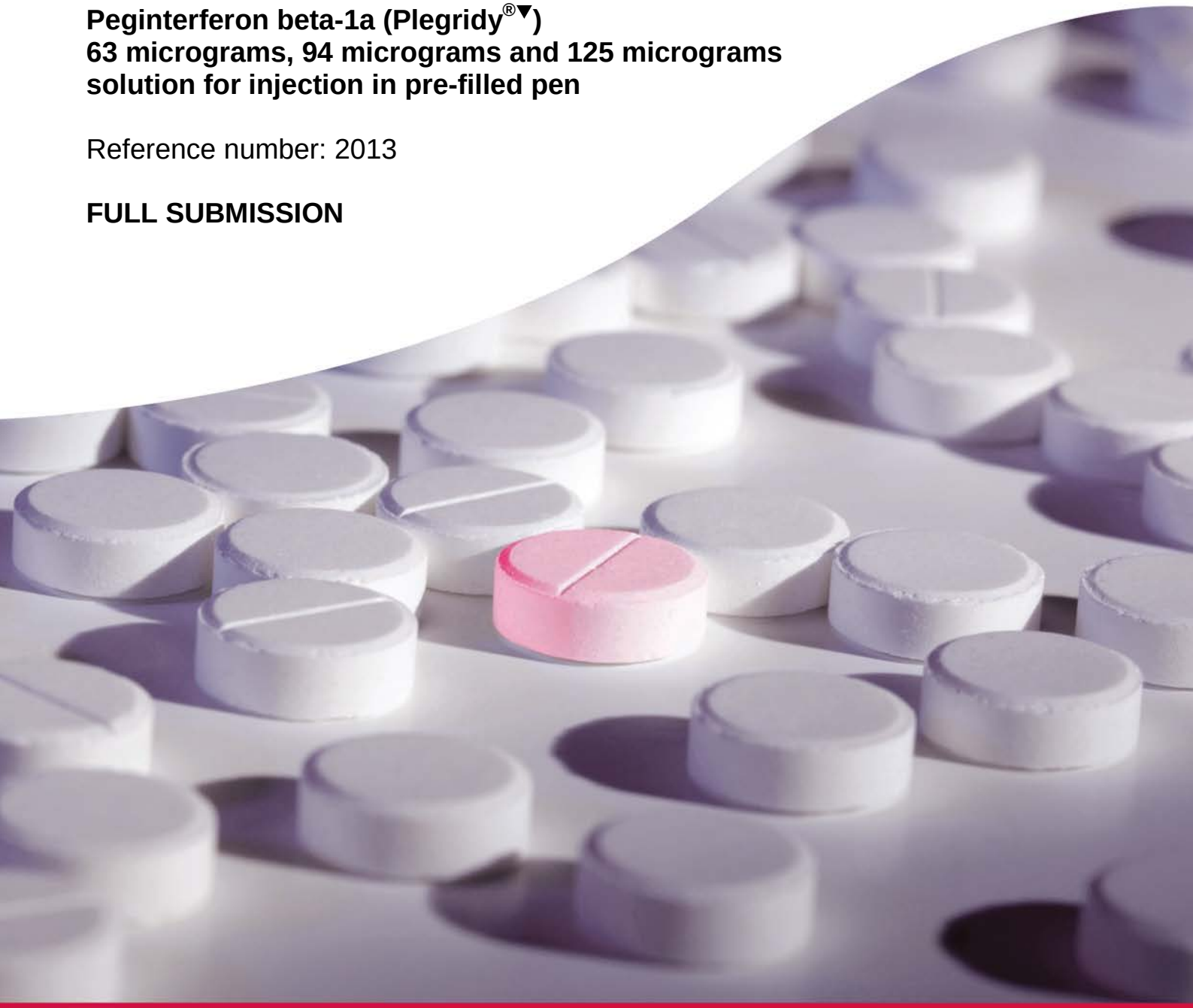
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Peginterferon beta-1a (Plegridy®▼)
63 micrograms, 94 micrograms and 125 micrograms solution for injection in pre-filled pen

Reference number: 2013

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Peginterferon beta-1a (Plegridy®▼) 63 micrograms, 94 micrograms and 125 micrograms solution for injection in pre-filled pen. Reference number: 2013.
May 2015.

