 24% vs. 19%<br>*P*=0.003 for 250 µg<br>*P*=0.117 for 160 µg/m$^2$ | 9% vs. 10% vs. 4%<br>*P*=0.002 for 250 µg<br>*P*=0.005 for 160 µg/m$^2$ |
| European Study Group 2001<br>N=718<br>Interferon β1-b SC 250 µg vs. placebo | 59.2% vs. 37.2%<br>*P*<0.0001 | NR | NR | NR | 22.8% vs. 8.9%<br>*P*<0.0001 | 1.4% vs. 1.1%<br>NS |

| Study | Flu-like syndrome | Injection site reactions | Depression | Elevated LFTs | Myalgia | Withdrawal due to adverse events |
|---|---|---|---|---|---|---|
| **Pooled analysis for 250 mcg dose vs. placebo RR (95% CI)** | **1.37 (1.02 to 1.85)** | | | | 1.77 (0.88 to 3.56) | **2.24 (1.26 to 4.00)** |

Abbreviations: IM, intramuscular; LFT, liver function test; NR, not reported; NS, not significant ; SC, subcutaneous.

A systematic review for the Cochrane collaboration reviewed the 2 placebo-controlled trials in primary progressive multiple sclerosis and although pooling did not allow interpretation for comparative effectiveness, it did find that for the interferons, the most significant adverse events were flu-like reactions (relative risk, 2.48; 95% CI, 1.60 to 3.83), injection site reaction (relative risk, 10.80; 95% CI, 3.34 to 35.03), and leukopenia (relative risk, 4.10; 95% CI, 1.34 to 12/57). There was no difference in the frequency of fatigue (relative risk, 1.62; 95% CI, 0.68 to 3.85) or anemia (relative risk, 2.51; 95% CI, 0.27 to 23.20) compared with placebo.[36]

Of the 5 observational studies in patients with relapsing-remitting multiple sclerosis, 3 met inclusion criteria for both effectiveness and harms analysis, and the best of these was a retrospective cohort study based on data from patients in Austria, Switzerland, and Germany, with 4754 patients exposed to 1 of the 3 interferons.[49] An analysis of the reasons for discontinuation of treatment indicated that discontinuations due to injection site reactions were significantly lower in the interferon beta-1a (Avonex®) 30 µg IM weekly group compared with either the interferon beta-1a SC (Rebif®) 22 mcg SC 3 times weekly or interferon beta-1b (Betaseron®) 250 µg SC every other day groups, but no different than the interferon beta-1a SC (Rebif®) 44µg SC twice weekly group. Differences in frequency of flu-like syndrome was statistically significant only for interferon beta-1a SC (Rebif®) 22 mcg group compared with the interferon beta-1b (Betaseron®) group with the interferon beta-1a SC (Rebif®) 22 mcg being lower. Discontinuations due to lack of efficacy was greatest in the interferon beta-1a SC (Rebif®) 22 mcg group, compared with the interferon beta-1a IM (Avonex®) group or the interferon beta-1b (Betaseron®) group (Table 26). The other 2 studies were of patients being treated at large multiple sclerosis specialty centers (1 in Spain, 1 in Italy), enrolled and followed every 3 months.[46, 47] These studies had a high risk of bias due to clinically important differences among groups at baseline, and because at the outset of data collection only Betaseron® was marketed in those countries, while Avonex® and Rebif® were approved during the time period of the study.

**Table 26. Discontinuation due to adverse events: Observational evidence in patients with relapsing-remitting multiple sclerosis[51]**

| Adverse event | Rates of discontinuation due to adverse events, adjusted analysis |
|---|---|
| Flu-like syndrome | Interferon β-1a SC (Rebif®) 22 mcg< Interferon β-1b (Betaseron®)<br>0.2% vs 1.2%, *P*=0.0038 |
| Injection-site reactions | Interferon β-1a IM (Avonex®)<Interferon β-1a SC (Rebif®) 22 mcg<br>0.1% vs 2%, *P*=0.0001<br>Interferon β-1a IM (Avonex®)<Interferon β-1b (Betaseron®)<br>0.1% vs 2.5%, *P*<0.0001 |
| Lack of efficacy | Interferon β-1a SC (Rebif®) 22 mcg> Interferon β-1a IM (Avonex®)<br>9.3% vs 7.4%, *P*=0.0027<br>Interferon β-1a SC (Rebif®) 22 mcg>Interferon β-1b (Betaseron®)<br>9.3% vs 6.8%, *P*<0.001 |

Abbreviations: IM, intramuscular; SC, subcutaneous.

Other non-trial evidence was limited and low quality, with 4 open-label studies of interferon beta-1b (Betaseron®),[133-138] 3 open-label studies of interferon beta-1a IM (Avonex®),[114, 139, 140] 3 open label studies of interferon beta-1a SC (Rebif®),[141, 142, 142], 3 studies (1 with 3 publications) reporting adverse event data for more than 1 beta interferon,[143-147] 1 study comparing open-label use of interferon beta-1b SC (Betaseron®) to an untreated control group,[148] and 1 study comparing interferon beta-1a IM (Avonex®) to alemtuzumab, a drug not available in the United States (Investigators 2008).[149] The observational study by Rio et al provided a median of 60 months of follow-up (range 12-115 months) on 146 patients receiving interferon beta-1b (Betaseron®).[150] They observed 4 deaths (3 sepsis and 1 pulmonary hemorrhage), 1 intracerebral hemorrhage, and 1 gastrointestinal hemorrhage, all of which were unexpected adverse events. The rest of the studies were not longer in duration than the trials, nor did they provide data on rare but serious adverse events. Because of the limitations of these designs and lack of controlling for potential confounding, these studies did not provide better information on tolerability than the trial data.

In a study of patient perceptions of adverse events associated with beta interferon therapy, 40 patients taking interferon beta-1b SC (Betaseron®) or interferon beta-1a IM (Avonex®) were questioned on the impact of adverse effects on their lives.[151] Results of this study indicated that most adverse effects were mild and did not have a strong impact on the lives of patients, although fatigue was rated moderate or severe. The study found wide variation in patient response to both systemic and local adverse events, but did not make comparisons between the products.

### Synthesis of direct and indirect evidence

Pooled rates of tolerability of adverse effects and discontinuation for each of the beta interferons, based on all head-to-head and placebo-controlled trial rates and controlling for study effects, are presented in Table 27 below. Given the differences in events reported with the different doses of interferon beta-1a SC (Rebif®), only data using the 44 µg dose was pooled. This analysis indicated higher rates of injection site reactions, fever, and overall or adverse event-related discontinuation with interferon beta-1b SC (Betaseron®). Interferon beta-1a IM (Avonex®) led to higher rates of flu-like syndrome than the others, but the lowest rates of fatigue, fever, injection-site reaction and overall or adverse event-related discontinuations. Interferon beta-1a SC

(Rebif®) 44 µg had slightly higher rates of fatigue, but lower rates of depression than the others. Although a small observational study of 225 patients with relapsing-remitting multiple sclerosis did not agree with the pooled evidence, suggesting that interferon beta-1a SC (Rebif®) 44 µg had the lowest overall rates of withdrawal due to adverse event or perceived lack of efficacy, the lower quality of the evidence precludes making any conclusion on its results.[152]

**Table 27. Interferon beta-1b and 1a: pooled adverse event rates**

| Adverse event | Interferon beta-1b SC (Betaseron®) | Interferon beta-1a IM (Avonex®) | Interferon beta-1a SC (Rebif®) 44µg |
|---|---|---|---|
| | Rate (95% CI) | Rate (95% CI) | Rate (95% CI) |
| Injection site reaction | 58.9% (48.6 to 69.3) | 8.5% (4.5 to 15.2) | 60.6% (22.8 to 88.9) |
| Flu-like syndrome | 41.7% (25.0 to 58.5) | 62.2% (39.0 to 80.8) | 28.7% (16.5 to 445.1) |
| Fatigue | -- | 26.3% (4.1 to 74.6) | 10.2% (2.8 to 30.9) |
| Myalgias | 29.1% (23.0 to 35.1) | | |
| Fever | 33.3% (19.0 to 47.6) | 20.4% (5.6 to 52.5) | 5.4% (2.2 to 12.9) |
| Depression | 18.4% (8.1 to 28.6) | 19.7% (10.8 to 33.1) | 14.4% (5.6 to 32.0) |
| Overall withdrawal | 19.4% (14.7 to 24.1) | 13.1% (8.7 to 19.4) | 14.2% (8.3 to 23.2) |
| Discontinuation due to adverse event | 7.5% (3.7 to 11.2) | 3.6% (1.7 to 7.4) | 6.1% (4.6 to 8.0) |

*Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a SC (Rebif®)*

The 2-year Koch-Henriksen study in patients with relapsing-remitting multiple sclerosis (N=301) directly compared interferon beta-1b SC (Betaseron®) to interferon beta-1a SC (Rebif®) but only reported combined incidence for a few selected adverse effects and found that withdrawal or early discontinuation due to an adverse event was not found to be different between the drugs. One retrospective observational study comparing the 3 different interferons (N=4754) found that flu-like syndrome was higher in the interferon beta-1b (Betaseron®) group (1.2% compared with 0.2%; *P*=0.0038), however, discontinuations due to lack of efficacy was greatest in the interferon beta-1a SC (Rebif®) 22 mcg group (9.3% compared with 6.8%; *P*<0.001).[49] A small observational study of patients with relapsing-remitting multiple sclerosis (N=454) compared injection site pain and injection site reactions in patients receiving interferon beta-1b SC (Betaseron®) with interferon beta-1b SC (Rebif®) 44 µg and found that interferon beta-1b SC (Betaseron®) had fewer injection site reactions (48.2% compared with 66.2%; *P*<0.0001) and greater patients that experience no pain, or the pain they did experience had no impact on continuing treatment (76.9% compared with 64.1%; *P*=0.006).(Baum 2007) The results of these studies however are contrary to the direct trial evidence. In reviewing the 4 placebo-controlled trials in patients with relapsing-remitting multiple sclerosis and 2 systematic reviews of the 4 trials, only the 3 times weekly interferon beta-1a SC (Rebif®) was not associated with significantly increased rates of flu-like syndrome, fever, and myalgias while leukopenia was significantly higher with this drug.[52-56] This was contrary to pooled analysis from the 5 trials of the beta interferons compared with placebo in secondary progressive multiple sclerosis which suggested that significantly higher rates of injection site reactions, abnormal liver function tests, and withdrawal due to adverse events with interferon beta-1a SC (Rebif®) and flu-like syndrome and withdrawal due to adverse events with interferon beta-1b SC (Betaseron®) compared with placebo. Our pooled analysis of all head-to-head and placebo-controlled trial data indicated that

interferon beta-1b SC (Betaseron®) had higher rates of injection site reactions, fever, overall withdrawal, and discontinuation rates due to adverse events (Table 27).

### *Interferon beta-1a IM (Avonex®) compared with interferon beta-1a SC (Rebif®)*

One head-to-head trial in relapsing-remitting multiple sclerosis reported adverse event data. The 16-month EVIDENCE trial (N=677) compared interferon beta-1a IM (Avonex®) 30 µg SC once weekly to interferon beta-1a SC (Rebif®) 44 µg SC 3 times weekly and found that significantly more patients taking interferon beta-1a SC (Rebif®) experienced injection site reactions (85% compared with 33%; $P<0.001$), abnormal liver function tests (18% compared with 10%; $P=0.003$), and leukocyte abnormalities (14% compared with 5%; $P<0.001$).[44] Significantly more patients taking interferon beta-1a IM (Avonex®) experienced flu-like symptoms (53% compared with 45%; $P=0.031$). Differences in withdrawal or early discontinuation overall or due to adverse events were not found. Data on compliance or patient satisfaction with treatment were not recorded. This study then had a crossover phase in which patients initially receiving weekly interferon beta-1a IM (Avonex®) once weekly were switched to interferon beta-1a SC (Rebif®) 3 times weekly while those taking interferon beta-1a SC (Rebif®) continued to do so.[45] For those transitioning to the interferon beta-1a SC (Rebif®) there was a significant increase in injection site reactions (10% compared with 23%), liver function abnormalities (3% to 6%), and white blood cell abnormality (1.5% compared with 4.5%). Similarly, there was a significant decrease in flu-like symptoms with the interferon beta-1a SC (Rebif®) (16% to 4%).

