Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

dimethyl fumarate 120mg, 240mg gastro-resistant hard capsules (Tecfidera®) SMC No. (886/13)

Biogen Idec Ltd

05 July 2013 *(Issued 07 March 2014)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dimethyl fumarate (Tecfidera®) is accepted for use within NHS Scotland.

Indication under review: treatment of adult patients with relapsing remitting multiple sclerosis.

Two phase III, placebo-controlled studies demonstrated significantly superior efficacy for dimethyl fumarate compared to placebo for the primary end-points of proportion of patients relapsed at two years (in one study) and the annualised relapse rate (in the other study).

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dimethyl fumarate. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adult patients with relapsing remitting multiple sclerosis.

Dosing Information

The starting dose is dimethyl fumarate 120mg twice a day. After 7 days, the dose is increased to the recommended dose of dimethyl fumarate 240mg twice a day.

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Product availability date

12 February 2014

Summary of evidence on comparative efficacy

Multiple sclerosis (MS) is a disease of the central nervous system where myelin within the brain or spinal cord becomes inflamed and is then destroyed by the immune system. The relapsing remitting form (RRMS), occurring in 80% of people at onset, is characterised by periods of good health or remission which are followed by sudden symptoms or relapses. The aim of treatment is to reduce the frequency and severity of relapses, reduce lesions, slow down physical disability and maintain and improve quality of life. Treatments for RRMS include subcutaneous or intramuscular interferon beta (any type) or subcutaneous glatiramer acetate, available through a risk-sharing scheme established in 2002. Patients should meet the criteria developed by the Association of British Neurologists to be eligible for treatment, and stopping criteria should be discussed and agreed with the patient before starting treatment.[1] Other treatments include intravenous natalizumab and oral fingolimod, where use is in specifically defined patient groups.

Dimethyl fumarate is a new oral treatment for RRMS in treatment-naïve and pre-treated patients. Its anti-inflammatory and cytoprotective properties are thought to be mediated partly through the activation of the nuclear factor (erythroid derived 2)-like 2 transcriptional pathway.[2]

Two phase III, placebo-controlled (of which one included an active reference) studies (DEFINE and CONFIRM) have been conducted in patients aged 18 to 55 years with a diagnosis of RRMS based on McDonald criteria 1 to 4.[2-5] Patients were required to have an Expanded Disability Status Scale (EDSS) baseline score of 0 to 5.0 (ranges from 0 to 10, with higher scores indicating greater disability) and to have disease activity defined as at least one clinically documented relapse within 12 months before randomisation or a brain magnetic resonance imaging (MRI) scan, obtained within six weeks before randomisation that showed at least one gadolinium-enhancing lesion. Patients were excluded if they had received treatment with interferon alpha or interferon beta within three months prior to randomisation. In the DEFINE study, treatment with glatiramer acetate within the previous three months was also an exclusion criterion. In addition, patients with a relapse (or treated with corticosteroids) within 50 days of randomisation or those not stabilised after a relapse were excluded from both studies.

In the DEFINE study, patients were randomised equally to double-blind treatment with dimethyl fumarate 240mg twice daily (n=410), dimethyl fumarate 240mg three times daily (n=416) or

placebo (n=408) for 96 weeks. In the CONFIRM study, patients were randomised equally to treatment with dimethyl fumarate 240mg twice daily (n=359), dimethyl fumarate 240mg three times daily (n=345), glatiramer acetate 20mg subcutaneous injection once daily (n=350) or placebo (n=363). The CONFIRM study was only partially-blinded as patients were aware of treatment allocation. Patients who had completed 48 weeks of study treatment were eligible to switch to an alternative therapy for MS if: in DEFINE, they had ≥1 confirmed relapses after 24 weeks; or in CONFIRM, at least two confirmed relapses at any point during the study. Efficacy analyses were performed in the intention-to-treat (ITT) populations which included all randomised patients who received at least one dose of study drug.