AWMSG Secretariat Assessment Report
Peginterferon beta-1a (Plegridy®▼) 63 micrograms, 94 micrograms and 125 micrograms solution for injection in pre-filled pen

This assessment report is based on evidence submitted by Biogen Idec Ltd on 23 January 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Peginterferon beta-1a (Plegridy®▼) is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis[2].
Dosing	The recommended dosage of peginterferon beta-1a is 125 micrograms injected subcutaneously every two weeks. It is recommended that patients start treatment with 63 micrograms at dose 1, increasing to 94 micrograms at dose 2, reaching the full dose of 125 micrograms by dose 3 and continuing with the full dose (125 micrograms) every 2 weeks thereafter. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	18 July 2014[3].

2.0 DECISION CONTEXT

2.1 Background

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system characterised by demyelination and axonal degeneration of the nerves in the brain and spinal cord[4,5]. MS is potentially highly disabling and symptoms are variable, patients can develop multiple neurological dysfunctions and experience visual and sensory disturbances, limb weakness, gait problems, bladder and bowel symptoms[5]. Onset of symptoms typically develops when patients are in their late 20s, with 85% of patients having relapsing-remitting MS (RRMS) where periods of stability (remission) are followed by episodes of exacerbations of symptoms (relapses)[4,5]. Although the number of relapses are random, they initially average 1.5 per year and steadily increase thereafter, with most patients developing progressive irreversible disability 10–15 years from disease onset[4].

It is estimated that about 100,000 people in the UK are affected by MS with incidence and prevalence varying regionally. One study based in south east Wales demonstrated an increase in prevalence from 101 to 146 patients per 100,000 population between 1985 and 2005, while incidence increased from 4.25 to 9.65 per 100,000 population between 1985 and 2007[6].

Disease Modifying Therapies (DMTs) can decrease the number of relapses and slow the progression of the disease[7]. Interferon betas are cytokines with immunomodulatory activity which target the inflammatory component of RRMS and inhibit the migration of activated T cells across the blood-brain barrier[4,8]. Peginterferon beta-1a is created by the conjugation of polyethylene glycol with interferon beta-1a; this pegylation prolongs

the half-life, which reduces the frequency of dosing required with peginterferon beta-1a compared to the unmodified interferon beta-1a[8].

DMTs (interferon beta 1a, interferon beta 1b and glatiramer acetate) have been made available on the NHS through a Risk-Sharing Scheme set up by the Department of Health (DoH) in 2002[9]. The scheme allows prescribing of these treatments by neurologists in 72 prescribing centres across the UK to all eligible patients according to the Association of British Neurologists guidelines[10,11]. The cost-effectiveness of each of the treatments in the scheme is monitored using data from a cohort of over 5,000 patients. These data are assessed every two years, actual and expected benefits are compared and if there is a significant shortfall in actual benefit the price of the product is reduced for the following two year period. Funding for the scheme is provided equally by the DoH and by four manufacturers of DMTs in the UK[9].The scheme is scheduled to run until 2015 once ten years of data have been collected[9].

2.2 Comparators

The comparators included in the company submission were:

- Interferon beta-1a (Avonex®)
- Interferon beta-1a (Rebif®)
- Interferon beta-1b (Betaferon®/Extavia®)
- Glatiramer acetate (Copaxone®)

The submission did not include comparison with first-line oral therapies; the company reported that peginterferon beta-1a would not be used where the benefits of oral therapy were required, but would be used as an alternative to current interferons where injectable therapy was appropriate[1].

2.3 Guidance and related advice

- NICE. Clinical Guideline (CG) 186. Multiple sclerosis: management of multiple sclerosis in primary and secondary care (2014)[5].
- Department of Health. The Risk Sharing Scheme for Disease modifying Therapies in MS (2010)[9].
- Association of British Neurologists. Revised guidelines for prescribing in multiple sclerosis (2009)[11].
- NICE TA32. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis (2002)[12].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of delta-9-tetrahydrocannabinol/cannabidiol (Sativex®▼) and fampridine (Fampyra®▼)[13,14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of one phase III study (ADVANCE) which investigated the clinical efficacy and safety of peginterferon beta-1a compared to placebo. In the absence of head-to-head comparative data, a systematic review and mixed treatment comparison (MTC) was also provided by the company.

3.1 ADVANCE study

ADVANCE was an international, multicentre, randomised, double-blind, parallel-group, placebo-controlled phase III study carried out in patients aged 18–65 years with RRMS (as defined by McDonald criteria 1–4 [see Glossary]) who had at least two relapses in the previous three years (one having occurred in the past 12 months) and a score of 0–5 on the Expanded Disability Status scale (EDSS)[15–17]. Patients (n = 1512) were randomised to receive either subcutaneous (SC) peginterferon beta-1a 125 micrograms every two weeks (Q2W [n = 512]), every four weeks (Q4W [n = 500])

or placebo (n = 500) for 48 weeks. At the end of 48 weeks, patients in the placebo group were randomly re-assigned to peginterferon beta-1a Q2W or Q4W[16]. The licensed dose for peginterferon beta-1a is Q2W; therefore, the results for Q4W are not discussed in detail.