One large retrospective observational study in patients with relapsing-remitting multiple sclerosis (N=4754) compared the 3 different interferons and found that discontinuations due to injection site reactions and lack of efficacy were higher in the interferon beta-1a (Rebif®) 22 µg group compared with the interferon beta-1a IM (Avonex®) group (2% compared with 0.1%; $P=0.0001$ and 9.3% compared with 7.4%; $P=0.0027$, respectively).[49] A short-term, 6-month, observational study compared interferon beta-1a IM (Avonex®) to interferon beta-1a (Rebif®) 44 µg and found that there were no notable differences between the 2 treatment groups regarding any of the adverse responses, with 1 patient in the interferon beta-1a (Rebif®) 44 µg group discontinuing due to an adverse event while 78.3% in the interferon beta-1a IM (Avonex®) group and 79.1% in the interferon beta-1a (Rebif®) 44 µg group reporting any adverse event.[147] In reviewing the 4 placebo-controlled trials and 2 systematic reviews of the 4 trials in patients with relapsing-remitting multiple sclerosis, interferon beta-1a IM (Avonex®) was associated with increased rates of flu-like syndrome, fever, and myalgias while interferon beta-1a (Rebif®) was associated with higher rates of leukocyte and liver enzyme abnormalities.[52-56] Our pooled analysis of all head-to-head and placebo-controlled trial data indicated that interferon beta-1a SC (Rebif®) had higher rates of injection site reactions and withdrawal due to adverse events (Table 27). Interferon beta-1a IM (Avonex®) was associated with higher rates of flu-like syndrome, fatigue, fever, and depression.

### *Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a IM (Avonex®)*

One head-to-head trial in patients with relapsing-remitting multiple sclerosis, the 2-year INCOMIN trial (N=188), compared interferon beta-1a IM (Avonex®) with interferon beta-1b SC (Betaseron®) and found both drugs equally tolerable, with the only difference being a higher incidence of injection site reactions and headaches in patients receiving interferon beta-1b SC (Betaseron®) (37% compared with 8%; $P<0.001$) compared with interferon beta-1a IM (Avonex®) (16% compared with 7%; $P=0.05$).[42]

The 1 retrospective observational study in patients with relapsing-remitting multiple sclerosis that compared the 3 different interferons (N=4754) found that discontinuation rates due to injection site reactions were higher in the interferon beta-1b (Betaseron®) group compared with the interferon beta-1a IM (Avonex®) group (2.5% compared with 0.1%; $P<0.0001$).[49]

In reviewing the 4 placebo-controlled trials and 2 systematic reviews of the 4 trials in patients with relapsing-remitting multiple sclerosis, interferon beta-1b SC (Betaseron®) was associated with higher flu-like syndromes, injection site reactions, leukopenia, and abnormal liver tests compared with interferon beta-1a IM (Avonex®).[52-56] Our pooled analysis of all head-to-head and placebo-controlled trial data indicates that interferon beta-1b SC (Betaseron®) had higher rates of injection site reactions, fever, and rates of overall withdrawal and discontinuation due to an adverse event (Table 27). Interferon beta-1a IM (Avonex®) was associated with higher rates of flu-like syndrome.

## Additional evidence of safety for beta interferon drugs

### *Thyroid function*

The effect of beta interferons on thyroid function in relapsing-remitting multiple sclerosis patients was assessed in 2 observational studies (Table 28). The larger study[153] found that thyroid autoimmunity was common at baseline in relapsing-remitting multiple sclerosis patients (8.5%), however this finding was not confirmed by the second, smaller study.[111] Thyroid dysfunction, defined as clinical or subclinical hyper- or hypothyroidism, was observed in 22% of interferon beta-1a IM (Avonex®) patients and in 27% of interferon beta-1b SC (Betaseron®) patients; this difference was not significant ($P=0.68$). Thyroid autoimmunity was the only outcome that was reported by both studies. Pooled relative risk of developing thyroid autoimmunity was 0.86 (95% CI, 0.43 to 1.72) for interferon beta-1a IM (Avonex®) and 0.63 (95% CI, 0.17 to 2.69) interferon beta-1b SC (Betaseron®). Based on this limited data, there appeared to be little difference between the 2 drugs regarding the risk of developing thyroid autoimmunity.

**Table 28. Effect of beta interferons on thyroid functioning**

| Trial | Design | Population | Intervention | Results |
|---|---|---|---|---|
| Caraccio 2005[153] | Prospective cohort; up to 84 mo follow-up | N=106 RRMS | Interferon β-1a: 6 MIU/wk IM<br>Interferon β-1b: 8 MIU every other day SC | Thyroid dysfunction: 22% interferon β-1a vs. 27% interferon β-1b<br>Thyroid autoimmunity: 20.8% interferon β-1a vs. 25% interferon β-1b |
| Martinelli 1998[111] | Prospective controlled cohort; up to 18 mo | N=17 RRMS | Interferon β-1a: 6 MIU/wk SC<br>Interferon β-1b: 8 MIU every other day SC | Thyroid autoimmunity: 25% interferon β-1a vs. 40% interferon β-1b |

Abbreviations: IM, intramuscular; mo, month; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneous; wk, week.

Three additional non-comparative observational studies of thyroid dysfunction in interferon beta-1b SC (Betaseron®) patients reported 17 cases of thyroid dysfunction in a total of 227 patients.[112, 154, 155] Of those 17 cases, there were 8 cases of clinical hyperthyroidism and 1

case of hypothyroidism in a patient with baseline subclinical hypothyroidism; all other cases were deemed subclinical.

### *Liver failure*

Liver failure has not been reported in trials of beta interferons, however 1 post-marketing case report of liver failure in an multiple sclerosis patient taking interferon beta-1a IM (Avonex®) appeared to be linked to beta interferon use.[156] The relationship between interferon beta-1a SC (Rebif®) 22 µg 3 times weekly and liver failure in a second case report was unclear due to concomitant use of a known hepatotoxic drug.[157] No cases of liver failure have been reported with interferon beta-1b SC (Betaseron®).

### *Alanine aminotransferase elevations*

Alanine aminotransferase elevations, the most commonly reported hepatic outcome, are classified according to the National Cancer Institute Common Toxicity Criteria for grade 1 (≥ 2.5 x upper limit of normal), grade 2 (2.5-5.0 x upper limit of normal) or grade 3 (5-20 x upper limit of normal) elevations. Although overall incidence of alanine aminotransferase elevations was lower in the placebo-controlled trials than in observational studies, alanine aminotransferase elevations are common with all 3 products (Table 29).

**Table 29. Proportion of beta interferon-treated patients experiencing alanine aminotransferase elevations (≥ grade 1; ≥ 1 year follow-up)**

| Intervention | Dosage | Trial data[a158] | Post-marketing data[159, 160] |
|---|---|---|---|
| Interferon β-1a IM (Avonex®) | 30 ug 1 time weekly | NR | 23%-38% |
| Interferon β-1a SC (Rebif®) | 22 ug 3 times weekly | 20% | 34%-53% |
| | 44 ug 3 times weekly | 27% | 38%-67% |
| Interferon β-1b SC (Betaseron®) | 250 ug every other day | 11% | 38%-39% |

Abbreviations: IM, intramuscular; NR, not reported; SC, subcutaneous.
[a] Data from "pivotal" placebo-controlled trials

### ***Interferon beta-1a***

A meta-analysis of 6 randomized, placebo-controlled trials ranging up to 2 years in duration assessed the risk of hepatic reactions, specifically alanine aminotransferase elevations, in interferon beta-1a-treated relapsing-remitting multiple sclerosis patients.[160] That review found that most patients taking 1 of the interferon beta-1a products were likely to develop elevated alanine aminotransferase levels at some time during treatment, and that onset of alanine aminotransferase elevation occurred fairly soon following treatment initiation (mean 2.1 to 2.9 months for all interventions). Male gender and concomitant propionic acid derivative use (for example naproxen or ibuprofen) significantly influenced the chances of developing elevated alanine aminotransferase levels ($P<0.001$ for both factors). Using age 39 as a cut-off point, younger patients developed elevated alanine aminotransferase levels less frequently than older patients. This difference reached statistical significance only when all interferon beta-1a-treated patients were combined (39% compared with 46%; $P=0.0001$). Alanine aminotransferase elevations also occurred more frequently in patients receiving interferon beta-1a SC (Rebif®) 44

ug 3 times a week ($P<0.001$) compared with the other interventions. Resolution of alanine aminotransferase elevations were only reported for interferon beta-1a SC (Rebif®) at the 22 and 44 ug 3 times weekly dose. Of those patients, 4.1% of 22 ug and 5.5% of 44 ug patients had persisting alanine aminotransferase elevations. Withdrawals due to alanine aminotransferase or other liver enzyme elevations were uncommon across the trials (0.4% of all interferon beta-1a-treated patients). The rate of serious, symptomatic changes in liver function, based on trial and postmarketing data of interferon beta-1a, is estimated to be 1/2300 patients. These findings were similar to those in 2 single-arm studies of interferon beta-1a IM (Avonex®)[110, 114] where ≥grade 1 alanine aminotransferase elevation rates ranged from 26% to 36%.

***Interferon beta-1b***

A prospective, 1-year study of 156 interferon beta-1b SC (Betaseron®)-treated relapsing-remitting multiple sclerosis patients found 37.5% had *de novo* liver function alteration (an endpoint that included both alanine aminotransferase and aspartate aminotransferase elevations).[161] That study also found that irrespective of severity of liver function alteration, all patients had liver functions within normal ranges by 3-6 months.

***Interferon beta-1a compared with interferon beta-1b***

A retrospective chart review of 844 patients compared alanine aminotransferase elevations based on treatment with interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®), or interferon beta-1b SC (Betaseron®).[159] There were significant baseline differences in the patients involved; differences in gender, age at initiation of treatment and at diagnosis with multiple sclerosis, median Expanded Disability Status Scale, and ethnicity were all statistically significant. Perhaps most important clinically, mean duration of treatment was also different among the included drugs, ranging from 14.7 months to 29.5 months. *De novo* alanine aminotransferase elevations ≥ grade 1 ranged from 23% for interferon beta-1a IM (Avonex®) to 38.9% for interferon beta-1b SC (Betaseron®). *De novo* changes ≥grade 2 and ≥grade 3 occurred less frequently (pooled rate 5.0% and 1.4% respectively, for all interferons; $P<0.005$); only 1 interferon beta-1a IM (Avonex®) patient had a ≥grade 2 elevation, and no interferon beta-1a IM (Avonex®) patient had a ≥grade 3 elevation (Table 30). While these changes were significant from baseline, there was no statistically significant difference in between-group comparisons.

## Table 30. Severity of alanine aminotransferase elevations in beta interferon-treated patients[159]

| Intervention | Dosage | Mean duration | Mean *de novo* ALT elevation | | |
|---|---|---|---|---|---|
| | | | ≥Grade 1 | ≥Grade 2 | ≥Grade 3 |
| Interferon β-1a IM (Avonex®) | 30 ug 1x/week | 14.7 months | 23. 0% | 1.9% | 0.0% |
| Interferon β-1a SC (Rebif®) | 22 ug 3x/week | 15.7 months | 33.6% | 4.7% | 1.6% |
| | 44 ug 3x/week | | 38.0% | 7.8% | 1.6% |
| Interferon β-1b SC (Betaseron®) | 250 ug every other day | 29.5 months | 38.9% | 4.3% | 1.1% |

Abbreviations: ALT, alanine aminotransferase; IM, intramuscular; SC, subcutaneous.