Only the twice daily dose of dimethyl fumarate is licensed, therefore efficacy results for this dose of dimethyl fumarate, placebo and glatiramer acetate (CONFIRM study) are presented.

The primary endpoint in the DEFINE study was the proportion of patients who had a relapse by two years (where relapses were defined as new or recurrent neurologic symptoms, not associated with fever or infection, that lasted for at least 24 hours and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation). The proportion of patients who relapsed by two years was 27% for dimethyl fumarate 240mg twice daily and 46% for placebo; hazard ratio 0.51 (95% confidence interval [CI] 0.40 to 0.66), p<0.001. Annualised relapse rate was a secondary endpoint and was defined as the total number of relapses divided by the number of patient-years in the study, excluding data obtained after patients switched to alternative MS medications. The annualised relapse rate at two years was 0.17 in the dimethyl fumarate twice daily group and 0.36 in the placebo group; rate ratio 0.47 (95% CI 0.37 to 0.61), p<0.001.

The primary endpoint in the CONFIRM study was annualised relapse rate at two years and was 0.22 in the dimethyl fumarate twice daily group, 0.29 in the glatiramer acetate group and 0.40 in the placebo group; percentage reduction (dimethyl fumarate twice daily versus placebo) 44% (95% CI 26 to 58), p<0.001. The proportion of patients who relapsed by two years was a secondary endpoint and was 29% for dimethyl fumarate 240mg twice daily, 32% for glatiramer acetate and 41% for placebo; hazard ratio (dimethyl fumarate twice daily versus placebo) 0.66 (95% CI 0.51 to 0.86), p≤0.01.

Confirmed progression of disability at two years was defined as at least a 1.0 point increase on the EDSS in patients with a baseline score of 1.0 or higher, or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks. Dimethyl fumarate twice daily was significantly superior to placebo for confirmed progression of disability at two years in the DEFINE study only. Dimethyl fumarate was significantly superior to placebo in both studies for the endpoints of number of gadolinium-enhancing T_2-weighted lesions at two years and enlarging hyperintense T_2-weighted lesions at 2 years.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the CONFIRM study, the proportion of patients who reported any adverse event was 94% (338/359) in the dimethyl fumarate twice daily group, 87% (304/351) in the glatiramer acetate group and 92% (333/363) in the placebo group. Serious adverse events occurred in 17% (61/359), 17% (60/351) and 22% (79/363) of patients respectively. The proportion of patients with an adverse event that led to discontinuation was 12% (44/359) in the dimethyl fumarate twice daily group, 10% (35/351) in the glatiramer group and 10% (38/363) in the placebo group. In the dimethyl fumarate twice daily group, most of these patients discontinued treatment because of flushing (3.9% [14/359]) versus no patients in the glatiramer acetate and placebo groups.

The most frequently reported adverse events occurring in a higher proportion of patients in the dimethyl fumarate twice daily than glatiramer acetate groups were flushing (31% [110/359] versus 1.7% [6/351]), nasopharyngitis (17% [62/359] versus 15% [51/251]), diarrhoea (13% [45/359] versus 4.0% [14/351]), nausea (11% [40/359] versus 4.3% [15/351]), upper respiratory tract infection (10.0% [36/359] versus 7.7% [27/351]) and upper abdominal pain (10% [36/359] versus 1.1% [4/351]). The most common serious adverse event was MS relapse. Other serious adverse events in the dimethyl fumarate twice daily group included gastroenteritis, cellulitus, abdominal pain and back pain (n=2 for each).

A similar proportion of patients in each group had alanine aminotransferase at least three times upper limit of normal (around 6%) and aspartate aminotransferase at least three times upper limit of normal (around 2%). Before starting treatment with dimethyl fumarate, renal and hepatic function and a full blood count should be performed. Whilst on treatment, renal function and hepatic function should be checked after three and six months of treatment and a complete blood count should be checked at six months. Thereafter, these should be checked every six to 12 months and as clinically indicated.[6]

The adverse events rates in the DEFINE study were similar to the CONFIRM study.