The primary efficacy endpoint was the annualised relapse rate (ARR) at week 48 (see Glossary for definition)[16]. At 48 weeks, the relapse rate was 0.256 relapses per patient per year in the Q2W group and 0.397 in the placebo group. This represents statistically significant reductions of 35.6% and 27.5% in ARR with peginterferon Q2W and Q4W respectively when compared with placebo[16].

Secondary endpoints included the proportion of patients with disability progression at 48 weeks (see Glossary for definition), the number of new or newly enlarging T2 hyper intense lesions and proportion of patients relapsed[1,16]. The results of the secondary endpoints were statistically significant in favour of peginterferon beta-1a compared to placebo[16].

Patient-reported quality of life outcomes were assessed using SF-12, EQ-5D and the MS Impact Scale-29. During year one and at 96 weeks, no significant change from baseline was demonstrated for all treatment groups[18].

3.2 Systematic review and MTC

The company provided a systematic review and used the results to perform an MTC of peginterferon beta-1a with comparator treatments. Eligibility criteria included:

- Adults with relapsed MS (RMS) or RRMS
- intervention treatment of interferon beta-1a, interferon beta-1b, glatiramer acetate or peginterferon beta-1a
- comparator of any of the included interventions, placebo or best supportive care
- randomised control trials (RCTs) with any blinding status
- study duration > six months[1].

Following assessment, 16 studies were considered to meet the inclusion criteria: one study examined peginterferon beta-1a, and the remaining 15 examined comparator interventions[1]. Bayesian network meta-analyses were performed for ARR, annualised hospital-treated relapse rate (ARR-HT), proportion of patients relapse free (PPR-F), confirmed disability progression sustained for three and six months (CDPS3M and CDPS6M). Both random and fixed effect models were produced for all efficacy outcomes; deviance was observed to be lower for the random effect model for the key outcome measure (ARR). The random effect model was preferred over the fixed effect model to account for heterogeneity due to indirect comparisons included in the MTC[1].

Peginterferon beta-1a was found to be better than intra-muscular (IM) interferon beta-1a 30 micrograms for CDPS6M. No statistically significant difference was indicated for any of the other outcomes or interventions[1]. A summary of the results are shown in Table 1.

Table 1. Summary of MTC results for peginterferon beta-1a versus comparators using random effect models

	Outcome measure				
Comparator	**ARR Rate ratio (95% CrI)**	**ARR-HT Rate ratio (95% CrI)**	**PPR-F 12 months Rate ratio (95% CrI)**	**CDPS3M Hazard ratio (95% CrI)**	**CDPS6M Hazard ratio (95% CrI)**
Interferon beta-1a 30 micrograms IM injection	0.877 (0.650–1.196)*	-	0.970 (0.188–11.91)*	0.737 (0.427–1.257)*	0.535 (0.282–0.987)†
Interferon beta-1a 22 micrograms SC injection	0.916 (0.642–1.300)*	0.987 (0.005–199.40)*	0.955 (0.181–4.520)*	0.749 (0.421–1.295)*	-
Interferon beta-1a 44 micrograms SC injection	0.984 (0.724–1.359)*	0.695 (0.001–301.70)*	0.876 (0.171–3.509)*	0.834 (0.485–1.425)*	0.553 (0.275–1.091)*
Interferon beta-1b 250 micrograms SC injection	0.954 (0.696–1.307)*	0.972 (0.002–484.40)*	1.077 (0.212–17.68)*	0.710 (0.419–1.172)*	0799 (0.229–3.313)*
Glatiramer acetate	1.001 (0.749–1.373)*	1.091 (0.002–461.40)*	1.101 (0.213–6.320)*	0.707 (0.420–1.159)*	0.619 (0.315–1.186)*
Placebo	0.650 (0.493–0.867)†	0.556 (0.007–42.020)*	1.282 (0.242–1.916)*	0.579 (0.366–0.891)†	0.431 (0.243–0.732)†

ARR: annualised relapse rate; ARR-HT: annualised hospital-treated relapse rate; CDPS3M: confirmed disability progression sustained for three months; CDPS6M: confirmed disability progression sustained for six months; CrI: credible interval; IM: intra-muscular; PPR-F: proportion of patients relapse free; SC: subcutaneous.
* no statistically significant difference
† indicates peginterferon beta -1a was significantly better for this outcome,
- indicates comparison was not possible

Sensitivity analyses for study duration, blinding and sample size were performed to support homogeneity between studies for the comparison of peginterferon beta-1a and comparators for ARR, CDPS3M and CDPS6M. These analyses showed no change in the direction of MTC results or the level of significance between any of the comparisons relative to the original analysis[1].