### *Depression*

A meta-analysis of 6 randomized controlled trials and 17 postmarketing, unpublished studies compared the rate of depression with interferon beta-1a use to placebo.[162] While these studies were primarily of interferon beta-1a SC (Rebif®), 1 trial of interferon beta-1a IM (Avonex®) was also included. This meta-analysis focused on making comparisons between the beta interferon products as a group to placebo; there was little evidence providing direct comparisons of beta interferon products. Six-month data, based on the 6 included randomized controlled trials, showed that a significantly higher percentage of interferon beta-1a patients reported depression as an adverse effect of treatment when compared with placebo patients ($P$=0.017) with little difference in depression rates between the interferon beta-1a products: 5% to 12% for interferon beta-1a SC (Rebif®) and 18% for interferon beta-1a IM (Avonex®). Long-term evidence, again based on the 6 included randomized controlled trials, showed that there was no longer a significant difference between interferon beta-1a SC (Rebif®) and placebo ($P$=0.83) at 2 years. Suicide or suicide attempt rates, adjusted for length of exposure, were similar for both interferon beta-1a and placebo groups (odds ratio, 0.77; 95% CI, 0.30 to 1.3) although results were not stratified by type of interferon beta-1a and dose. Similarly, withdrawal rates due to depression as an adverse event were not significantly different between the interferon beta-1a products (1.3% in trials, 1.5% in postmarketing studies) and placebo (0.6% in trials; $P$=0.116).

Rates of depression were reported in 3 trials in patients with secondary progressive multiple sclerosis (Table 31), with no statistically significant difference found between either interferon beta-1a formulation or their respective placebo groups. Depression was not a reported outcome in the trials of interferon beta-1b (Betaseron®). In the SPECTRIMS trial of interferon beta-1a (Rebif®), the proportion of patients reporting depression was higher in the beta interferon groups, but evaluation of validated depression scales did not reveal a difference between beta interferon and placebo groups.[132]

Two other small, single-arm studies assessed depression symptom scores with beta interferon use. A study (N=106) of interferon beta-1a IM (Avonex®) showed no difference in baseline and 1-year follow-up depression ratings in relapsing-remitting multiple sclerosis patients ($P$=0.63), although a depression scale that included somatic complaints commonly linked to multiple sclerosis was used (Beck Depression Inventory II).[163] An open-label study (N=90) of interferon beta-1b SC (Betaseron®) found that depression scores of patients improved following 2 years of treatment.[164]

Our own analysis of the all published trials reporting rates of depression indicates a non-significant increase in risk for both interferon beta-1a products and a non-significant decrease in risk with interferon beta-1b SC (Betaseron®) (Table 31). Our adjusted indirect analysis (Table 32) indicates no significant difference among the interferons for risk of depression although the relative risks favored interferon beta-1b SC (Betaseron®) over the beta-1a products, and interferon beta-1a SC (Rebif®) 44 μg had a higher pooled estimate compared with interferon beta-1a IM (Avonex®). Because these analyses are based on so few trials, these results should be interpreted with caution. These results do, however agree with the results of the meta-analysis above.

**Table 31. Risk of depression with interferons in placebo-controlled trials**

| Drug | N studies | Relative risk (95% CI) |
|---|---|---|
| Interferon β-1a IM (Avonex®) vs. placebo | 1 | 1.15 (0.82 to1.60) |
| Interferon β-1a SC (Rebif®) 44µg vs. placebo | 1 | 1.21 (0.91 to1.61) |
| Interferon β-1b SC (Betaseron®) vs. Placebo | 1 | 0.90 (0.53 to 1.54) |

Abbreviations: IM, intramuscular; SC, subcutaneous.

**Table 32. Adjusted indirect analysis of risk of depression with interferon use**

| Comparison | Relative risk (95% CI) |
|---|---|
| Interferon β-1b SC (Betaseron®) vs. interferon β-1a SC (Rebif®) 44µg | 0.74 (0.401 to 1.36) |
| Interferon β-1b SC (Betaseron®) vs. interferon β-1a IM (Avonex®) | 0.79 (0.42 to1.48) |
| Interferon β-1a SC (Rebif®) 44 µg vs. interferon β-1a IM (Avonex®) | 1.05 (0.68 to 1.63) |

Abbreviations: SC, subcutaneous.

### *Glatiramer acetate*

#### Beta interferons compared with glatiramer acetate

Two head-to-head trials in patients with relapsing-remitting multiple sclerosis compared glatiramer acetate to a beta interferon and reported adverse events (Table 33).[58, 59] The BEYOND trial (N=2244), comparing daily glatiramer acetate (Copaxone®) 20 mg SC to interferon beta-1b (Betaseron®) 250µg or 500µg SC every other day in patients with relapsing-remitting multiple sclerosis, lasted 3.5 years and was a good-quality study,[59] while the REGARD trial (N=764) compared daily glatiramer acetate (Copaxone®) 20 mg SC to interferon beta-1a (Rebif®) 44 µg SC 3 times per week, lasted 96 weeks, and was of fair quality.[58, 59] Adverse events from these 2 trials suggested that both drugs have similar tolerability, with severe adverse events being reported by 11% of patients taking interferon beta-1b (Betaseron®) 250µg and 13% of patients taking glatiramer acetate in the BEYOND trial, and no significant differences in withdrawal due to adverse events noted in the REGARD trial.[58, 59] Overall, the interferons had higher frequency of influenza-like illness ($P<0.001$), elevated liver enzymes ($P<0.0001$), and fever ($P=0.003$) in the BEYOND trial, with similar findings as well as headache and myalgia in the REGARD trial.[58] Glatiramer acetate had higher frequency of injection site reactions and post-injection systemic response (which may include dyspnea, chest pain, flushing, or post-procedural complication).[58, 59] Lipoatrophy was only reported in patients receiving glatiramer acetate.[58, 59]

**Table 33. Adverse events: Glatiramer acetate compared with interferons in relapsing-remitting multiple sclerosis**

| Adverse event | Interferon beta-1b SC (Betaseron®) 250µg or 500µg[59] | Interferon beta-1a SC (Rebif®) 44 µg[58] | Glatiramer acetate (Copaxone®)[58, 59] |
|---|---|---|---|
| Flu-like syndrome | 40%-45% | 31% | 6% (BEYOND), *P*<0.0001<br>1% (REGARD), *P*<0.0001 |
| Any injection site reaction | 48%-55% | | 58% (BEYOND), *P*=0.0005 |
| Injection site pruritus | 1%-2% | 2% | 8% (BEYOND), *P*<0.0001<br>20%, (REGARD), *P*<0.0001 |
| Injection site swelling | 1% | 1% | 4%, BEYOND), *P*=0.005<br>11%, (REGARD), *P*<0.0001 |
| Injection site induration | 1%-2% | 2% | 5% (BEYOND), *P*<0.0001<br>7%, (REGARD), *P*=0.005 |
| Fever | 9%-13% | 6% | 5% (BEYOND), *P*=0.003<br>4% (REGARD), *P*=0.18 |
| Myalgias | | 6% | 2% (REGARD), *P*=0.01 |
| Fatigue | 22%-24% | NR | 21% (BEYOND), NS |
| Headache | 32%-33% | 19% | 27% (BEYOND), NS<br>9%, *P*<0.0001 |
| Increased AST | 9%-13% | NR | 3% (BEYOND), *P*<0.0001 |
| Increased ALT | 11%-16% | 6% | 4% (BEYOND), *P*<0.0001<br>1% (REGARD), *P*=0.002 |
| Post injection systemic reaction | 5%-6% | 0% | 17% (BEYOND)<br>5% (REGARD), *P*<0.0001 |
| Withdrawal due to adverse event | NR | 6% | 5% (REGARD), NS |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported; SC, subcutaneous.

An additional 6 publications in relapsing-remitting multiple sclerosis provided data on the long-term safety of glatiramer acetate use.[165-170] Miller et al provided the longest safety data with up to 22 years of follow-up. In 1978 a placebo-controlled randomized pilot study was initiated for patients with relapsing-remitting multiple sclerosis.[170] Patients enrolled in this trial were allowed to participate in an open-label, compassionate-use trial of glatiramer acetate SC 20 mg daily in 1986. Adverse events were reported monthly using a self-evaluation form. Forty-six patients were included in the long-term safety analysis with the duration of therapy ranging from 0.7 to 22.1 years, mean 10.1 +/- 6.6 years for all patients. As of October 2004, 60.8% had discontinued therapy: 7% due to adverse event and 57% withdrawing consent (reason not disclosed) or lost to follow-up. The most common adverse event was injection site reactions. Additionally, 33% of the 18 planning to continue glatiramer acetate beyond the October 2004 study close date had reported lipoatrophy. These patients had been on the study drug the longest of the cohort.

One of the glatiramer acetate placebo-controlled trials, Johnson, et al,[66] was extended to an open-label phase in which all patients had the option of receiving glatiramer acetate treatment.

Results of this study have been reported at 6, 8, and 10 years following randomization.[166-168] Of 232 who received at least 1 dose of glatiramer acetate, 108 (47%) were still enrolled at the 10-year follow-up. In this study, adverse events accounted for the greatest number of withdrawals (87/124; 70%), however, patients stayed on the drug for an extended period of time with a Kaplan-Meier estimate of median time from initiation of therapy with glatiramer acetate to withdrawal of 9.2 years. No serious adverse events were reported over the course of follow-up. Injection-site reactions and post-injection systemic reactions were the most commonly reported adverse events, although incidence of both appeared to dissipate with long-term use.[168] These data should be interpreted as representing a highly selected population of patients tolerant to and receiving benefit from glatiramer acetate.

An open-label trial compared the effects of glatiramer acetate in relapsing-remitting multiple sclerosis patients who were prior users of interferon beta-1b SC (Betaseron®) compared with treatment-naive patients.[165] Patients were followed for a mean of 14.8 and 20.3 months respectively. Reported adverse events (most commonly injection-site reactions) and rates were similar between the 2 groups and to those reported in the placebo-controlled trials. For both groups in this study, withdrawal rates due to adverse events were significantly higher when compared with the placebo-controlled trials (10.9% compared with 3.7%; $P$=0.001). The reason for this difference may be due to study design. The open-label trial enrolled patients based on compassionate-use and used very few exclusion criteria, while the placebo-controlled trials were more restrictive in enrolling patients.

Another open-label observational study conducted in France between 1997 and 2002, when glatiramer acetate was restricted to patients with relapsing-remitting multiple sclerosis that had contraindications or intolerance to beta interferons, also found that the drug was well tolerated.[169] Two hundred and five patients were followed from 3.5 to 8 years for long-term safety analysis (55% being treated for at least 4 years) and found similar results.

While these data appeared to support the superiority of glatiramer acetate in tolerability over interferon, the fact that no difference was found in the direct comparison studies raises the concern that potentially important differences among the population treated with glatiramer acetate compared with the others may have contributed to these results. Further good-quality direct comparison studies are needed to confirm the findings.

An early, good-quality study of glatiramer acetate (Copaxone®) was conducted in a population of 106 patients described as chronic progressive (a chronic progressive course for at least 18 months, no more than 2 exacerbations in the past 2 years, Expanded Disability Status Scale ≥2 and ≤6.5, and exhibiting progression in a pre-trial period).[97] The glatiramer acetate group experienced significantly more injection site reactions than the placebo group: soreness 83% compared with 47%, itchiness 61% compared with 17%, swelling 80% compared with 47%, and redness 85% compared with 30%; $P$=0.001 overall. Significantly more patients taking glatiramer acetate reported vasomotor symptoms (flushing, palpitations, muscle tightness, difficulty breathing, and anxiety) transiently during treatment (24% compared with 5.5%; relative risk, 4.31; 95% CI, 1.41 to 13.7). No differences were seen between the groups in reporting of other adverse events. Withdrawals due to adverse events were not discussed in detail.