Summary of clinical effectiveness issues

In the pivotal studies, dimethyl fumarate twice daily was significantly superior to placebo for the primary endpoints of proportion of patients relapsed (DEFINE) and annualised relapse rate (CONFIRM) at two years. However, for the confirmed progression of disability endpoint, dimethyl fumarate twice daily was significantly superior to placebo in one study only. In the CONFIRM study, the results of the primary and secondary outcomes for dimethyl fumarate twice daily were similar for glatiramer acetate, which was included as an active reference. However, the study was not designed to test the superiority or non-inferiority of dimethyl fumarate versus glatiramer acetate. The duration of the studies was adequate and appropriate endpoints were used.[7]

In the pivotal studies, patients were excluded if they had relapsed within 50 days prior to randomisation, received interferon alpha or interferon beta within the previous three months, and in the DEFINE study, glatiramer acetate within the previous three months. Therefore there may be some limitations in the generalisability of the study results. However, the studies did

recruit treatment-naïve and previously-treated patients, which concurs with the patient group eligible for treatment within the licensed indication. The mean duration of MS was around 5.6 years in the DEFINE study and 41% of patients had prior treatment with an approved medication for MS. In the CONFIRM study, the mean duration of MS was 4.9 years and 29% of patients had prior treatment with an approved disease modifying drug. Moreover pre-specified sub-group analyses of the treatment naïve and pre-treated (any medication for MS) sub-groups were generally consistent with the whole population.

Clinical experts consulted by SMC considered that safer, more efficacious, cost-effective, first-line treatments for RRMS are required. Current treatments for RRMS include beta interferon 1a, beta interferon 1b and glatiramer acetate.[1] In addition, fingolimod and natalizumab may be used in highly active RRMS in patients with high disease activity despite treatment with a beta-interferon or in rapidly evolving severe RRMS.[8,9] Direct active-comparative efficacy data are limited to the CONFIRM study where glatiramer acetate was included as an active reference only. Consequently, the submitting company presented a mixed treatment comparison (MTC) using a frequentist approach and conducted in patients with relapsing remitting multiple sclerosis. It included 27 studies using placebo as the common comparator in order to compare dimethyl fumarate with the main comparators (beta interferons, fingolimod and glatiramer acetate). Nine efficacy outcome measures were analysed as well as discontinuation rates and safety. The key efficacy outcomes for the economic analysis were annualised relapse rate and disability progression sustained for three months at 24 months. For annualised relapse rate, dimethyl fumarate twice daily was significantly superior to comparators with the exception of natalizumab and fingolimod, where natalizumab was significantly superior and fingolimod similar to dimethyl fumarate. There was no significant difference between dimethyl fumarate and comparators for the disability progression outcome. There was some heterogeneity between the studies in terms of study and baseline characteristics. Covariate analyses were presented, although the submitting company did not consider adjustment for covariates was necessary as there was not a considerable change in relative effect between the unadjusted and adjusted MTC. The statistician consulted by SMC considered the exploration of covariates and heterogeneity to be useful, and commented that the adjusted MTC results accounted for some of the heterogeneity and therefore were preferable.

Dimethyl fumarate is administered orally twice daily in contrast to interferon treatments (administered as subcutaneous or intramuscular injections every other day to once weekly), glatiramer acetate (subcutaneous injection once daily), natalizumab (intravenous infusion once monthly) and fingolimod (orally once daily). Oral administration may be preferred by some patients. Clinical experts consulted by SMC consider there is unmet need in this area and the availability of an oral treatment that can be used first line is welcomed.

In the pivotal studies, one-third of patients experienced flushing with dimethyl fumarate. Results of the MTC indicated that flushing as well as flu-like symptoms, diarrhoea and nausea were significantly more frequent with dimethyl fumarate than glatiramer acetate. There are no safety or efficacy data beyond a treatment duration of two years.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis over a 30 year time horizon comparing dimethyl fumarate with a range of comparators: beta interferon 1a (Avonex), beta interferon 1a (Rebif), beta interferon 1b (Betaferon/Extavia), glatiramer acetate, fingolimod and natalizumab.