3.3 Safety

In the ADVANCE study, the incidence of adverse events (AEs) was higher in the peginterferon beta-1a Q2W group compared with placebo (94% versus 83%). The most common AEs with an incidence of ≥ 10% in the peginterferon beta-1a Q2W group were injection site erythema, influenza-type illness, pyrexia, headache, myalgia, chills, injection site pain and injection site pruritis. Peginterferon beta-1a was not associated with an increased risk of neutralising antibodies against interferon compared with placebo.

Comparative safety data was obtained from results of the MTC: the annualised risk of developing any AE was 77% for peginterferon beta-1a Q2W versus 66.3% for glatiramer acetate, 72.6% for interferon beta-1a 30 micrograms (weekly) and 57.5% for interferon beta-1a 44 micrograms (three times weekly). It should be noted that the data for peginterferon beta-1a Q2W are only over one year, whereas most data from the comparator studies were of two years duration. Annualised risks were reported for specific AEs where there was a ≥ 5% point difference between peginterferon beta-1a and the comparator treatments. A ≥ 5% incidence of gastrointestinal disorders and

injection site reactions were reported for peginterferon beta-1a compared to the comparator treatments. Peginterferon beta-1a demonstrated at least 5% lower incidence of depression, fatigue, neutralising antibodies and rash than any of the other comparator treatments[1]. CHMP concluded that the safety profile of peginterferon beta-1a appeared generally consistent with that of existing non-pegylated beta interferon MS therapies[8].

3.4 AWTTC critique

- Efficacy of peginterferon beta-1a in patients with RRMS in terms of ARR compared to placebo was demonstrated by data from the ADVANCE study. CHMP noted that, although the effect size was modest, the relative effect size of around 30% reduction in relapse rate was comparable to other interferons and considered clinically relevant[8].
- In their submission, the company included a systematic review and MTC to address the lack of direct comparative evidence. Broadly, peginterferon beta-1a was shown to be comparable with other non-pegylated interferons and glatiramer acetate[19], although MTC results should be interpreted with caution due to heterogeneity of the studies with regard to patient population, duration of treatment, background treatments and study design.
- The lack of data on efficacy of peginterferon beta-1a after switching from a non-pegylated interferon beta should be considered when switching patients between pegylated and non-pegylated interferons and has been highlighted in the SPC[2].
- The ADVANCE study demonstrated a low incidence of neutralising interferon antibodies over two years; the incidence rate was also lower than that demonstrated by the other active comparators in the MTC[1]. CHMP concluded that the duration of treatment was too short to fully elucidate the exact degree and impact of antibody formation on safety; therefore, immunogenicity has been referred to in the risk management plan and will be monitored further in the extension study[8].
- Peginterferon beta-1a is administered subcutaneously every two weeks via an auto-injector device, which requires no reconstitution or assembly and may be more convenient for patients[1,2]. All other injectable treatments require administration more frequently[20–24]. Less frequent injections may lead to improvement in adherence, and may reduce the opportunity for injection related AEs to occur[1,25]. The company noted that SC administration may also be considered preferable to IM administration[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of peginterferon beta-1a 125 micrograms SC injection compared to current injectable therapies: interferon beta-1a (Avonex®) 30 micrograms IM injection, interferon beta-1a (Rebif®) 22 micrograms SC injection, interferon beta-1a (Rebif®) 44 micrograms SC injection, interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection and glatiramer acetate (Copaxone®) 20 mg SC injection. Whilst glatiramer acetate (Copaxone®) SC injection and interferon-beta-1a (Rebif®) 22 micrograms SC injection were included for completeness, the company reported that they were not considered to be the most appropriate comparators. The company stated that glatiramer acetate may be used as a first-line choice, and is more generally used in clinical practice in Wales as a switch therapy for patients receiving interferons who are suffering flu-like symptoms[1]

Peginterferon beta-1a is indicated in adult patients for the treatment of RRMS. The patient population described within the company submission reflects a subset of the

licensed population i.e. only those patients who are treated with a self-injectable therapy. For these patients, clinical experts in Wales validated the potential comparators.