A study by Tremlett and Oger reviewed the adverse drug reactions reported to the Canadian Adverse Drug Reaction Monitoring Program between 1995 and March 2006. A total of 888 reports were extracted concerning the interferons and glatiramer acetate (Copaxone®).[171] The average age of the patients was 45 years, with 74% being female. Of the events reported, 92.2%

were considered serious. There were 49 deaths with no clear pattern to the underlying reasons. There were 16 adverse reactions related to pregnancy involving interferon beta-1b (Betaseron®) and glatiramer acetate with the majority due to miscarriage or congenital malformations.

### *Tolerability*

Two observational studies in patients with relapsing-remitting multiple sclerosis evaluated tolerability. One found no difference in discontinuation rate at 6 months but less discontinuation of glatiramer acetate (Copaxone®) at 24 months compared with all 3 of the interferons.[62] A Brazilian observational study also found a lower discontinuation rate with glatiramer acetate over the beta interferons.[172] This study followed patients with relapsing-remitting multiple sclerosis and analyzed those who had continuous use of at least 1 of the beta interferons or glatiramer acetate for 3-5 years (N=152), comparing the rates and reasons for discontinuation.[172] They found 32% discontinued the drug with a mean time to discontinuation of 2.5 years. Interferon beta-1a (Rebif®) had the greatest discontinuation rate but it took the longest time to do so. Only 1 patient discontinued glatiramer acetate but did so within the shortest amount of time (interferon beta-1a [Rebif®] 50%, 2.5 years; interferon beta-1b [Betaseron®] 25%, 1.9 years; interferon beta-1a [Avonex®] 18.75%, 2.1 years; glatiramer acetate 2%, 0.5 years). The main reason for discontinuation was lack of efficacy.

There was little additional evidence regarding the comparative safety of interferons and glatiramer acetate based on data from observational and other non-randomized studies (Table 34).[144, 173-175] While the types of adverse events reported in these studies and the rates of withdrawals due to adverse events were similar to those reported in controlled trials of these drugs, rates of other adverse events varied widely. These discrepant rates may have been the result of study design, as higher rates of flu-like syndrome, injection-site reactions, and fever were found in the trials, regardless of intervention.

**Table 34. Tolerability outcomes of beta interferons compared with glatiramer acetate: trials compared with non-randomized studies**

| Intervention | Flu-like syndrome | | Injection-site reaction | | Fever | | Withdrawals due to AEs | |
|---|---|---|---|---|---|---|---|---|
| | Trials | Non-RCTs | Trials | Non-RCTs | Trials | Non-RCTs | Trials | Non-RCTs |
| Interferon β-1a IM (Avonex®) | 62% | 35% | 9% | 8% | 20% | 12% | 4% | 2% |
| Interferon β-1a SC (Rebif®) | 29% | 6% | 61% | 6% | 5% | 3% | 6% | 8% |
| Interferon β-1b SC (Betaseron®) | 42% | 15% | 59% | 24% | 33% | 17% | 8% | 5% |
| Glatiramer acetate[a] | 3% | 0.2% | 75% | 24% | 4% | 0% | 4% | 8% |

Abbreviations: AE, adverse event; RCT, randomized controlled trial; SC, subcutaneous.
[a] Systemic reactions were also reported in 24% and 7% of glatiramer patients in trials and non-RCTs respectively; there are no reports of this outcome associated with beta interferon use.

### *Depression*

A small (N=163) cohort study by Patten, et al[176] used a Canadian reimbursement database to assess the incidence of depression in relapsing-remitting multiple sclerosis patients receiving any beta interferon (n=66) compared with glatiramer acetate (Copaxone®) (n=97). There was some heterogeneity between the groups. Specifically, the beta interferon-treated patients had slightly higher Expanded Disability Status Scale and depression scores and slightly lower quality of life scores at baseline. In addition, depression was common among multiple sclerosis patients, both at baseline (28.8% for beta interferons and 22.7% for glatiramer acetate) and at follow-up, regardless of intervention. While glatiramer acetate-treated patients tended to have lower depression scores, there was no significant difference in depression score at 3-month follow-up between beta interferons and glatiramer acetate (40.0% compared with 21.3% respectively, $P$=0.12). This difference remained insignificant when any time points of follow-up were considered: 34.0% for beta interferons and 25.3% for glatiramer acetate; $P$=0.312.

### *Cancer*

A cohort of patients in Israel with multiple sclerosis (type not specified) treated with beta interferons or glatiramer acetate (Copaxone®) was compared with healthy controls to assess the incidence of cancer and the effect of beta interferon or glatiramer acetate use on cancer rates.[177] This study found that baseline non-breast cancer incidence was lower in women with multiple sclerosis when compared with the general population and that use of either beta interferons or glatiramer acetate may increase the risk of developing cancer in women. However, this difference did not reach statistical significance and there was no significant risk difference for breast cancer in women or men. Larger studies could potentially validate a causal link between beta interferon or glatiramer acetate use and increased cancer risk, however based on the results of this study no such link can be proven or disproven.

### *Lipoatrophy*

Evidence on the safety of glatiramer acetate (Copaxone®) from 5 non-comparative, non-randomized studies was consistent with that from previously discussed trials.[178-181] No additional serious adverse events were reported in any of these studies, with the exception of the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use.[182] One long-term follow-up study and 1 small retrospective study found evidence of lipoatrophty.[170, 182] The small retrospective study found that 34 of 76 (45%) patients identified through chart review had evidence of lipoatrophy. Five of these cases were identified as severe, all cases occurred in women, and 4 withdrawals were attributed to lipoatrophy. The Miller study, which had the longest follow-up of up to 22 years, found 33% of 18 patients had developed lipoatrophy.[170]

Overall, the observational studies agreed with the direct and placebo-controlled trials. Most patients experience at least 1 adverse event with the most common being injection site reactions and post-injection systemic reactions, however, treatment was generally well tolerated for years and treatment discontinuation due to an adverse event was uncommon. Lipoatrophy did appear to be a concern with long-term use.

## ***Natalizumab***

No studies compared natalizumab (Tysabri®) to another disease-modifying drug for multiple sclerosis. Two well-conducted trials compared natalizumab (Tysabri®) to placebo in patients

with relapsing-remitting multiple sclerosis (Table 35).[67, 68] Patient population, natalizumab dose, and study duration were similar in the 2 trials, however in 1 of these trials,[68] interferon beta-1a IM (Avonex®) was used concomitantly in both groups. Adverse events were reported by most patients in these 2 trials, regardless of intervention. Combined data from both trials found that 97% of natalizumab patients and 98% of control patients reported some adverse event (*P*=0.086), although more natalizumab patients withdrew due to adverse events compared with control patients (2.9% compared with 0.89%; *P*=0.549). Overall, rates of non-serious adverse events were similar in both trials (Table 35).

**Table 35. Adverse events in natalizumab trials in patients with relapsing-remitting multiple sclerosis (natalizumab compared with control)**

| Trial | Any adverse event | Headache | Depression | Flu-like illness | Injection-site reactions |
|---|---|---|---|---|---|
| Polman 2006[67] | 95% vs. 96%<br>*P*=0.459 | 38% vs. 33%<br>*P*=0.137 | 19% vs. 16%<br>*P*=0.197 | NR | 3% vs. 2%<br>*P*=0.386 |
| Rudick 2006[68] | 99% vs. 99%<br>*P*=0.772 | 46% vs. 44%<br>*P*=0.439 | 21% vs. 18%<br>*P*=0.195 | 20% vs. 19%<br>*P*=0.679 | NR |

Serious adverse events were reported in both trials, however there were no significant differences in adverse event rates between the interventions. The exception was 2 cases of progressive multifocal leukoencephalopathy, a potentially fatal neurologic disorder, that were reported in patients enrolled in the SENTINEL trial and were possibly linked to natalizumab use.[68] This led to early cessation of the SENTINEL trial. No cases of progressive multifocal leukoencephalopathy were reported in the AFFIRM trial.[67] Further discussion of the association between natalizumab use and progressive multifocal leukoencephalopathy appears below.

Four trials compared natalizumab (Tysabri®) to placebo in a mixed population of relapsing-remitting and secondary progressive multiple sclerosis patients.[89-91] No serious treatment-related adverse events were reported in any of the trials with the exception of 1 anaphylactic reaction in a natalizumab 3 mg/kg patient. In 1 trial, a significantly higher number of natalizumab patients reported fatigue compared with placebo patients (*P*=0.065) but there were no other significant differences in adverse events between the natalizumab and placebo groups. Other adverse event rates were similar across the 4 trials. The only safety outcome that was reported in all 4 trials was the total number of patients reporting any adverse event (Table 36). Again, the percentage of patients varied widely across the trials (5.4% to 91% for natalizumab and 9.9% to 89% for placebo), but in all of them there was no significant difference between the natalizumab and placebo arms.

**Table 36. Tolerability of natalizumab compared with placebo in relapsing-remitting and secondary progressive multiple sclerosis**

| Adverse event | Miller et al 2003[89] N=213 | Tubridy 1999[91] N=72 | Sheremata 1999[183] N=28 | O'Connor 2004 N=180 |
|---|---|---|---|---|
| Total patients reporting any adverse event | 3 mg/kg: 5/68 (7.4%)<br>6 mg/kg: 4/74 (5.4%)<br>placebo: 7/71 (9.9%) | 3 mg/kg: 19/37 (51.4%)<br>placebo: 24/35 (68.6%) | All doses: 17/21 (81%)<br>Placebo: 6/7 (85.7%) | 3mg/kg: 54/60 (90%)<br>1mg/kg: 52/57 (97%)<br>Placebo: 56/63 (89%) |
| Withdrawals due to adverse events | 3 mg/kg: 4/68 (5.9%)<br>6 mg/kg: 3/74 (4.1%)<br>placebo: 3/71 (4.2%) | NR | NR | NR |
| Headache | 3 mg/kg:27/68 (39.7%)<br>6 mg/kg:20/74 (27%)<br>placebo: 27/71 (38%) | NR | NR | 3mg/kg: 28/60 (47%)<br>1mg/kg: 19/57 (33%)<br>Placebo: 25/63 (40%) |
| Infections | 3 mg/kg: 15/68 (22.1%)<br>6 mg/kg: 14/74 (18.9%)<br>placebo: 11/71 (15.5%) | NR | NR | NR |
| Urinary tract infections | 3 mg/kg: 15/68 (22.1%)<br>6 mg/kg: 13/74 (17.6%)<br>placebo: 11/71 (15.5%) | NR | NR | NR |
| Weakness/muscle weakness | 3 mg/kg: 12/68 (17.6%)<br>6 mg/kg: 7/74 (9.5%)<br>placebo: 11/71 (15.5%) | NR | NR | NR |
| Fatigue/tiredness | | 3 mg/kg: 12/37 (32.4%)<br>Placebo: 4/35 (11.4%) | | NR |

Abbreviations: NR, not reported.

Data from 2 post-marketing observational studies of patients with relapsing-remitting multiple sclerosis in Europe, 1 in Italy with 909 cases and 1 in Denmark with 234 cases, provide additional safety data.[184, 185] Both were of relatively short duration, 15 months by the Italian Drug Agency and a median period of 11.3 months (range 3.0-21.5) in the Danish nationwide study. There were no cases of progressive multifocal leukoencephalopathy. There were a high

percentage of infections in the Danish study, 58%, although none severe. Neutralizing antibodies were found in 4% of the Danish group.[185] There were allergic reactions in 5% of the Italian group, none serious, whereas 4% in the Danish study, 2 cases of which were serious anaphylactic reactions.

### Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy is a serious, progressive neurologic disorder caused by infection of the central nervous system by JC virus, a member of the papovavirus family. JC virus is carried in a latent form by 70% to 75% of the general population but generally does not cause symptoms. Progressive multifocal leukoencephalopathy is rare, but when it occurs it frequently results in irreversible neurologic deterioration and death, and there is no known effective treatment for the disease.[186]

From initial trial data, 2 patients with multiple sclerosis and 1 with Crohn's disease treated with natalizumab (Tysabri®) were reported to have developed progressive multifocal leukoencephalopathy.[187-189] An evaluation of all patients who had received natalizumab in clinical trials or via compassionate use criteria or after US Food and Drug Administration approval (n=3417) was undertaken.[190] 3389 patients were followed up, using neurological exam, brain magnetic resonance imaging, and cerebrospinal fluid samples. 44 patients (1.3%) had findings of possible progressive multifocal leukoencephalopathy. Data were then examined by an expert panel; 43 potential cases were ruled out, and 1 patient refused further follow-up. The authors then estimated the incidence of progressive multifocal leukoencephalopathy at 1.0 per 1000 treated patients (95% CI, 0.2 to 2.8 per 1000) based on the 3 original cases. Because these 3 patients had also been receiving immunomodulators or immunosuppressants, it was recommended that natalizumab be used only as monotherapy.

Since that time, additional cases have been reported in patients on monotherapy as well. The risk appeared to increase with greater time on therapy. According to the US Food and Drug Administration who have reviewed all the cases of progressive multifocal leukoencephalopathy, there have been no reports of progressive multifocal leukoencephalopathy in patients treated for less than 12 months since the remarketing of natalizumab (Tysabri®) in 2006. In patients treated with 24 to 36 infusions, the overall worldwide rate and the rate in the United States of developing progressive multifocal leukoencephalopathy is similar to the rate seen during clinical trials (1 case per 1000 patients treated). For unknown reasons, the rate outside of the United States is approximately 2 cases per 1000 patients. As of June 2010, 55 cases of progressive multifocal leukoencephalopathy associated with natalizumab use have been reported worldwide. At the first signs of progressive multifocal leukoencephalopathy, patients are to receive plasma exchange or immunoadsorption to decrease circulating natalizumab (Tysabri®) levels which can lead to the development of immune reconstitution inflammatory syndrome. Immune reconstitution inflammatory syndrome is characterized by a severe inflammatory response as the immune system recovers and can cause a profound decline in a patient's condition.

## *Mitoxantrone*

No studies offered direct evidence comparing mitoxantrone (Novantrone®) to another disease-modifying drug for multiple sclerosis. A well-conducted systematic review compared mitoxantrone (Novantrone®) to placebo using data from 4 trials (Table 37).[92] Pooled data found withdrawals due to adverse events to be significantly higher among mitoxantrone patients

relative to placebo (9.4% compared with 2.3%; *P*=0.145). No serious adverse events were reported in any of the 4 included trials, including serious cardiac events. A non-serious decrease in left ventricular ejection fraction below 50% was reported in 5 of 138 (3.6%) mitoxantrone patients; this was not statistically significant compared with placebo patients (*P*=0.1). Other commonly-reported adverse events in mitoxantrone patients were nausea and vomiting, alopecia, amenorrhea, and urinary tract infection (Table 37).

**Table 37. Adverse events in placebo-controlled trials of mitoxantrone[92]**

| Adverse event | Mitoxantrone (%) | Placebo (%) | *P* value |
|---|---|---|---|
| Amenorrhea[a] | 20/77 (26%) | 0/75 (0%) | *P*=0.0004 |
| Cardiac: LVEF <50% | 5/138 (3.6%) | 0/130 (0%) | *P*=0.1 |
| Nausea/vomiting | 86/138 (62.3%) | 20/130 (15.4%) | *P*<0.00001 |
| Alopecia | 65/135 (47.1%) | 25/130 (19.2) | *P*<0.00001 |
| Urinary tract infection | 35/138 (25.4%) | 14/130 (10.8%) | *P*=0.003 |

Abbreviations: LVEF, left ventricular ejection fraction.
[a] Amenorrhea persisted in 6/77 (7.8%) of mitoxantrone patients following treatment cessation.

One small trial compared mitoxantrone to placebo in 51 patients with relapsing-remitting multiple sclerosis.[72] No patients reported any serious adverse events, and there were no withdrawals from either group due to adverse events. Transient amenorrhea was reported in 5 of 17 (29%) women in the mitoxantrone group and these cases resolved with treatment cessation. Other adverse events reported in mitoxantrone patients were nausea and vomiting (18%), urinary tract infection (6%), headache (6%), and respiratory infection (4%). For unexplained reasons, no adverse event data for the placebo arm was provided by the study authors.

One non-randomized open-label study compared mitoxantrone to cyclophosphamide whereby patients with relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis were alternately prescribed 1 of the study drugs, although given the safety profile of each drug, patients with higher post-void residual were given mitoxantrone and patients with reduced left ventricular systolic function were given cyclophosphamide.[191] The mean duration of treatment was 1.9 years with the mean duration of follow-up 3.6 years. The mean age of patients in the mitoxantrone group was 43.3 years, 65% were female, and mean Expanded Disability Status Scale was 5.0. Consistent with the placebo-controlled trials, the most common side effects were nausea (27%), amenorrhea (38%), and mild alopecia (17%). The drug was discontinued in 5% of patients due to side effects. Transthoracic echocardiograms were repeated at 6, 12, and 24 months and no cases of cardiac side effects were reported.

Small (N=7 to 31) before-after studies of patients with various categories of multiple sclerosis have been reported.[192-194] These studies used differing dosing and schedules (5 mg/m$^2$ every 3 months x 12, compared with 8 mg/m$^2$ every 3 weeks x 7, compared with 10mg/m$^2$ every month x 3, then every 3 months to a total dose of 150 mg/m$^2$). The most common adverse events reported were nausea (39 to 71%), alopecia (13 to 29%), fatigue (7%), and in 1 study 57% of women reported transient secondary amenorrhea.

## Cardiotoxicity

Thirteen percent of 31 patients receiving 5 mg/m$^2$ every 3 months required discontinuation of treatment due to reduction of left ventricular ejection fraction to </= 50%, although cumulative dose at the time of discontinuation was not reported.[192] In a very small study, 7 patients who had received cumulative doses of 66 to 198 mg/m$^2$ had "normal quantitative cardiac function" after 12 months of treatment.[194]

The long-term risk of serious cardiac adverse events with mitoxantrone (Novantrone®) use in patients with relapsing-remitting, secondary progressive, or primary progressive multiple sclerosis, or another/unknown diagnosis was assessed in a meta-analysis of 3 studies.[195] The meta-analysis was based on patient data (N=1378) from 1 phase-III trial and 2 open-label, noncomparative studies available in abstract form only. The full results of the trial[96] were included in the Martinelli Boneschi systematic review discussed above. Two cases of fatal congestive heart failure were reported (0.15%; 95% CI, 0.02 to 0.52%), although 1 of the congestive heart failure deaths could not be definitively linked to mitoxantrone use. Asymptomatic left ventricular ejection fraction<50% was reported in 17/779 patients for whom data was available (2.18%; 95% CI, 1.28 to 3.47%). Further analysis by the study's authors found that patients receiving a cumulative dose <100mg/m$^2$ had a lower incidence of asymptomatic left ventricular ejection fraction <50% than those patients receiving ≥100mg/m$^2$, although this did not reach statistical significance (incidence of 1.8% compared with 5.0%; $P$=0.06).

Observational studies have reported a reduction in left ventricular ejection fraction in the 3-5 % range.[196, 197] One small study of 18 patients monitored cardiac function with repeat transthoracic echocardiograms every 3 months before each infusion and found 4 cases in 18 patients (22%).[198] Further monitoring found that these were transient in 2 of these cases, bringing their percentage to 11%, but they do suggest that more frequent cardiac monitoring might influence the infusion regimen and minimize risk of non-reversible cardiotoxicity. Long-term randomized trials would help to better appreciate whether these transient changes have any long-term associated harm.

## Cancer

The risk of therapy-related acute leukemia (t-AL) in a mixed multiple sclerosis population (N=1378) was assessed in a meta-analysis that included patient data from 3 studies (1 placebo-controlled trial and 2 open-label studies; mean length of follow-up 36 months).[199] There were 2 reports of t-AL, both in young women who had received 70 mg/m$^2$ cumulative dose of mitoxantrone (incidence 0.15%). An additional 9 publications (1 trial, 1 open-label study, and 7 abstracts) comprising 242 multiple sclerosis patients were searched for reports of t-AL, however no additional cases were identified.

## Amenorrhea

Amenorrhea has been reported as a frequent side effect in the placebo-control trials of mitoxantrone but the degree of permanent amenorrhea affecting fertility remains unclear. The FEMIMS study assessed the frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis.[196] It was a retrospective observational study of 189 Italian female patients with relapsing-remitting (57%), secondary progressive (41%), and primary progressive multiple sclerosis (2%) who had received at least 3 cycles of mitoxantrone before the age of 45. The mean

age of the patients was 37 years with a median follow-up of 26 months after discontinuing the drug. The median cumulative dose of mitoxantrone was 100 mg/m$^2$ (range 30-140 mg/m$^2$) over a median period of 15 months (range 3-55 months).[196] Their findings suggested that older age (odds ratio, 1.18; 95% CI, 1.10 to 1.27; *P*=0.01) and higher cumulative dose (odds ratio, 1.02; 95% CI, 1.01 to 1.04; *P*=0.01) were associated with increase risk of permanent amenorrhea whereas concomitant use of estrogen-progesterone therapies was associated with a decrease risk (odds ratio, 0.31; 95% CI, 0.13 to 0.7; *P*=0.01).

## Key Question 6. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

### Summary of the Evidence

- Observational studies did not show increased risk of adverse pregnancy outcomes associated with exposure to beta interferons or glatiramer (Copaxone®), but studies were too small to make strong conclusions about the safety of multiple sclerosis drugs in pregnancy.
- A post hoc subgroup analysis of a head-to-head trial of interferon beta-1a products (Avonex® and Rebif®) found that African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with white patients over the course of the study.
- There was some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors 1 product over another.
- Due to small sample sizes and other concerns regarding study design, it was impossible to draw conclusions about the use of multiple sclerosis drugs in subpopulations based on the available data.

### Detailed Assessment

#### *Race*

A post hoc subgroup analysis of EVIDENCE, a head-to-head trial of interferon beta-1a products (Avonex® and Rebif® 44 mcg) compared the response to treatment in African-American and white patients.[200] The proportion of African-American patients in the EVIDENCE trial was small (6%). The subgroup analysis found that although the 2 groups were similar at baseline, the African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with the white patients over the course of the study. The small number of patients in the African-American group meant that these results should be interpreted with caution. This analysis was not intended to identify differences in response between the products. The disproportionate numbers of patients in this group randomized to Avonex® (N=23) compared with Rebif® (N=13) greatly hindered that ability to make any comparisons between the treatments.

### *Pregnancy*

In a meta-analysis of individual patient data from 8 studies of interferon beta-1a SC (Rebif®) or IM (Avonex®), including open-label extension phase studies and involving patients with relapsing-remitting or secondary progressive multiple sclerosis or clinically isolated syndrome, 41 pregnancies occurred with in utero exposure to interferon. Twenty-two pregnancies occurred in women with previous exposure (discontinued interferon more than 2 weeks prior to conception) and only 6 occurred in women receiving placebo.[201] In the group with in utero exposure to interferon beta-1a, pregnancy loss occurred in 29%, compared with 0 in either the placebo or prior exposure groups. The authors indicated that the rate of pregnancy loss with in utero exposure was greater than the average reported in the overall population, although they reported that taking the small sample size into consideration, the rate may be within the expected range. Prematurity and full-term infants with congenital anomalies occurred in 4.9% of the in utero exposure group, 9.1% in the prior treatment group, and 16.7% in the placebo group, and no teratogenic effects were seen.