The analysis included both treatment naïve and treatment experienced patients with RRMS. Expert responses suggested that dimethyl fumarate would be considered a first-line option, which indicates that the beta interferons and glatiramer acetate are possibly the main comparators. However, some experts suggested it may be also be used second-line as an alternative to fingolimod and natalizumab.

A Markov cohort model was used based on a previous model developed for the National Institute for Health and Care Excellence (NICE). Patients entered the model at a baseline EDSS health state based on the pivotal studies. Patients could then remain in that health state or move to a higher or lower disability EDSS state. The model also allowed for patients progressing to secondary progressive multiple sclerosis (SPMS). Patients were assumed to remain on treatment until they progressed to EDSS score 7 or died.

The clinical evidence used in the analysis was based on the unadjusted results of the MTC. The outcome measures used were 'confirmed disability progression sustained for 3 months at 24 months' and 'annualised relapse rate'. The results of the MTC for the disability progression outcome measure showed there is no significant difference between dimethyl fumarate and the comparator treatments. The model assumed there was a waning of the treatment effect for all treatments with treatment efficacy reduced to 75% at year 3 and 50% from year 6 onwards.

The utility values were estimated using EQ-5D data collected in the dimethyl fumarate studies combined with RRMS and SPMS utility values from a UK MS survey. In addition to the health benefits of patients, the quality-adjusted life-years (QALYs) in the model also included disutilities associated with carers. These were applied in the model according to patients' EDSS states with the maximum carer disutility estimated to be 0.14.

Resource use included drug acquisition, patient monitoring and administration costs where applicable. A number of MS-related resources were also included, such as inpatient admissions, day case neurology visits, specialist visits, GP visits and residential care costs. The costs were included according to each EDSS health state and also where patients progressed to SPMS or experienced a relapse. The list of resources included seemed reasonable and was broadly consistent with previous submissions for MS treatments.

The submitting company estimated the following incremental cost-effectiveness ratios (ICERs):

Dimethyl fumarate versus	**Incremental costs**	**Incremental QALYs**	**ICER for dimethyl fumarate vs comparator**
Beta interferon 1a (Avonex)	£30,915	0.20	£154,781
Beta interferon 1a (Rebif) 22 microgram	£35,494	0.285	£124,337
Beta interferon 1a (Rebif) 44 microgram	£28,621	0.163	£175,779
Beta interferon 1b (Betaferon/Extavia)	£28,417	0.385	£73,724
Glatiramer acetate	£33,957	0.33	£102,830
Fingolimod	-£12,693	0.265	Dominant

Natalizumab	-£14,990	-0.102	£146,300*

*dimethyl fumarate is less costly but also less effective.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a confidential discount on the list price of the medicine was offered. With the PAS, the company estimated the following ICERs:

Dimethyl fumarate versus	**Incremental costs**	**Incremental QALYs**	**ICER for dimethyl fumarate vs comparator**
Beta interferon 1a (Avonex)	-£347	0.20	Dominant
Beta interferon 1a (Rebif) 22 microgram	£4,232	0.285	£14,823
Beta interferon 1a (Rebif) 44 microgram	-£2,642	0.163	Dominant
Beta interferon 1b (Betaferon/Extavia)	-£2,845	0.385	Dominant
Glatiramer acetate	£2,694	0.330	£8,159
Fingolimod	-£43,955	0.265	Dominant
Natalizumab	-£46,252	-0.102	£451,419*

*dimethyl fumarate is less costly but also less effective.

Sensitivity analysis was only provided to test the results with the PAS and only for the comparison with beta interferon 1a (Avonex). The results were sensitive to the disability progression rate, with the ICER increasing to £45k per QALY when the rate in the dimethyl fumarate arm was increased by 20%. Similarly, reducing the disability progression rate in the beta interferon 1a (Avonex) arm increased the ICER to £174,018 per QALY. The results of the PSA indicated there was a 73% probability that dimethyl fumarate was cost-effective at £20k per QALY and 75% at £30k per QALY.