The model uses a cohort-based Markov approach to estimate the incremental costs and health outcomes over a 30–year time horizon with cycle duration of one year. The model is based on the widely used School of Health and Related Research (ScHARR) model originally developed for NICE, which has been used in previous MS health technology assessments[26]. Patients enter the model at a baseline RRMS state and can move to a higher (worse) or lower (better) EDSS state, where each EDSS state represents one or two EDSS scores, or remain in the same state. Patients may also progress to secondary progressive multiple sclerosis (SPMS), from where they can progress to a higher EDSS state or remain in the same state, but not move to a lower state. The model assumes that treatments delay the progression of disease and reduce the frequency of relapses, and are thus discontinued on entering the SPMS state or upon reaching EDSS 7. Relapse and death were also included in the model.

Data used to populate the model were obtained largely from the pivotal phase III ADVANCE study, MTC[19], a UK MS survey, the published literature and expert opinion[16,19]. The UK MS survey included people with RRMS, SPMS, and primary-progressive MS (PPMS), and the results were based on 2,048 responses. For data from the published literature, a systematic review was only conducted for efficacy and safety. Expert opinion was obtained from a neurologist in England.

Patient characteristics at baseline were pooled from the peginterferon beta-1a and placebo arms of the ADVANCE study. Annual transition probabilities within RRMS health states were obtained from the placebo arm of ADVANCE up to health state EDSS 5. Annual transition probabilities for health states EDSS 6–9 were obtained from the London Ontario Multiple Sclerosis registry[27–30], due to the limited number of observations for these states in ADVANCE. The RRMS to SPMS and within SPMS transition probabilities were also estimated from the London Ontario dataset[27–30]. Relapse rates were obtained from pooled baseline data from ADVANCE for health states up to EDSS 5.5 with data for the more severe health states obtained from a separate study[31]. Efficacy inputs for each treatment for disability progression sustained for three months and ARR were derived from the MTC. These were only applied to RRMS-RRMS transitions as patients with SPMS are assumed not to receive treatment.

Utility weights for RRMS EDSS states were derived by combining data from the placebo arm of ADVANCE (EDSS 0–5) with UK multiple sclerosis survey data (EDSS 6–9). The disutilities associated with AEs and caregivers were also included in the model.

Costs included in the model were medicine acquisition costs, administration costs, disease management costs, monitoring costs and the cost of managing AEs. Medicine acquisition costs were calculated using the cost per dose and dosing recommendations from the Risk Sharing Scheme[32]. The company also provided an analysis using NHS list prices. Administration costs were based on nurse time to teach patients how to self-administer and were therefore assumed to be the same for each treatment. The costs of disease management by EDSS level were based on a published study[33]. Monitoring costs were based on the relevant product information for each treatment. The cost of managing each AE was estimated and validated by a Delphi panel conducted by the company. Information about the composition of this panel was not included.

4.1.2 Results

Results of the base case analysis suggest that peginterferon beta-1a 125 micrograms SC injection dominates interferon beta-1a (Avonex®) 30 micrograms IM injection, interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection and interferon

beta-1a (Rebif®) 22 micrograms SC injection, and suggest incremental cost-effectiveness ratios (ICERs) of £4,011 and £17,491 per quality-adjusted life-year (QALY) gained compared to interferon beta-1a (Rebif®) 44 micrograms SC injection and glatiramer acetate (Copaxone®) 20 mg SC injection in adult patients with RRMS (Table 2). The disutility associated with AEs only had a small impact on the difference in QALYs between peginterferon beta-1a and the comparators. Instead, the difference in QALYs was attributable to patients receiving peginterferon beta-1a spending more time in the less severe EDSS states.

The results of the analysis using NHS list prices suggest either the same or improved cost-effectiveness for peginterferon beta-1a 125 micrograms SC injection versus comparators. This is because the Risk Sharing Scheme acquisition prices are the same or lower than the NHS List price.

Table 2. Company-reported results of the base case analysis

Treatment	Total cost	Total LYs	Total QALYs	ICER for peginterferon beta-1a (LYs)	ICER for peginterferon beta-1a (QALYs)
Peginterferon beta-1a 125 micrograms SC injection	£102,427	17.17	7.32	-	-
Interferon beta-1a (Rebif®) 44 micrograms SC injection	£101,181	17.14	7.01	£44,319	£4,011
Interferon beta-1a (Avonex®) 30 micrograms IM injection	£108,718	17.13	6.88	Peginterferon beta-1a dominates	Peginterferon beta-1a dominates
Interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection	£106,129	17.13	6.88	Peginterferon beta-1a dominates	Peginterferon beta-1a dominates
Glatiramer acetate (Copaxone®) 20 mg SC injection	£95,072	17.13	6.90	£174,490	£17,491
Interferon beta-1a (Rebif®) 22 micrograms SC injection	£108,215	17.14	6.99	Peginterferon beta-1a dominates	Peginterferon beta-1a dominates
ICER: incremental cost effectiveness ratio; IM: intramuscular; QALY: quality-adjusted life-year; LY: life-year; SC: subcutaneous					

The company conducted univariate, two-way and probabilistic sensitivity analyses to address uncertainty in model parameters. In general, the results suggested peginterferon beta-1a was to be cost-effective in most scenarios compared to the current injectable treatments. Of the analyses included in the univariate sensitivity analysis, the parameters having most impact on cost-effectiveness were the disability progression hazard ratios for peginterferon beta-1a and comparators. The sensitivity analyses that result in an ICER above £20,000 per QALY gained are presented in Table 3.