In a prospective cohort study conducted in Germany between 1996 and 2007, pregnancy outcomes for women who were exposed to beta interferons (n=69) or glatiramer (n=31) during pregnancy were compared with 2 control groups: pregnant women with multiple sclerosis who had not taken beta interferons or glatiramer (n=64), and pregnant women without multiple sclerosis (n=1557).[202] Overall, the miscarriage rate in all 4 cohorts was within normal range and did not differ among the cohorts. Among interferon-exposed pregnancies, however, there was a significantly higher rate of miscarriage in the interferon beta-1b group (27.8%; 5 of 18) compared with the interferon beta-1a group (4.8%; 2 of 42; *P*=0.02), the non-multiple sclerosis control group (9.1%; *P*=0.02), and the glatiramer group (3.9%; *P*=0.03). Two major birth defects (club feet and atrioventricular canal) occurred in the glatiramer group, but the rate was not significantly different from the comparison cohorts. Birth weight was within normal range in all groups, but was significantly lower in the (combined) interferon group. Birth weight was also lower in the subgroup of women who relapsed during pregnancy, regardless of drug exposure.

A small study described as a longitudinal controlled cohort study evaluated the risk of exposure to beta interferons during pregnancy.[203] This study reported that the beta interferon-exposed pregnancies were more likely to result in non-live birth compared with the healthy cohort (odds ratio, 6.94; 95% CI, 1.18 to 40.70). The group with multiple sclerosis *not* exposed to beta interferons also had an increased risk of non-live birth (odds ratio, 2.91) but statistical significance was not reached (95% CI, 0.48 to 31.67). A direct comparison of the beta interferon exposed and unexposed multiple sclerosis group was not presented. Mean birth weight was lower in the beta interferon-exposed group (3189 g) compared with in the unexposed group with multiple sclerosis (3498 g). This study presented a number of concerns in terms of study validity because of potential confounding, recall bias, use of a statistical model with multiple parameters, and too few data. Therefore, these results should be interpreted cautiously and be used as the basis for future research rather than for treatment decisions.

### *Men*

Two studies analyzed the association of gender with response to glatiramer or beta interferons.[204, 205] In the PROMISE trial of glatiramer (Copaxone®) in primary progressive multiple sclerosis, there was no effect of glatiramer on progression of disability in the total

group,[87] but a post hoc subgroup analysis showed a delayed time to progression of disability in the subgroup of men randomized to glatiramer (hazard ratio, 0.71; 95% CI, 0.53 to 0.95).[204] An observational study of 2570 patients with relapsing remitting multiple sclerosis treated with beta interferon and followed for up to 7 years found a lower risk of relapse in men compared with women, especially in the subgroup of patients with lower pre-treatment disease activity (less than 1 relapse in the year before treatment initiation). Although these studies suggested that men with multiple sclerosis may respond differently than women to treatment, they did not provide evidence to make conclusions about comparative effectiveness or safety of the different products in men.

## SUMMARY

The results of this review are summarized in Table 38, below, and Appendix E summarizes the strength of the evidence for each key question.

No study met criteria to be classified as an effectiveness study, therefore applicability of the results of this review to patients seen in usual care may be limited.

The strength of evidence in patients with relapsing remitting multiple sclerosis was moderate. We found fair direct evidence that interferon beta-1a SC (Rebif®) 44 µg SC 3 times weekly and interferon beta-1b (Betaseron®) 250 µg SC every other day were similarly efficacious for preventing relapse, while interferon beta-1a IM (Avonex®) 60 µg IM once weekly was less effective than interferon beta-1a SC (Rebif®) on this measure. There was conflicting evidence in disease progression outcomes between the interferons, and it is likely that any differences are small and clinically insignificant. Fair evidence showed no difference between glatiramer and interferon beta-1a SC (Rebif®) or interferon beta-1b (Betaseron®). The strength of the evidence in other populations was low. There was no direct evidence in patients with primary and secondary progressive multiple sclerosis, and no evidence in patients with progressive relapsing multiple sclerosis. There is moderate evidence that the beta interferons are similar in harms.

The strength of the evidence for the presence and clinical effect of neutralizing antibodies was low, with no head-to-head trials. Observational studies were limited by lack of control for confounding factors and insufficient duration to make conclusions.

The strength of the evidence for comparative effectiveness in patients with a clinically isolated syndrome was low, with no head-to-head trials. Evidence of efficacy compared with placebo was available for glatiramer (Copaxone®), interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®), and interferon beta-1b (Betaseron®). There was no evidence for mitoxantrone (Novantrone®) or natalizumab (Tysabri®) in this population.

We identified no trials in progress that would meet inclusion criteria for this review and potentially change conclusions.

## Table 38. Summary of the evidence

| Key Question | Quality of the evidence | Conclusion |
|---|---|---|
| Key Question 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration? | Fair | *Relapsing remitting multiple sclerosis*<br>• Direct evidence from 4 fair-quality head-to-head trials showed little difference in relapse outcomes between interferon β-1a SC (Rebif®) and interferon β-1b (Betaseron®), while interferon β-1a IM (Avonex®) was less effective than interferon β-1a SC (Rebif®) and interferon β-1b (Betaseron®) on this measure.<br>• Direct evidence from 5 fair-quality head-to-head trials showed conflicting evidence in disease progression outcomes between the interferons.<br>• Pooled analysis of direct and indirect trial data found no difference between the interferons on changes in EDSS and no difference between interferon β-1a SC (Rebif®) and interferon β-1a IM (Avonex®) on disease progression but did find interferon β-1b (Betaseron®) to be superior to interferon β-1a IM (Avonex®) on disease progression (RR, 0.48; 95% CI, 0.27 to 0.86).<br>• There was no difference in relapse or disease progression between Glatiramer and interferon β-1a SC (Rebif®) or interferon β-1b (Betaseron®) based on 2 head-to-head trials. Glatiramer was more effective than placebo in relapse rate based on 3 small fair-quality trials but no difference on the percentage relapse free. The evidence on the effect of glatiramer on disease progression is inconclusive based on data from 1 trial. Natalizumab and mitoxantrone were more effective than placebo for relapse-related and disease progression outcomes in placebo-controlled trials. Evidence was based on a small number of trials (2 for natalizumab and 1 for mitoxantrone).<br><br>*Secondary progressive multiple sclerosis*<br>• There is no direct evidence. Evidence from placebo-controlled trials showed that the all of β interferons were similarly effective at reducing relapse rates. A positive effect on disease progression was observed with interferon β-1b (Betaseron®) although similar effects were not consistently observed with the interferon β-1a products.<br><br>*Primary progressive multiple sclerosis*<br>• The only evidence available (from 1 small, good quality trial comparing interferon β-1a IM (Avonex®) to placebo) is insufficient to make any judgments regarding effectiveness in PPMS patients.<br><br>*PRMS:*<br>• No studies of DMD use in PRMS patients were identified through literature searches. |
| Key Question 2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of | Fair | Evidence for interferon β-1b SC (Betaseron®) and interferon β-1a SC (Rebif®) indicates that consistent positive neutralizing antibody status with high titer adversely affects the impact of these drugs on relapse rates, by one-half to two-thirds, during longer periods of follow-up.<br>This difference is not seen for any of the products in shorter follow-up (2 years or less), and there is inadequate evidence to conclude that there is an impact on disease progression. |

| Key Question | Quality of the evidence | Conclusion |
|---|---|---|
| interferon beta neutralizing antibodies? | | |
| Key Question 3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis? | Fair | Interferon β-1a IM (Avonex®) appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2-8.5% reported, starting around 9 months of treatment, while evidence indicates that with interferon β-1a SC (Rebif®) antibodies occur somewhat later (9 months) with rates of immunogenicity as low as 12% and as high as 46%, and with interferon β-1b SC (Betaseron®) neutralizing antibodies appear as early as 3 months into treatment in 30-40% of patients. Importantly, 40-50% of antibody positive patients will become antibody negative over time, while small numbers of patients will become antibody positive into the second year of treatment. |
| Key Question 4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome? | Fair to poor | No direct evidence comparing 1 DMD to another in patients with a clinically isolated syndrome was available. Placebo-controlled trials of glatiramer (Copaxone®), interferon β-1a IM (Avonex®), interferon β-1a SC (Rebif®) and interferon β-1b (Betaseron®) found them all more effective than placebo at reducing the probability of converting to clinically definite MS. The drugs had higher rates of adverse events relative to placebo.<br><br>There is no evidence mitoxantrone (Novantrone®) or natalizumab (Tysabri®) use in clinically isolated syndromes. |
| Key Question 5. Do disease-modifying treatments for multiple sclerosis differ in harms? | Fair | *Withdrawals due to adverse events*<br>No difference in withdrawal rates among β interferons in head-to-head trials, although adverse events in generally were poorly reported in these trials. Withdrawal rates ranged from 3% (glatiramer acetate) to 9% (Interferon β-1b SC [Betaseron®]) in placebo-controlled trials.<br><br>*Serious adverse events*<br>NAbs: The clinical impact of the presence of neutralizing antibodies is unclear although limited data suggests they may negatively impact relapse rate after 3-4 years of treatment.<br>Liver function: ALT elevations are common with all β interferon products, with little difference in rates of occurrence. Most elevations are asymptomatic and transitory.<br>Thyroid function: Limited data from 2 observational studies found similar rates of clinical and subclinical thyroid autoimmunity with Interferon β-1a IM (Avonex®) and Interferon β-1b SC (Betaseron®)<br>Depression: There was a lower rate of depression in patients taking interferon β-1a (Rebif®) compared with the other interferons based on limited trial data. One small observational study comparing β interferons and glatiramer also found no differences in depression rates, although our own analysis of the all published trials reporting rates of depression indicates an increase in risk for all interferon β1 products.<br>Cancer: Data from 1 cohort study found a potentially increased risk of cancer development in women with either β interferon or glatiramer acetate use; these results are inconclusive. Therapy-related acute leukemia was reported in 2/1620 patients taking mitoxantrone.<br>Cardiotoxicity: Two cases of congestive heart failure were |

| Key Question | Quality of the evidence | Conclusion |
|---|---|---|
| | | potentially linked to mitoxantrone use in 1 meta-analysis of 3 (2 unpublished) studies (incidence 0.15%)<br>Progressive multifocal leukoencephalopathy: Estimates of progressive multifocal leukoencephalopathy incidence with natalizumab use is 1.0/1000 patients.<br><br>*Tolerability*<br>Flu-like syndrome: Interferon β-1a IM (Avonex®) was associated with the highest rates of flu-like syndrome compared with the other β interferons (~62% compared with 28%).<br>Injection-site reactions: Interferon β-1b SC (Avonex®) was associated with the lowest rates of injection site reactions (8.5%) whereas Interferon β-1b SC (Betaseron®) and Interferon β-1b SC (Rebif®) had similar rates (58.9% and 60.6%).<br>Systemic reactions: Post-injection systemic reactions were observed in patients receiving glatiramer acetate, although these were usually limited to a single episode. There were no events reported of this outcome in trials of β interferons, natalizumab or mitoxantrone.<br><br>*Long-term safety in observational studies*<br>Long-term safety data from comparative and non-comparative, non-randomized studies was consistent with that reported in trials. Significant concerns include progressive multifocal leukoencephalopathy in patients receiving natalizumab >12 months, lipoatrophy with prolonged use of glatiramer and permanent amenorrhea in older women receiving higher total dose of mitoxantrone. |
| Key Question 6: Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events? | Poor | Observational studies did not show increased risk of adverse pregnancy outcomes associated with exposure to beta interferons or glatiramer, but studies were too small to make strong conclusions about the safety of MS drugs in pregnancy.<br><br>A post hoc subgroup analysis of a head-to-head trial of interferon β-1a products (Avonex® and Rebif®) found that African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with white patients over the course of the study.<br><br>There is some evidence that response to beta interferons and glatiramer differs in men and women, but there is no evidence that this difference favors 1 product over another.<br><br>Due to small sample sizes and other concerns regarding study design, it is impossible to draw conclusions about the use of MS drugs in subpopulations based on the available data. |

Abbreviations: ALT, alanine aminotransferase; EDSS, Expanded Disability Status Scale; IM, intramuscular; DMD; disease-modifying drug; MS, multiple sclerosis; NAb, neutralizing antibody; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SC, subcutaneous.