The following limitations were noted:

- The base case analysis included disutilities associated with carers, which is not appropriate. SMC guidance does allow for these health outcomes to be considered, but only as a sensitivity analysis. The company subsequently provided a revised base analysis with carer disutilties excluded. In this analysis dimethyl fumarate remained the dominant treatment in the comparisons with beta-interferon 1a (Avonex, Rebif 44 microgram), fingolimod and beta-interferon 1b (Betaferon/Extavia) with the PAS included. The ICER in the comparisons with beta-interferon 1a (Rebif 22 microgram) and glatiramer increased to £16,290 and £9,048 per QALY respectively. For the comparison with natalizumab, dimethyl fumarate remained less costly but also less effective.
- Clinical data used in the model relating to disability progression and relapse rates were based on the unadjusted indirect comparison results and included non-significant differences. A revised analysis which removes the non-significant differences was requested from the company. However, the company argued that their analysis which

included non-significant differences was appropriate as the evidence from the MTC suggests there is a numerical advantage in favour of dimethyl fumarate for all comparisons, except the comparison with natalizumab. While we note the arguments the company has made, the committee would nevertheless have found this analysis useful. The one-way sensitivity analysis conducted on the disability progression rate indicated that the results were sensitive to changes in this parameter. The company presented some supplementary evidence to show the impact of equalising the disability progression parameter in the analysis versus beta-interferon 1a (Avonex, Rebif 44 microgram). With the PAS, this resulted in a cost per QALY of £19,614 versus beta-interferon 1a (Avonex) and dominance versus beta-interferon 1a (Rebif 44 microgram).

- The model structure does not allow for patients moving to subsequent lines of therapy. The model structure has been used in previous submissions for MS treatments and was appropriate when there were no other treatment options. However, as there are now other therapies available, the model structure does not reflect practice. The company acknowledged that modelling treatment sequences was an option, but given the lack of data and complexity involved, a simpler approach was considered more appropriate. This seemed a reasonable justification for the approach used.
- The results presented above do not take into account the discounted price for fingolimod that applies under the PAS. Analysis was provided by the submitting company to show the impact of incorporating a wide range of discounted prices for fingolimod and this information was used by SMC. SMC would wish to present this analysis but is unable to do so as the manufacturer of fingolimod has not provided the information to the submitting company.

Despite these issues, the economic case for dimethyl fumarate was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from the MS Society.

Additional information: guidelines and protocols

NICE published multiple technology appraisal 32; Beta interferon and glatiramer acetate for the treatment of multiple sclerosis in January 2002.[10]

- On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of MS in the NHS in England and Wales.
- The Committee considered that the Department of Health, the National Assembly for Wales and manufacturers, might usefully consider what actions could be taken, jointly, to enable any of the four medicines appraised for this guidance to be secured for patients in the NHS in England and Wales, in a manner which could be considered to be cost effective.

The Department of Health published health services circular 2002/004; cost effective provision of disease modifying therapies for people with multiple sclerosis in February 2002.[11]

- The Department of Health, National Assembly for Wales, Scottish Executive and Northern Ireland Department of Health, Social Services & Public Safety have reached agreement with manufacturers on a risk-sharing scheme for the supply of disease modifying treatments for MS on the NHS. The scheme involves detailed monitoring of a cohort of patients to confirm the cost-effectiveness of these treatments.

- All patients with RRMS, and those with SPMS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the scheme.

The Scottish Executive Health Department published HDL (2002)6 in February 2002.[12] This confirmed agreement with manufacturers on a risk sharing scheme for the supply of disease modifying treatments for MS on the NHS.

NICE published clinical guideline 8; multiple sclerosis in 2003.[1]
People with RRMS, and those with SPMS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the risk-sharing scheme.