Table 3. Company-reported results of the sensitivity analyses with an ICER above £20,000 per QALY gained

	Base case ICER (QALYs)	Sensitivity analysis ICER (QALYs)	Plausibility
Interferon beta-1a (Rebif®) 22 micrograms SC injection			
Interferon-beta-1a (Rebif®) 22 micrograms SC injection disability progression rate reduced by 20%	peginterferon beta-1a dominates	peginterferon beta-1a less costly, less effective	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Interferon beta-1a (Rebif®) 44 micrograms SC injection			
Interferon beta-1a (Rebif®) 44 micrograms SC injection disability progression rate reduced by 20%	£4,011	£47,088	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Peginterferon beta-1a 125 micrograms SC injection disability progression rate increased by 20%	£4,011	£24,897	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Interferon-beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection			
Interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection disability progression rate reduced by 20%	peginterferon beta-1a dominates	peginterferon beta-1a less costly, less effective	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Glatiramer acetate (Copaxone®) 20 mg SC injection			
Glatiramer acetate (Copaxone®) 20 mg SC injection disability progression rate reduced by 20%	£17,491	peginterferon beta-1a dominated	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Peginterferon beta-1a 125 micrograms SC injection disability progression rate increased by 20%	£17,491	£45,848	Appropriate to vary as base case uses numerical differences from MTC. Unclear whether more plausible than base case.
Utility values by EDSS level reduced by 20%	£17,491	£20,687	More conservative approach but also associated with uncertainty. Unclear if more plausible than base case.
Peginterferon beta-1a 125 micrograms SC injection discontinuation rate reduced by 20%	£17,491	£23,314	More conservative approach but also associated with uncertainty. Unclear if more plausible than base case.
Glatiramer acetate (Copaxone®) 20 mg SC injection discontinuation rate increased by 20%	£17,491	£21,517	More conservative approach but also associated with uncertainty. Unclear if more plausible than base case.

ICER: incremental cost-effectiveness ratio; IM: intramuscular; MTC: mixed treatment comparison; QALY: quality-adjusted life-year; SC: subcutaneous.

For the comparison with interferon beta-1a (Avonex®) 30 micrograms IM injection, peginterferon beta-1a 125 micrograms SC injection remained dominant for all analyses included in the univariate sensitivity analysis.

Probabilistic sensitivity analysis undertaken for the base-case analysis indicates that the probability that peginterferon beta-1a is cost-effective compared to interferon beta-

1a (Avonex®) 30 micrograms IM injection, interferon beta-1a (Rebif®) 22 micrograms SC injection, interferon beta-1a (Rebif®) 44 micrograms SC injection, interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection and glatiramer acetate (Copaxone®) 20 mg SC injection was 95.9%, 90.9%, 70.8%, 92.4% and 50.5%, respectively, at a cost-effectiveness threshold of £20,000 per QALY gained.

Scenario analyses have been conducted based on (i) waning effects over different time periods; (ii) different discount rates for costs and benefits (iii) exclusion of caregiver utility; (iv) different time horizons; and (v) use of natural history transition probabilities from the London Ontario dataset only. Peginterferon beta-1a 125 micrograms SC injection remained dominant compared with interferon beta-1a (Avonex®), 30 micrograms IM injection, interferon beta-1a (Rebif®) 22 micrograms SC injection and interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection in all scenarios tested. The ICER for peginterferon beta-1a 125 micrograms SC injection was considered cost-effective (i.e. remained below £20,000 per QALY gained) compared to interferon beta-1a (Rebif®) 44 micrograms SC injection in all scenarios tested. For the comparison with glatiramer acetate (Copaxone®) 20 mg SC injection, the ICER exceeded £20,000 per QALY gained with different time horizons (10 years; 20 years), discount rates (6% costs, 6% benefits; 0% costs, 6% benefits) and use of transition probabilities from the London Ontario dataset only.