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# Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

*Absolute risk:* The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

*Add-on therapy*: An additional treatment used in conjunction with the primary or initial treatment.

*Adherence:* Following the course of treatment proscribed by a study protocol.

*Adverse drug reaction*: An adverse effect specifically associated with a drug.

*Adverse event:* A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

*Adverse effect:* An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

*Active-control trial:* A trial comparing a drug in a particular class or group with a drug outside of that class or group.

*Allocation concealment:* The process by which the person determining randomization is blinded to a study participant's group allocation.

*Applicability:* see *External Validity*

*Before-after study:* A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

*Bias:* A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

*Bioequivalence*: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

*Black box warning:* A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

*Blinding:* A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

*Case series:* A study reporting observations on a series of patients receiving the same intervention with no control group.

*Case study:* A study reporting observations on a single patient.

*Case-control study:* A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

*Clinical diversity:* Differences between studies in key characteristics of the participants, interventions or outcome measures.

*Clinically significant:* A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

*Cohort study:* An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

*Combination Therapy*: The use of two or more therapies and especially drugs to treat a disease or condition.

*Confidence interval:* The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

*Confounder:* A factor that is associated with both an intervention and an outcome of interest.

*Controlled clinical trial:* A clinical trial that includes a control group but no or inadequate methods of randomization.

*Control group:* In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

*Convenience sample:* A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

*Crossover trial:* A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

*Direct analysis:* The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

*Dosage form:* The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

*Dose-response relationship:* The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

*Double-blind:* The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

*Double-dummy:* The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

*Effectiveness:* The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

*Effectiveness outcomes:* Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

*Effect size/estimate of effect:* The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

*Efficacy:* The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

*Equivalence level*: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

*Equivalence trial:* A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

*Exclusion criteria:* The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

*External validity*: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

*Fixed-effect model*: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

*Fixed-dose combination product*: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

*Forest plot:* A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

*Funnel plot:* A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

*Generalizability:* See *External Validity.*

*Half- life:* The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

*Hazard ratio:* The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

*Head-to-head trial:* A trial that directly compares one drug in a particular class or group with another in the same class or group.

*Health outcome:* The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

*Heterogeneity:* The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

$I^2$: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of $I^2$ suggest heterogeneity. $I^2$ is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

*Incidence:* The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

*Indication:* A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

*Indirect analysis:* The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

*Intention to treat:* The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

*Internal validity:* The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

*Inter-rater reliability:* The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

*Intermediate outcome:* An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

*Logistic regression:* A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

*Masking*: See *Blinding*

*Mean difference:* A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

*Meta-analysis:* The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

*Meta-regression:* A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

*Mixed treatment comparison meta analysis:* A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

*Monotherapy:* the use of a single drug to treat a particular disorder or disease.

*Multivariate analysis:* Measuring the impact of more than one variable at a time while analyzing a set of data.

*N-of-1 trial:* A randomized trial in an individual to determine the optimum treatment for that individual.

*Noninferiority trial:* A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

*Nonrandomized study:* Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

*Null hypothesis:* The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

*Number needed to harm:* The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

*Number needed to treat:* An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

*Observational study:* A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

*Odds ratio:* The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

*Off-label use:* When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

*Outcome:* The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

*Outcome measure:* Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

*One-tailed test (one-sided test):* A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

*Open-label trial:* A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

*Per protocol:* The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

*Pharmacokinetics:* the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

*Placebo:* An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

*Placebo-controlled trial:* A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

*Point estimate:* The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

*Pooling:* The practice of combing data from several studies to draw conclusions about treatment effects.

*Power:* The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

*Precision:* The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

*Prospective study:* A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

*Prevalence:* How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

*Probability:* The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

*Publication bias:* A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

*P value:* The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

*Q-statistic:* A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

*Random-effects model:* A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

*Randomization:* The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

*Randomized controlled trial:* A trial in which two or more interventions are compared through random allocation of participants.

*Regression analysis:* A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

*Relative risk:* The ratio of risks in two groups; same as a risk ratio.

*Retrospective study:* A study in which the outcomes have occurred prior to study entry.

*Risk:* A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

*Risk difference:* The difference in size of risk between two groups.

*Risk Factor:* A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

*Risk ratio:* The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

*Run-in period*: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

*Safety:* Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

*Sample size:* The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

*Sensitivity analysis*: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

*Side effect:* Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

*Standard deviation (SD):* A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

*Standard error (SE):* A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

*Standard treatment:* The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

*Statistically significant:* A result that is unlikely to have happened by chance.

*Study:* A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

*Study population:* The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

*Subgroup analysis:* An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

*Superiority trial:* A trial designed to test whether one intervention is superior to another.

*Surrogate outcome:* Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

*Survival analysis:* Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

*Systematic review:* A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

*Tolerability:* For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

*Treatment regimen*: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

*Two-tailed test (two-sided test):* A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

*Type I error:* A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

*Type II error:* A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

*Validity:* The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

*Variable:* A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

*Washout period*: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

# Appendix B. Black Box warnings for included drugs

| Drug names | Active ingredients | Boxed warnings |
|---|---|---|
| Tysabri | Natalizumab | WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY<br>TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI as monotherapy[see *Warnings and Precautions (5.1)*].<br>• Because of the risk of PML, TYSABRI is available only through a special restricted distribution program called the TOUCH® Prescribing Program. Under the TOUCH® Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH® Prescribing Program [see *Warnings and Precautions (5.1, 5.2)*].<br>• Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended [see *Contraindications (4), Warnings and Precautions (5.1)*]. |
| Novantrone® | Mitoxantrone | NOVANTRONE® (mitoxantrone for injection concentrate) should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents. NOVANTRONE® should be given slowly into a freely flowing intravenous infusion. It must never be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See ADVERSE REACTIONS, General, Cutaneous and DOSAGE AND ADMINISTRATION, Preparation and Administration Precautions).<br>NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See WARNINGS, General)<br>Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE® therapy generally should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NOVANTRONE® .<br>Cardiotoxicity: Congestive heart failure (CHF), potentially fatal, may occur either during therapy with NOVANTRONE® |

| Drug names | Active ingredients | Boxed warnings |
|---|---|---|
| | | or months to years after termination of therapy.<br>Cardiotoxicity risk increases with cumulative NOVANTRONE dose and may occur whether or not cardiac risk factors are present. Presence or history of cardiovascular disease, radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or use of other cardiotoxic drugs may increase this risk. In cancer patients, the risk of symptomatic CHF was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m2. To mitigate the cardiotoxicity risk with NOVANTRONE, prescribers should consider the following:<br>NOVANTRONE mitoXANTRONE for injection<br><br>All Patients:<br>All patients should be assessed for cardiac signs and symptoms by history, physical examination, and ECG prior to start of NOVANTRONE® therapy.<br>All patients should have baseline quantitative evaluation of left ventricular ejection fraction (LVEF) using appropriate methodology (ex. Echocardiogram, multi-gated radionuclide angiography (MUGA), MRI, etc.).<br>Multiple Sclerosis Patients:<br>MS patients with a baseline LVEF below the lower limit of normal should not be treated with NOVANTRONE® .<br>MS patients should be assessed for cardiac signs and symptoms by history, physical examination and ECG prior to each dose.<br>MS patients should undergo quantitative reevaluation of LVEF prior to each dose using the same methodology that was used to assess baseline LVEF. Additional doses of NOVANTRONE® should not be administered to multiple sclerosis patients who have experienced either a drop in LVEF to below the lower limit of normal or a clinically significant reduction in LVEF during NOVANTRONE® therapy.<br>MS patients should not receive a cumulative NOVANTRONE dose greater than 140 mg/m2.<br>-MS patients should undergo yearly quantitative LVEF evaluation after stopping NOVANTRONE to monitor for late occurring cardiotoxicity.<br>Secondary Leukemia: NOVANTRONE® therapy in patients with MS and in patients with cancer increases the risk of developing secondary acute myeloid leukemia.<br>For additional information, see WARNINGS and DOSAGE AND ADMINISTRATION. |

# Appendix C. Search strategies for Update 1

Database: Ovid MEDLINE(R) <1996 to December Week 4 2009>
Search Strategy:

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1 exp Multiple Sclerosis/
2 "first demyelinating event".mp.
3 1 or 2
4 Mitoxantrone.mp.
5 1 and 4
6 glatiramer.mp.
7 interferon beta.mp.
8 natalizumab.mp.
9 5 or 6 or 7 or 8
10 3 and 9
11 limit 10 to (english language and humans)
12 (2007$ or 2008$ or 2009$ or 2010$).ed.
13 11 and 12

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2009>
Search Strategy:

---

1 multiple sclerosis.mp.
2 first demyelinating event.mp.
3 1 or 2
4 mitoxantrone.mp.
5 1 and 4
6 glatiramer.mp.
7 interferon beta.mp.
8 natalizumab.mp.
9 5 or 6 or 7 or 8
10 3 and 9

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2009>
Search Strategy:

---

1 multiple sclerosis.mp.
2 first demyelinating event.mp.
3 1 or 2
4 mitoxantrone.mp.
5 1 and 4
6 glatiramer.mp.
7 interferon beta.mp.
8 natalizumab.mp.
9 5 or 6 or 7 or 8
10 3 and 9

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2009>
Search Strategy:
---
1 multiple sclerosis.mp.
2 first demyelinating event.mp.
3 1 or 2
4 mitoxantrone.mp.
5 1 and 4
6 glatiramer.mp.
7 interferon beta.mp.
8 natalizumab.mp.
9 5 or 6 or 7 or 8
10 3 and 9

# Appendix D. Excluded trials

1=foreign language, 2=outcome not included, 3=intervention not included, 4=study design not included, 5=publication type not included, 6=study design not included.

| Excluded trials | Exclusion code |
|---|---|
| *Active-control trials* | |
| Baum K, Mannitol Formulation Study G. Safety and tolerability of a 'refrigeration-free' formulation of interferon beta-1b--results of a double-blind, multicentre, comparative study in patients with relapsing-remitting or secondary progressive multiple sclerosis. Journal of International Medical Research. Jan-Feb 2006;34(1):1-12. | 3 |
| Havrdova E, Zivadinov R, Krasensky J, et al. Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. Multiple Sclerosis. 2009. | 6 |
| Hellwig K, Schimrigk S, Lukas C, et al. Efficacy of mitoxantrone and intrathecal triamcinolone acetonide treatment in chronic progressive multiple sclerosis patients. Clinical Neuropharmacology. Sep-Oct 2006;29(5):286-291. | 6 |
| Kalanie H, Gharagozli K, Hemmatie A, Ghorbanie M, Kalanie AR. Interferon Beta-1a and intravenous immunoglobulin treatment for multiple sclerosis in Iran. European Neurology. 2004;52(4):202-206. | 3 |
| Palumbo R, Salmaggi A, La Mantia L, Solari A, Milanese C. Treatment with Interferon beta 1b and Azathioprine in the relapsing- remitting MS. Clinical and quality of life evaluation. Rivista di Neurobiologia. 1999;45(5-6):519-521. | 1 |
| Perini P, Calabrese M, Tiberio M, et al. Mitoxantrone versus cyclophosphamide in secondary-progressive multiple sclerosis: a comparative study. Journal of Neurology. Aug 2006;253(8):1034-1040. | 6 |
| *Head-to-head trials* | |
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|---|---|
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| Excluded trials | Exclusion code |
|---|---|
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# Appendix E. Strength of evidence