- People with RRMS should be offered interferon beta (any type) or glatiramer acetate provided that the following four conditions are met:
    - can walk 100 metres or more without assistance
    - have had at least two clinically significant relapses in the past 2 years
    - are aged 18 years or older
    - do not have contraindications
- People with RRMS offered treatment with interferon beta or glatiramer acetate should have the following stopping criteria discussed and agreed before starting treatment:
    - intolerable side effects
    - being pregnant or planning pregnancy
    - occurrence of two disabling relapses within a 12-month period
    - development of SPMS (glatiramer acetate only)
    - secondary progression with an observable increase in disability over a 6-month period (interferon beta only)
    - loss of ability to walk, with or without assistance, that has persisted for longer than 6 months.

The Association of British Neurologists (ABN) guidelines for prescribing in multiple sclerosis were revised in 2009.[13] The following recommendations are included:
In patients with RRMS*;* beta interferon or glatiramer acetate

- Patients with a diagnosis of active MS with relapsing onset; active disease is defined by two clinically significant relapses in the previous two years.
- Neurologists may, in certain other circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits.

Recommendations for discontinuation of treatment;

- Decisions to start or stop treatment, or to perform MRI for diagnosis and management, should recognise the central importance of patient choice; patients should be fully informed of relevant facts and uncertainties before making a decision in discussion with their treating neurologist.
- It is not feasible to have mandatory stopping criteria that apply in all cases. The guidance included some scenarios which are suggestive of loss of or limited benefit from treatment and should be taken into account when deciding whether treatment should be discontinued

NB; The ABN receives donations for educational support of the annual scientific symposium from Pharmaceutical Companies that market treatments for multiple sclerosis.

Additional information: comparators

Beta interferon 1a, beta interferon 1b, glatiramer acetate, fingolimod and natalizumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dimethyl fumarate	**120mg orally twice daily for one week then 240mg orally twice daily thereafter**	**17,849**
Fingolimod	500 micrograms orally once daily	19,110
Natalizumab	300mg as an intravenous infusion every four weeks	14,690
Beta interferon 1a (Rebif®) *	After initial titration, 44 micrograms as a subcutaneous injection three times weekly	10,572
Beta interferon 1a (Avonex®) *	30 micrograms as an intramuscular injection once weekly	8,502
Beta interferon 1b (Betaferon®) *	After initial titration, 250 microgram as a subcutaneous injection every other day	7,239
Beta interferon 1b (Extavia®) *	After initial titration, 250 microgram as a subcutaneous injection every other day	7,239
Glatiramer acetate *	20mg as a subcutaneous injection once daily	6,681

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis 22 April 2013, MIMS (for glatiramer acetate) and from company's submission (for dimethyl fumarate). Costs do not take any patient access or risk sharing schemes into consideration.
*Included in the Multiple Sclerosis Risk Sharing Scheme

Additional information: budget impact

With PAS: The gross impact on the medicines budget was estimated to be £292k in year 1 and £3.593m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £48k in year 1 and £592k in year 5.

Comments from SMC clinical experts suggest that the company may have underestimated the likely uptake.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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4. Biogen Idec Ltd. 109MS301: DEFINE - A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG00012 in subjects with relapsing-remitting multiple sclerosis. Clinical study reports. 2011.
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7. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. CPMP/EWP/561/98 Rev. 1 (November 2007)
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10. NICE. Multiple technology appraisal 32; betaferon and glatiramer (2002) www.nice.org
11. Department of Health. Health services circular 2002/004; Cost effective provision of disease Modifying therapies for people with Multiple sclerosis. February 2002.
12. Scottish Executive Health Department. HDL (2002)6; Cost effective provision of disease Modifying therapies for people with Multiple sclerosis. February 2002.
13. Association of British Neurologists. Guidelines for prescribing in multiple sclerosis (revised 2009). http://www.theabn.org/abn/userfiles/file/ABN_MS_Guidelines_2009_Final(1).pdf

This assessment is based on data submitted by the applicant company up to and including 14 June 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.