The scenario of removing caregiver disutility is very plausible though this does not greatly impact the results. The 30-year analysis, as used in the base case, is more appropriate. Similarly, the discount rates used in the base case analysis are more appropriate as they are those specified by AWMSG. It is unclear whether the use of transition probabilities from the London Ontario dataset only is plausible. It is a more conservative approach but also associated with uncertainty.

4.1.3 AWTTC critique

The main strength of the company's economic evidence is that the model structure is clear and based on an existing model used in a number of health technology assessments.

Limitations of the economic evidence include:

- The company's analysis is based on numerical differences in efficacy between the treatments from the MTC, whereas these differences were not shown to be statistically significant.
- Relapse rates for the more severe health states (EDSS > 5.5) were obtained from a study published in 1982[31]. The company did not provide any discussion of their relevance to clinical practice today.
- As the only comparators included in the economic analysis were current injectable therapies, the economic analysis was effectively limited to a subset of the licensed population i.e. only those patients who still choose a self-injectable therapy. The resulting ICER may therefore not be reflective of the whole licensed indication.
- Utility weights were obtained from different sources: the placebo-arm of ADVANCE and UK multiple sclerosis survey data hence adding uncertainty to the analysis. However, the difference in QALYs between peginterferon beta-1a and the comparators was largely due to patients receiving peginterferon beta-1a spending more time in the less severe EDSS health states.
- The company's inclusion of a disutility associated with caregivers in the base case analysis is not appropriate as carers disutilities is not a factor included in the costing perspective considered by AWMSG for personal social services. However, the company conducted a scenario analysis which excluded the caregiver utility and the resulting ICERs were still less than £20,000 per QALY gained.
- The company's analysis only includes direct medical costs to the NHS in Wales and did not include costs to Personal and Social Services in Wales.

4.2 Review of published evidence on cost-effectiveness

No studies were identified that assessed the cost-effectiveness of peginterferon beta-1a compared to the identified comparators. However, one study was identified that estimated potential relapse-associated cost savings with investigational use of peginterferon beta-1a administered every two or four weeks versus placebo over one year in patients with RRMS[34].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on an adult population for Wales of 2,452,201[35], the proportion of patients with RRMS of 85%[36] and published epidemiology data for Wales – a prevalence of MS of 146 per 100,000 and an incidence of MS of 9.65 per 100,000[6], the company assumes there are 3,043 existing patients with RRMS and 201 new patients diagnosed every year in Wales. With the introduction of new oral treatments, the company estimates a reduction in the proportion of patients treated with injectable DMTs over time. They estimate that this will decrease from 35% in year one to 14% in year five. In addition, they estimate that the proportion of patients treated with injectable DMTs who will receive peginterferon beta-1a will increase from 6.5% in year one to 52.6% in year five. Consequently, the overall proportion of RRMS patients receiving peginterferon beta-1a is expected to range from 2.3% in year one to 7.4% in year five. Thus the number of patients receiving peginterferon beta-1a treatment will increase from 44 in year one to 177 in year five. The budget impact analysis only included medicine acquisition costs.

5.1.2 Results

The company estimated the number of patients and costs for the use of peginterferon beta-1a for the treatment of adult patients with RRMS. The estimated number of patients and the associated costs as described by the company in their budget impact analysis are summarised in Table 4. The total cost includes medicine acquisition costs only. The company excluded administration and monitoring costs as they were either the same or similar for each treatment. The company assumes that the use of peginterferon beta-1a will displace interferon beta-1a (Avonex®) 30 micrograms IM injection—50%, interferon beta-1a (Rebif®) 44 micrograms SC injection—40%, and interferon beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection—10%. No market share is assumed to be taken from interferon-beta-1a (Rebif®) 22 micrograms SC injection and glatiramer acetate (Copaxone®) 20 mg SC injection as these are not considered to be relevant comparators for peginterferon beta-1a. Consequently, the overall net costs are based on this.

Table 4. Company-reported costs associated with use of peginterferon beta-1a 125 micrograms SC injection for the treatment of adults with RRMS

	Year 1	Year 2	Year 3	Year 4	Year 5
Total relapsing MS population	3,244	3,445	3,646	3,847	4,048
Total % uptake of peginterferon beta-1a	2.30%	4.30%	5.70%	6.70%	7.40%
Number of patients treated with peginterferon beta-1a	44	87	123	152	177
Cost of peginterferon beta-1a per patient, per annum	£8,502	£8,502	£8,502	£8,502	£8,502
Total cost of peginterferon beta-1a per annum	£374,267	£743,072	£1,042,473	£1,292,915	£1,502,607
Incremental cost of peginterferon beta-1a per patient per annum (RSS prices)*	−£52	−£52	−£52	−£52	−£52
Incremental cost of peginterferon beta-1a per patient, per annum (list prices)*	−£704	−£704	−£704	−£704	−£704
Total incremental cost of peginterferon beta-1a per annum (RSS prices)*	**−£2,276**	**−£4,519**	**−£6,339**	**-−£7,862**	**−£9,137**
Total incremental cost of peginterferon beta-1a per annum (list prices)*	**−£30,978**	**−£61,503**	**−£86,284**	**−£107,013**	**−£124,369**