## Key Question 1: Evidence profile of the comparative efficacy of disease-modifying treatments for patients with multiple sclerosis

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of studies; Number of subjects** | **Risk of bias (design/ quality)** | **Consistency** | **Directness** | **Precision** | **Summary effect size (95% CI)** | **High, moderate, low, insufficient** |
| **Outcome 1. Comparative effectiveness of Interferon beta-1b SC (Betaseron®) vs Interferon beta-1a IM (Avonex®) on relapse-related outcomes – RRMS** | | | | | | |
| % Relapse Free<br>2 head-to-head trials/278 | Medium | Consistent | Direct | Imprecise | Betaseron superior to Avonex RR=1.51 (1.11to 2.07) | Moderate |
| 2 systematic reviews | Medium | Consistent | Indirect | Imprecise | Bayesian meta-analysis %relapse-free RR, 1.48 (1.11, 2.02) | |
| **Outcome 2. Comparative effectiveness of Interferon beta-1b SC (Betaseron®) vs Interferon beta-1a IM (Avonex®) on disease progression outcomes – RRMS** | | | | | | |
| 1 head-to-head trial of dp/188;<br>3 H-to-H trials of EDSS change/325 | Medium | Inconsistent | Direct | Imprecise | % progressed: Betaseron superior to Avonex i 30% vs 13%, p=0.003; EDSS change[a] no difference −0.330(−0.686-0.025), $I^2$=59.9% | Low |
| 2 systematic reviews | | | Indirect | | Bayesian meta-analysis progression rate: Betaseron superior to Avonex RR, 0.48 (0.27-0.86) | |
| **Outcome 3. Comparative effectiveness of Interferon beta-1a IM (Avonex®) vs Interferon beta-1a SC (Rebif®) on Relapse-related outcomes – RRMS** | | | | | | |
| 2 head-to-head trials/767 | Medium | Consistent | Direct | --- | % Relapse free: Rebif superior to Avonex (56-57% vs 20-48 | Moderate |
| 2 systematic reviews of 3 PCTs | | | Indirect | | Bayesian MA RR=1.22 (1.06-1.41) | |
| **Outcome 4. Comparative effectiveness of Interferon beta-1a IM (Avonex®) vs Interferon beta-1a SC (Rebif®) on Disease progression outcomes – RRMS** | | | | | | |
| 3 head-to-head trials/814 % progressed<br>1HtoH/677 EDSS<br>2HtoH/137 | Medium | Consistent | Direct | Imprecise | % dprogressed: no difference (54% vs 57%); EDSS: | Moderate |
| 2 systematic reviews of 3 PCTs | | | Indirect | | % progressed: Bayesian meta-analysis: RR 1.05 (0.93-1.22) | |

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of studies; Number of subjects** | **Risk of bias (design/ quality)** | **Consistency** | **Directness** | **Precision** | **Summary effect size (95% CI)** | **High, moderate, low, insufficient** |
| **Outcome 5. Comparative effectiveness of Interferon beta-1b SC (Betaseron®) vs Interferon beta-1a SC (Rebif®) on relapse-related outcomes – RRMS** | | | | | | |
| 2 head-to-head trials/391 % relapse free | Medium | Consistent | Direct | Imprecise | RR 1.51 (1.11 to 2.07) | Moderate |
| 2 systematic reviews of 3 PCTs | | | Indirect | | Bayesian meta-analysis RR 0.85 (0.56 – 1.25) | |
| **Outcome 6. Comparative effectiveness of Interferon beta-1b SC (Betaseron®) vs Interferon beta-1a SC (Rebif®) on disease progression outcomes – RRMS** | | | | | | |
| 3 head-to-head trials/438 %progressed: 1 HtoH/301 EDSS 2HtoH/137 | Medium | Inconsistent | Direct | Imprecise | % progressed: no difference 36% vs 33%; EDSS change -0.1to -0.7 vs -0.3 to -0.4 | Moderate |
| 2 systematic reviews of 3 PCTs | | | Indirect | | Bayesian meta-analysis progression rate RR= 1.18 (0.80, 1.71) and EDSS change[a] -0.30 (-0.60, 0.015) | |
| **Outcome 7. Comparative effectiveness of glatiramer actetate vs Interferon β or placebo on relapse and disease progression outcomes – RRMS** | | | | | | |
| 2 head-to-head trials/3008 | Medium | Consistent | Direct | Imprecise | Annualized relapse rate (0.29-0.34 vs 0.30-0.33), p=0.42-0.83; % relapse free (59-62% vs 58062% ), p=0.17-0.96; disease progression (8.7-21% vs 11.7-27% interferons), p=0.12-0.71. Glatiramer superior to placebo in mean relapse rate [-0.64(-1.19 – 10.09)], no dif in % relapse-free (RR 1.23, p=0.086) | Moderate |
| 1MA and 1 SR of 3 PCTs | | | Indirect | | | |
| **Outcome 8. Comparative effectiveness of natalizumab vs placebo on relapse, disease progression, and health-related quality of life outcomes – RRMS** | | | | | | |
| 2 placebo-controlled trials/2113 | Low | Consistent | Indirect | --- | % progressed(17-23% vs 29%, p<0.001 to 0.02), annualized relapse rate (023-0.34 vs 0.73-0.75, p≤0.001), % relapse free 61-67% vs 37-41%, p<0.001), HRQofL physical component of SF-36 OR 1.47-1.54 (1.06-2.23) | Moderate |
| **Outcome 9. Comparative effectiveness of mitoxantrone vs placebo on disease progression outcomes – RRMS** | | | | | | |
| 1 placebo-controlled trial/51 | Medium | --- | Indirect | --- | Absolute difference in risk 30% (95% CI 8-52%), NNT=3 | Insufficient |

| | Domains pertaining to strength of evidence | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of studies; Number of subjects** | **Risk of bias (design/ quality)** | **Consistency** | **Directness** | **Precision** | **Summary effect size (95% CI)** | **High, moderate, low, insufficient** |
| **Outcome 10. Comparative effectiveness of Interferon β vs placebo on relapse and disease progression outcomes – SPMS** | | | | | | |
| 5 placebo-controlled trials/3075 | Medium | Inconsistent | Indirect | --- | Betaseron superior to placebo in disease progression HR 0.79 (0.66-0.93; Avonex superior to placebo in MSFC (-0.362 vs -0.495, p=0.033) Interferon β superior to placebo in ARR Betaseron:0.16-0.44 vs 0.28 – 0.64, p=0.002-0.009 Rebif: RR 0.69 (0.56-0.85) and RR=0.9(0.64-1.27) Avonex ARR 0.2 vs 0.3, p=0.008 | Moderate |
| **Outcome 11. Comparative effectiveness of Interferon β vs placebo on relapse and disease progression outcomes – PPMS** | | | | | | |
| 1 placebo-controlled trial/50 | Medium | --- | Indirect | --- | no difference in time to sustained progression | Low |

## Key Question 4: Evidence profile of the comparative effectiveness of disease modifying treatments for patients with a clinically isolated syndrome

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Drug; Number of studies; Number of subjects** | **Risk of bias (design/ quality)** | **Consistency** | **Directness** | **Precision** | **Estimate of effect[a] (95% CI)** | **High, moderate, low, insufficient** |
| **Outcome: Progression to clinically definite multiple sclerosis** | | | | | | |
| Avonex; 2 fair quality placebo-controlled trials; 600 | Medium | Consistent | Indirect | Precise | 0.56 (0.38 to 0.81)<br>0.63 (0.46 to 0.85) | Low |
| Rebif; 1 fair-quality placebo-controlled trial; 309 | | | | | 0.65 (0.45 to 0.94) | |
| Betaseron; 1 good quality placebo-controlled trial; 468 | | | | | 0.50 (0.36 to 0.70) | |
| Glatiramer; 1 fair quality placebo-controlled trial; 481 | | | | | 0.55 (0.40 to 0.77) | |

[a] Relative risk or hazard ratio.

## Key Question 5: Evidence profile of the comparative harm of disease-modifying treatments for patients with multiple sclerosis

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of studies; Number of subjects** | **Risk of bias (design/ quality)** | **Consistency** | **Directness** | **Precision** | **Summary effect size (95% CI)** | **High, moderate, low, insufficient** |
| **Outcome 1. Comparative harm of interferon beta-1b SC (Betaseron®) vs. interferon beta-1a SC (Rebif®). vs interferon beta-1a IM (Avonex®)** | | | | | | |
| 3H-toH/1166 RRMS<br><br>2 SR of 6 PCT in RRMS<br><br>5 PCT in SPMS/3075<br><br>1 SR in PPMS | Moderate | Consistent | Indirect | Imprecise | Injection site reaction least with Avonex 8.5% (4.5to15.2); Flu-like syndrome greatest with Avonex 62.2% (39.0to80.8); Fever greatest with Betaseron 33.3% (19.0 to 47.6); Overall withdrawal greatest with Betaseron 7.5% (3.7 to 11.2) | Moderate |
| **Outcome 2. Comparative safety of Interferon beta-1b SC (Betaseron®) vs. Interferon beta-1a SC (Rebif®) vs. Interferon beta-1a IM (Avonex®) on depression** | | | | | | |
| Depression: 1 MA<br><br>4 PCT | Moderate | Consistent | Indirect | Imprecise | Betaseron vs Rebif 44 µg RR 0.72(0.40-1.29); Betaseron vs Avonex RR 0.79(0.42-1.48); Rebif vs Avonex RR 1.05(0.68-1.63) | Moderate |
| **Outcome 3. Comparative harm of glatiramer acetate vs. Interferon beta-1b SC (Betaseron®) or Interferon β-1a (Rebif®)** | | | | | | |
| 2 H-to-H/3008 | Moderate | Consistent | Direct | Imprecise | injection site reactions 58% vs 48% (1 trial), post-injection systemic responses 17% vs 0-5% (2 trials), influenza-like illness 1-6% vs 31-40%, elevated liver enzymes , 1-4% vs 6-11%, fever 4-5% vs 6-9%,, | |
| **Outcome 4. Comparative harm of mitoxantrone vs. placebo** | | | | | | |
| 1 SR | Moderate | Consistent | Indirect | --- | amenorrhea 29% vs 0% p=0.0004,, LVEF <50% 2.18%, (95%CI 1.28-3.47%),, nausea with vomiting 62.3% vs 15.4% p<0.00001, Acute leukemia incidence 0.15% at 70mg/$m^2$; Fatal congestive heart failure 0.15%, 95%CI 0.02-0.52%; ; Permanent amenorrhea associated with older age (OR 1.02, 10.1-1.04) and higher cumulative dose (OR 1.18, 1.10-1.27) | Low |

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| Number of studies; Number of subjects | Risk of bias (design/ quality) | Consistency | Directness | Precision | Summary effect size (95% CI) | High, moderate, low, insufficient |
| **Outcome 5. Comparative harm of natalizumab vs. placebo** | | | | | | |
| 5 PCT/2578 | Moderate | Consistent | Indirect | --- | 55 cases of PML reported–estimated incidence is 1.0 per 1000 treated patients (95% CI, 0.2 to 2.8 per 1000) | Moderate |