MS: multiple sclerosis; RSS: risk sharing scheme
*Compared to interferon-beta-1a (Avonex®) 30 micrograms IM injection, interferon-beta-1a (Rebif®) 44 micrograms SC injection, and interferon-beta-1b (Betaferon®/Extavia®) 250 micrograms SC injection based on annual % displacement by peginterferon beta-1a

5.1.3 AWTTC critique

The company estimated the eligible patient numbers based on incidence rates and assumptions rather than attempt to estimate the actual number of eligible patients in Wales.

In addition:

- The company has not incorporated discontinuation rates into their analysis.
- The company's analysis estimates the cost of comparators using both list prices and prices from the Risk Sharing Scheme. This highlights the potentially larger savings when using list prices alone as the list prices are either the same or higher than the Risk Sharing Scheme prices.

5.2 Comparative unit costs

In addition to the comparators used in the economic analysis, there are also a number of oral agents indicated for the treatment of adults with RRMS: finogolimod (Gilenya®▼); dimethyl fumarate (Tecfidera®) and teriflunomide (Aubagio®▼). The costs of these potential treatments for adult patients with RRMS are highlighted in Table 5 below. The cost per patient per year ranges from £6,701 for glatiramer acetate (Copaxone®) 20 mg SC injection to £19,163 for finogolimod (Gilenya®▼). This compares to a cost per patient per year for peginterferon beta-1a of £8,502.

Table 5. Example of cost per patient per year for adult patients with RRMS

Regimen	Dose	Cost per year*
Peginterferon beta-1a (Plegridy®▼) 125 micrograms SC injection	125 micrograms every two weeks	£8,502
Interferon beta-1a (Avonex®) 30 micrograms IM injection	30 micrograms every week	£8,502
Interferon-beta-1a (Rebif®) 22 micrograms SC injection	22 micrograms three times a week	£7,513
Interferon-beta-1a (Rebif®) 44 micrograms SC injection	44 micrograms three times a week	£10,572
Interferon-beta-1b (Betaferon®) 250 micrograms SC injection	250 micrograms on alternate days	£7,260
Interferon-beta-1b (Extavia®) 250 micrograms SC injection	250 micrograms on alternate days	£7,260
Glatiramer acetate (Copaxone®) 20 mg SC injection	20 mg every day	£6,701
Teriflunomide (Aubagio®▼) 14 mg oral	14 mg orally every day	£13,529
Dimethyl fumarate (Tecfidera®) 120–240 mg oral	120 mg orally twice daily, then 240 mg orally twice daily after seven days	£17,555
Finogolimod (Gilenya®▼) 500 micrograms oral	500 micrograms orally every day	£19,163
IM: intramuscular; SC: subcutaneous *Costs based on British National Formulary, February 2015[37]		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, peginterferon beta-1a (Plegridy®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that peginterferon beta-1a (Plegridy®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted an ongoing extension study, although results are unlikely to be published in full in the next 6–12 months:

- NCT01332019. Long-term safety and efficacy study of BIIB017 (PEGylated Interferon Beta-1a) (ATTAIN). Patients who complete two years in the ADVANCE study will continue in the extension study ATTAIN and provide four years of patient data[38].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 5 February 2015.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

McDonald Diagnostic Criteria (1–4) for Multiple Sclerosis[15]

Clinical Presentation	Additional Data needed for MS diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by MRI or two or more MRI-detected lesions consistent with MS plus positive CSF or await further clinical attack implicating a different site.
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by MRI or second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI or two or more MRI-detected lesions consistent with MS plus positive CSF and dissemination in time, demonstrated by MRI or second clinical attack
CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; MS: multiple sclerosis	

Relapse
New or recurrent neurological symptoms not associated with fever or infection, lasting for at least 24 hours, accompanied by new objective neurological findings confirmed by an independent neurological evaluation committee and separated from the onset of other confirmed relapses by at least 30 days[16].

Disability progression
An increase of Expanded Disability Status Scale score of at least 1.0 point for patients with a baseline score of 1.0 or more, or an increase of at least 1.5 points for patients with a baseline score of 0, confirmed after 12 weeks[16].

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